Cell. Mol. Biol. (ISSN: 1165-158X)

Journal Homepage: www.cellmolbiol.org

Cellular and Molecular Biology

Review

Recent advances in immunotherapy in cancer treatment

Ayyub A. Patel*

Department of Clinical Biochemistry, College of Medicine, King Khalid University Abha, Kingdom of Saudi Arabia

Article Info

Article history:

Received: December 23, 2023
Accepted: March 01, 2024
Published: May 31, 2024

Use your device to scan and read the article online

Abstract

Immunotherapy has emerged as a transformative approach in cancer treatment, leveraging the body's immune system to recognize and eradicate cancer cells. This review provides an overview of the recent advances and aspects of immunotherapy in cancer biology, from established therapies like checkpoint inhibitors and CAR-T cells to emerging innovative approaches and the challenges associated with their clinical translation. The exploration includes an examination of checkpoint inhibitors, elucidating the mechanisms behind programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors. Recent clinical successes and ongoing trials demonstrate the efficacy of checkpoint inhibitors across diverse malignancies, underscoring the potential for durable responses and improved patient outcomes. CAR-T cell therapy represents a groundbreaking avenue in immunotherapy, involving the genetic modification of a patient's T cells to express chimeric antigen receptors (CARs) for targeted cancer cell recognition. Furthermore, the review touches on the challenges associated with immunotherapy, including resistance mechanisms and adverse effects. Insightful discussions on overcoming resistance through combination therapies, adaptive treatment strategies, and emerging technologies underscore the ongoing efforts to enhance the long-term efficacy of immunotherapeutic interventions. In summary, this extensive review provides a comprehensive overview of recent advances in immunotherapy in cancer biology, highlighting the transformative impact of these therapies on patient outcomes, the challenges faced, and the promising directions for future research and clinical applications.

Keywords: Cancer therapy; Checkpoint inhibitors; Biomarkers; CAR-T cells; Cancer vaccines; Immune system

1. Introduction

Cancer is one of the most complicated and deadly diseases affecting the health of human. A number of genes and factors are involved in it [1]. There are several forms of cancer affecting almost every vital and not vital part of the body including stomach, cervix, breast, lung, throat, blood, and skin [2, 3]. It is a multifaceted disease and a multifaceted approach is essential to combat it [4]. One of the targeted therapies include the use of RNAs (long non-coding RNAs and microRNA) which have showed effective contribution in eliminating tumors owing to their role in many cellular processes and chemical reactions inside the human body [5] [6]. They can be effective biomarkers in targeted cancer therapy as biomarkers are quite helpful in the diagnosis of cancer and its early treatment [7]. CDH1and DCC genes which are silenced by hypermethylation in gastric cancer, their bioinformatics analysis at the genome and proteome level and evaluation show that these tumor suppressor genes can be utilized for targeted treatments in cancer [8]. Further, metal and metal-based nanoparticles have shown progress in increasing anticancer mechanism [9]. But, due to the unwanted side effects of such metal based and other synthetic compounds based cancer therapy, research is more focused on harnessing anticancer agents from the natural products (plants, marine and microorganisms) [10]. One study explored interaction of α-pinene, a plant product, with testis-specific protein on Y chromosome (TSPY), whose expression has been observed in in gonadoblastoma and carcinoma [11]. Based on in silicomolecular docking analysis, this interaction can be helpful in developing α-pinene as a promising candidate for the new anticancer agent.

Immunotherapy has emerged as a revolutionary approach in cancer therapy, representing a paradigm shift in the treatment of various malignancies [12, 13]. Unlike traditional treatments such as chemotherapy and radiation that directly target cancer cells, immunotherapy harnesses the body's immune system to recognize and combat cancer by selectively attacking cancer cells, often sparing normal cells from the collateral damage associated with traditional treatments [14]. This approach has demonstrated the potential for prolonged and durable responses in some patients. Unlike conventional therapies that may require continuous treatment, immunotherapy such as checkpoint inhibitors and adoptive cell therapies, has shown the ability to induce long-lasting remissions and also cures, in

* Corresponding author.
E-mail address: ayyub@kku.edu.sa (A. A. Patel).
Doi: http://dx.doi.org/10.14715/cmb/2024.70.5.13

some cases.

Most of the cancer types have been life-threatening and greatest challenges in the medical field. Immunotherapy has shown efficacy in cancers that were historically challenging to treat, including some metastatic or advanced-stage cancers [15]. This has expanded treatment options for patients with limited alternatives and poor prognoses. It also often results in fewer side effects compared to traditional treatments like chemotherapy. As it heightens the body's immune system, the adverse effects are typically related to immune activation and are generally milder than the toxicities related to traditional therapies. Moreover, immunotherapy can be combined with other treatment modalities, including chemotherapy, radiation, and targeted therapies, to enhance overall treatment efficacy. This synergistic approach has the potential to overcome resistance mechanisms and improve outcomes.

In the realm of cancer vaccines and adoptive cell therapies, advances in immunotherapy can contribute to the growing field of personalized medicines. Tailoring treatments based on individual patient profiles, including immune system status and tumor characteristics, allows for more effective and precise interventions. One of the several benefits that immunotherapy offers, is that it has the unique advantage of potentially inducing immunological memory [16]. It means that even after treatment is completed, the immune system may "memorize" and recognize cancer cells, providing ongoing protection against recurrence. The approval of various immunotherapies across different cancer types has expanded the treatment landscape [17]. Immunotherapy is now a standard of care for certain cancers and ongoing research continues to explore its potential in additional malignancies. The success of immunotherapy has sparked considerable research and innovation in the field. Ongoing studies aim to refine existing therapies, discover new targets, and develop novel approaches, fostering a dynamic and rapidly evolving landscape in cancer treatment.

2. Brief historical context of cancer immunotherapy

The roots of cancer immunotherapy can be traced back to the late 19th century. Even before that, in the late 1800s, William Coley, a surgeon, observed that some cancer patients experienced spontaneous remission after bacterial infections [18]. He began injecting cancer patients with a mixture of heat-killed bacteria, known as Coley's toxins. Although the mechanisms were not well understood at that time, this marked an early attempt at stimulating the immune system to attack cancer. Later, scientists identified tumor-specific antigens, substances unique to cancer cells, in the 1950s and 1960s [19]. This laid the groundwork for developing strategies to target these antigens, aiming to trigger an immune response against cancer. In the 1970s, researchers began to uncover the role of lymphocytes, particularly T cells, in recognizing and attacking cancer cells [20]. T cells play a crucial role in the immune system, responsible for recognizing and attacking abnormal cells [21]. This period marked a shift in understanding the importance of the cellular immune response in cancer surveillance. The development of monoclonal antibodies in the late 20th century marked the targeted recognition of specific antigens on cancer cells [22]. Rituximab, the first monoclonal antibody approved for cancer treatment [23], became a landmark in immunotherapy by targeting B-cell lymphomas[24]. Tremelimumab, another monoclonal antibody targeting CTLA-4 underwent clinical evaluation. However, it was dosed less frequently due to its longer half-life [25].

Interleukin-2, a cytokine involved in immune cell activation, gained attention in the 1980s for its potential to enhance the body's immune response against cancer [26]. High does IL-2 was one of the first immunotherapies to demonstrate efficacy [27], leading to its approval for metastatic melanoma and renal cell carcinoma [28]. It was the identification of immune checkpoint molecules, such as CTLA-4 [29] and PD-1 [30], in the 1990s and early 2000s, that paved the way for the development of checkpoint inhibitors. Blocking both PD-1 and CTLA-4 in combination enhanced the infiltration of effector T-cells into B16 melanoma in mice. This led to an increased ratio of effector to regulatory T-cells within the tumor [31]. Ipilimumab, the first CTLS-4 inhibitor, was improved in 2011 for metastatic melanoma [32], marking a breakthrough in unleashing the immune system against cancer.

Chimeric Antigen Receptor T-cell (CAR-T) therapy emerged as a revolutionary approach. In the 2010s, CAR-T therapies like Kymriah and Yescarta were approved for certain types of leukaemia and lymphoma [33], showcasing the power of genetically engineered T-cells in targeting cancer. Cancer immunotherapy's groundbreaking researches were recognized with Nobel Prizes when James Allison and Tasuku Honjo were awarded the Nobel prize in physiology in 2018 for their contributions to immune checkpoint inhibitions [34]. The field of cancer immunotherapy continues to advance rapidly with ongoing research focusing on combination therapies, personalized vaccines, and innovative approaches. The development of new immunotherapies and the expansion of indications for existing ones underscore the dynamic nature of the field.

3. Immune checkpoint inhibitors

The immune system plays a critical role in surveillance and elimination of aberrant cells, including cancer cells. Immune checkpoint is a kind of signal (stimulatory or inhibitory) for regulating the antigen recognition of T cell receptors in the process of immune response of attacking pathogens and protecting the normal tissues from damage. However, cancer cells can exploit these regulatory mechanisms to evade immune detection and destruction. Immune checkpoint proteins play a significant role in cancer evasion [35]. These molecules are expressed on the surface of immune cells that regulate the intensity and duration of immune responses. They serve as 'brakes' to prevent overactivation of the immune system and maintain self-tolerance [36]. Cancer cells often upregulate the expression of checkpoint proteins or their ligands as a mechanism of immune evasion. By engaging these proteins, cancer cells can suppress T cell activity, avoid immune detection, and establish an immunosuppressive microenvironment. This evasion strategy allows cancer cells to proliferate and resist immune-mediated elimination. Therapy based on these checkpoint proteins relies on functioning immune system with agonists of stimulatory signals or antagonists of inhibitory signals. Table 1 represents several immune checkpoint proteins that play crucial roles in regulating the immune response. Immune checkpoint inhibitors (Figure 1), negative regulators of the immune system, are key regulators in maintaining immune homeostasis and pre-

venting excessive immune responses [37, 38]. Common checkpoint proteins include programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CLTA-4).

PD-1 is expressed on the surface of T-cells, while PD-L1 is often upregulated on the surface of cancer cells and other immune cells with in the tumor microenvironment. When PD-1 on T-cells binds to PD-L1 in cancer cells, it leads to a suppression of T-cell activity. This interaction inhibits the immune system's ability to recognize and eliminate cancer cells, allowing them to evade surveillance [39]. PD-1 inhibitors, such as pembrolizumab and nivolimab, block this interaction, preventing the suppression of T-cell responses [40]. PD-1 inhibitors have received FDA approval for various cancer types including melanoma, non-small cell lung cancer (NSCLC) [41], and renal cell carcinoma. These drugs have demonstrated durable responses and improved survival rates in a subset of patients. On the other hand, PD-L1 inhibitors, such as atezolizumab and durvalumab, directly target the ligand expressed in cancer cells [42]. By inhibiting the PD-1/PD-L1 interaction, these drugs enhance T-cell activity and promote anti-tumor immune responses. Recent assessments in humans, marking the first use of PD-L1 imaging agents, have introduced non-invasive, molecularly targeted quantitative measures. These measures aim to guide and evaluate the immune response to immune checkpoint therapy [43]. Furthermore, the expression of PD-L1 on tumor cells is often used as a biomarker to predict responsiveness to these inhibitors which have shown efficacy in various cancers, including bladder cancer, triple-negative breast cancer, and NSCLC [44, 45].

CTLA-4 is another checkpoint protein expressed in T cells. It competes with the co-stimulatory molecules CD28 for binding to B7 ligands on antigen-presenting cells (APCs) [46]. Thus, CTLA-4 inhibits T-cell activation and dampens the immune response [47]. Cancer cells can exploit this pathway to evade immune detection by down-regulating co-stimulatory signals necessary for effective T cell activation. CTLA-4 inhibitors, such as ipilimumab, block CTLA-4 leading to enhanced T-cell activation and proliferation [48]. These inhibitors have demonstrated efficacy in metastatic melanoma. Ipilimumab was the first immune checkpoint inhibitor to receive FDA approval in 2011. The combination of CTLA-4 and PD-1 inhibitors has further improved outcomes in melanoma and other malignancies [49], but not without the increased incidence of adverse effects.

However, not all patients respond to checkpoint inhibitors and resistance mechanisms can develop. Immune-related adverse events, although generally manageable, can occur and require vigilant monitoring. Identification of predictive biomarkers, such as microsatellite instability (MSI), PD-L1 expression on tumor cells and tumor mutational burden (TMB), has become crucial for selecting patients who are likely to respond to checkpoint inhibitors [50, 51]. This has paved the way for personalized medicine in the field of immunotherapy. Thus, despite the success of checkpoint inhibitors, challenges such as resistance mechanisms and immune-related adverse events persist. Ongoing research aims to unravel the complexities of the tumor microenvironment, identify additional checkpoint pathways, and develop novel targets and combination therapies to enhance the efficacy of immunotherapy and overcome resistance.

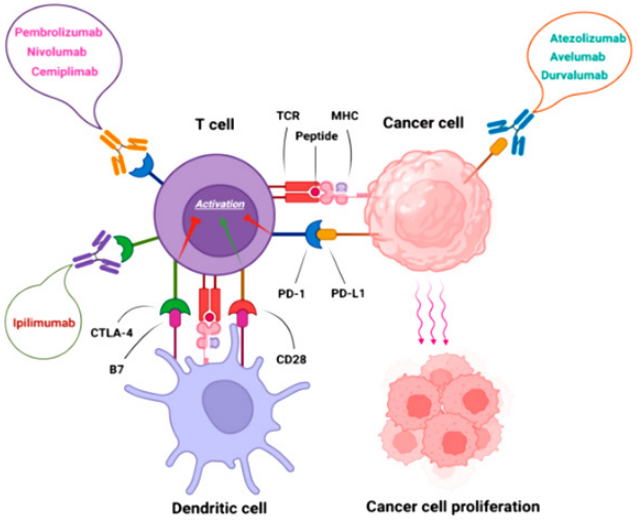

Fig. 1. FDA-approved inhibitors for immune checkpoint therapy (Image source-[75]).

4. Enhancing the efficacy of checkpoint inhibitors

Antitumor therapies and immune checkpoint inhibitors have proved clinical efficacy for some indications, but are limited by toxicity and resistance development. Several emerging strategies are being explored to optimize the effectiveness of checkpoint inhibitors. One strategy is combination therapies. To maximize the probability of therapeutic success, it is imperative that those strategies must be able to increase tumor immunogenicity, favor intra-tumor T cell trafficking and reduce tumor burden. Combining inhibitors targeting different checkpoint proteins, such as PD-1 and CTLA-4, has shown synergistic effects in clinical trials [49]. The combination of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) has shown potential treatment for certain cancers, like NSCLC and melanoma [76, 77]. Furthermore, combining checkpoint inhibitors with target therapies such as tyrosine kinase inhibitors [78] such as lenvatinib in combination with pembrolizumab [79, 80] or PARP inhibitors [81, 82], is being explored to address specific vulnerabilities within the tumor microenvironment and enhance the overall antitumor response in advanced breast cancers that are resistant to the conventional therapeutic protocols. However, optimizing combination therapies involves a multifaceted approach. Key considerations encompass the identification of reliable biomarkers for treatment response prediction, vigilant monitoring of responses and side effects, precise patient stratification based on individual characteristics, understanding potential drug interactions, anticipating and addressing resistance mechanisms, ensuring patient adherence, determining optimal timing for treatment components, embracing personalized medicine, considering immunogenicity, and evaluating potential long-term effects. By addressing these aspects comprehensively, the development and implementation of combination therapies can be refined to enhance efficacy and patient outcomes.

Another approach is engineering bispecific antibodies to simultaneously target two different antigens [83-85]. These antibodies can engage both a checkpoint protein and a tumor-specific antigen, further activating T cells and enhancing their cytotoxic activity [86]. Such method has the

Table 1. Immune checkpoint proteins in the regulation of the immune response.

S. No.	Immune checkpoint proteins	Expression on	Mechanism of action	Immune checkpoint inhibitors	Reference
1.	PD-1	Surface of T cells	binds to PD-L1 causing suppression of T-cell activity	Nivolumab, Pembrolizumab, and Cemiplimab	[39] [40]
2.	PD-L1	on the surface of cancer cells and other immune cells with in the tumor microenvironment		Atezolimumab, Durvalumab and Avelumab	[42]
3.	CTLA-4	T cells	Binds to B7 ligands on APCs), inhibiting T cell activation	Ipilimumab	[48]
4.	Lymphocyte activation gene 3 (LAG-3)	Activated T cells and regulatory T cells	Binds to MHC-II molecules on APCs, inhibiting T-cell activation	Small molecule	[52, 53] [54]
5.	T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3)	T cells and other immune cells	Interacts with galectin-9 and other ligands, regulating T cell function	Cobolimab, LY3321367, or sabatolimab	[55, 56] [57]
6.	V-domain Ig suppressor of T cell activation (VISTA)	Myeloid cells and T cells	Inhibits T cell activation, involved in maintaining immune tolerance	CA-170	[58-60] [61]
7.	T cell immunoreceptor with Ig and ITIM domains (TIGIT)	T cells and natural killer (NK) cells	Binds to CD155 on APCs, inhibiting T cell and NK cell activity	TgMab-2	[62] [63]
8.	B- and T- lymphocytes attenuator (BTLA)	B cells, T cells and dendritic cells.	Suppresses immune response	Anti-BTLA Antibody	[64, 65]
9.	CD40/CD40L (CD154)	APCs and activated T cells respectively	Crucial for T cell priming and B cell activation	Small molecules	[66, 67]
10.	Ox40 (CD134)	Activated T cells	Interacts with Ox40 ligand on APCs, promoting T cell survival and function.	OX40L-Fc fusion proteins	[68, 69]
11.	Siglec-15	Macrophages and myeloid cells	Involved in immune regulation associated with tumor-associated macrophages	anti-Siglec-15 mAb	[70, 71]
12.	4-1BB (CD137)	Activated T cells	Interacts with its ligand (4-1BBL) enhancing T cell proliferation and cytokine production	PRS-343	[72, 73] [74]

potential to trigger a more focused immune system activation, resulting in increased effectiveness and minimized peripheral side effects. Bispecific T cell engagers (BiTEs) are an example of this approach [87]. Additionally, stimulator of interferon genes (STING) activation can enhance the release of pro-inflammatory signals, promoting the recruitment and activation of immune cells within the tumor microenvironment, thus sensitizing tumors to checkpoint inhibition [88, 89]. Recently, a study suggested that paclitaxel, a widely used chemotherapy agent in breast cancer, has the capability to produce micronuclei, aligning with the activation of cyclic GMP-AMP synthase-STING in post-mitotic triple-negative breast cancer cells that survive [90]. Additionally, in a cGAS-dependent manner, paclitaxel can also prompt the polarization of macrophages towards an M1 phenotype. This process may play a role in lymphocyte recruitment in certain TNBC samples, potentially contributing to improved patient survival when undergoing combination therapy, though *in vivo* studies are needed to confirm these findings. Combining cancer vaccines with checkpoint inhibitors can be another strategy which is being explored to induce a more robust and sustained antitumor immune response [91]. Continued studies show that the combination can elevate the antitumor efficacy with safety and toxicity in an acceptable range compared to single-agent vaccine or inhibitors alone [92]. Strategies to improve antigen presentation, such as dendritic cell-based therapies, are also under investigation [93, 94]. Such therapies aim to improve antigen presentation potency to elicit powerful immune responses against tumor cells. The novel approach of combining dendritic cell-based cell therapy with monoclonal antibodies against novel immune checkpoints holds promise to increase the response rate of cancer patients [95].

5. Chimeric antigen receptor T cell (CAR-T) therapy

Cart-T therapy is an innovative form of immunotherapy that harnesses the patient's immune cells, specifically T cells, to recognize and attack cancer cells [96]. It is a personalized and highly targeted approach that has shown remarkable success, particularly in treating certain types of blood cancers. The CAR typically consists of three main components [97]. The first one is extracellular domain which is responsible for recognizing specific antigens on the surface of cancer cells. It is often derived from an antibody and is designed to target a particular protein expressed in the cancer cell. Second is transmembrane domain that anchors the CAR within the T cell membrane, ensuring stability. The last one intracellular domain which contains signalling domains that activate the T cell upon binding to the cancer cell. Common signalling domains include CD3-zeta and co-stimulatory domains like CD28 or 4-1BB.

The therapy begins with the extraction of T cells from the patient's body and is genetically modified in the laboratory [98]. The key modification involves introducing a chimeric antigen receptor (CAR) into the T-cells. This CAR is a synthetic receptor that combines components from both the immune system and antibodies. These genetically modified T-cells equipped with CAR, are cultured to multiply these CAR-T-cells and activate T-cells which are primed to specifically recognise and target cancer cells expressing the antigen targeted by the CAR. The expanded and activated T-cells are then infused back into the patient's blood. These engineered T-cells are designed to persist and continue their anti-cancer activity. When the CAR recognizes the specific antigen on the surface of a cancer cell, it triggers the activation of the T-cell. Activated CAR-T-cells release cytotoxic substances and initiate immune responses, leading to the destruction of cells. Additionally, the targeted and specific nature of CAR-T-cells minimize damage to healthy cells. CAR-T-cells can persist in the patient's body for an extended period providing ongoing surveillance and memory against cancer cells, thus offering the potential for long term protection against disease recurrence. However, keeping in mind the spectrum of infections encountered in CAR T-cell therapy, including bacterial, viral, and fungal infections, understanding the risk factors, spectrum of infections, and implementing appropriate prophylactic measures are essential to optimize outcomes in patients undergoing CAR T-cell therapy [99].

6. Innovative approaches in immunotherapy

In recent years, immunotherapy has witnessed rapid advancements, leading to innovative approaches that are transforming the landscape of cancer treatment. These approaches leverage the body's immune system to recognize and attack cancer cells, offering new possibilities for improved patient outcomes [100]. Neoantigens are unique proteins present on the surface of cancer cells as a result of mutations. Neoantigen vaccines are personalized vaccines designed to stimulate the immune system specifically against these individualized cancer markers [101]. This approach holds promise for enhancing the precision and effectiveness of immunotherapy. Presently, neoantigen-based tumor vaccines primarily consist of peptides, DNA, RNA, and dendritic cells, tailored to the unique profiles of individual patients. The notable immunogenicity of neoantigens enables these vaccines to stimulate and proliferate antigen-specific CD4+ and CD8+ T-cells, thereby enhancing the immune response against tumors [102]. Beyond neoantigen vaccines, there is ongoing research into developing broader cancer vaccines that target shared tumor-associated antigens [103]. These vaccines aim to train the immune system to recognize and attack common features present in various cancer types, providing a more off-the-shelf solution. Oncolytic viruses are engineered or naturally occurring viruses that selectively infect and destroy cancer cells. These viruses not only cause direct lysis of cancer cells but also stimulate the immune system by releasing tumor antigens. Talimogene laherparepvec (T-VEC) is an example of an oncolytic virus used in the treatment of advanced melanoma [104]. Administered through direct intratumoral injection, T-VEC initiates both local and systemic immunologic responses. This process aims to induce tumor cell lysis, resulting in the release of tumor-derived antigens and the subsequent activation of tumor-specific effector T-cells. Currently, T-VEC is under evaluation in combination with other immune checkpoint inhibitors like ipilimumab and pembrolizumab, and there is intriguing confirmation of activity, even at the systemic level [105].

In addition to CAR-T-cell therapy, which involves genetically modifying T-cells with chimeric antigen receptors, other adoptive cell therapies are emerging. This includes T-cell receptor (TCR-T) therapy, where T-cells are engineered to express specific TCRs for cancer antigens [106]. As research in this domain advances, insights

into discovering and cloning personalized TCRs specific to tumor antigens are emerging, employing cutting-edge techniques [107]. Despite progress, enhancing the anti-tumor effectiveness of TCR-T immunotherapy faces challenges. These include safely elevating therapeutic TCR avidity, identifying shared tumor-specific antigens and TCRs in patient populations, applying personalized TCRs in cancer patients, and understanding the interactions or signals that regulate TCR expression and function optimally [108]. There is increasing recognition of the role of the gut microbiome in influencing responses to immunotherapy [109, 110]. Modulating the microbiome through prebiotics, probiotics, or faecal microbiota transplantation is being explored as a strategy to enhance the efficacy of immunotherapies [111, 112].

Artificial intelligence and machine learning are being employed to analyse vast amounts of patient data, predict responses to immunotherapy, and identify potential biomarkers. Interestingly, integrating artificial intelligence (AI) and machine learning algorithms (MLA) to analyse complex datasets, including genetic and imaging data, also holds promise for identifying novel predictive factors and optimizing treatments strategies for checkpoint inhibitors [113, 114]. Currently, many predictive models based on AI and MLA algorithms have emerged due to the development and popularization of digital images worldwide and each model or algorithm has its strength and weakness [114, 115]. Attempts are being made in researches for predicting mutations via such approaches to advance precision oncology [116]. These technologies contribute to the development of more personalized and effective treatment strategies. Moreover, researchers are exploring the power of combining different immunotherapies or combining immunotherapy with other treatment modalities such as chemotherapy or radiation therapy. Combinatorial approaches aim to address the complexity of the tumor microenvironment and overcome resistance mechanisms.

7. Resistance mechanism and overcoming challenges

Resistance mechanisms pose significant challenges in cancer treatment, particularly in the context of targeted therapies and immunotherapies [117, 118]. As cancer cells evolve and adapt, they can develop mechanisms to evade the effects of treatments, leading to reduced efficacy over time. In the case of targeted therapy resistance, cancer cells may develop genomic alterations and acquire mutations that alter the target of the therapy, rendering it ineffective. Other than this, cells can also activate alternative signalling pathways to bypass the targeted pathway. In immunotherapy resistance, tumor cells may downregulate or lose expression of the targeted antigens, evading recognition by the immune system. Immunosuppressive cells and molecules in the tumor microenvironment hinder the activity of immune cells. Resistance developed during chemotherapy is another nuisance to drug efflux and DNA repair mechanisms [119]. Cancer cells may develop pumps that actively remove chemotherapy drugs from the cell [120]. Further, enhanced DNA repair capabilities in cancer cells can counteract the damage caused by chemotherapy [121]. Heterogeneity is another form of resistance mechanism of cancer cells [122, 123]. Over time, selective pressure can lead to the dominance of resistant clones within the tumor [124].

Overcoming these challenges requires a comprehensive understanding of the underlying resistance mechanisms and the development of strategies to counteract them. For instance, using drug combinations that target multiple pathways can reduce the likelihood of resistance emerging. Studies have shown that combining different immunotherapies with other modalities can enhance the overall anti-cancer response [125]. Adaptive treatment strategies can also be employed in which treatment schedule adjustment, such as intermittent dosing, may help prevent or delay the onset of resistance [126, 127]. Recently drug cycling has gained recognition. It involves rotating between drugs which can limit the adaptation of cancer cells to a specific treatment [128]. Using personalized medicines is gaining popularity over resistance challenges. Identifying predictive biomarkers helps tailor treatments to the individual patient, increasing the likelihood of treatment success. Moreover, circulating tumor DNA can be monitored through liquid biopsies enabling real time assessment of tumor evolution and the emergence of resistance [129]. Overcoming immunotherapy resistance is a major challenge. Researchers have tried combining checkpoint inhibitors to target different pathways with the aim of enhancing T-cell activation. Strategies to alter the immune-suppressive microenvironment, such as depleting regulatory T-cells, are under investigation. In addition to these strategies, developing new drugs that target resistance mutations or alternative pathways can overcome acquired resistance. The therapeutic effect can be further enhanced by engineering antibodies to simultaneously target multiple antigens or cells.

8. Conclusion and future prospective

In the realm of cancer treatment, the challenges posed by resistance mechanisms underscore the complexity of the disease and the need for innovative therapeutic strategies. Targeted therapies, immunotherapies, and traditional treatments face the hurdle of cancer cells evolving and adapting to survive. While advancements have been made in understanding resistance mechanisms, successfully overcoming these challenges requires a multifaceted and personalized approach. Combination therapies that target multiple pathways simultaneously have emerged as a promising strategy to mitigate resistance. The integration of immunotherapies, such as checkpoint inhibitors and CAR-T-cell therapies, has ushered in a new era of cancer treatment, demonstrating unprecedented successes, especially in haematological malignancies. Personalized medicine, guided by predictive biomarkers and liquid biopsies, enables tailored interventions that consider the unique genetic and molecular profiles of individual patients. The future of cancer treatment lies in continued research and development, focusing on novel agents that can address emerging resistance mechanisms. Advancements in technologies like artificial intelligence and machine learning hold the potential to unravel complex biological interactions, identify new therapeutic targets, and predict treatment responses with greater accuracy.

Ongoing research holds promising prospects in cancer treatment through immunotherapy. Refining the implementation of precision medicine through the identification of additional biomarkers and the integration of omics data can enable more precise and effective targeting of cancer cells. Further optimizing immunotherapies, including the development of new CAR-T-cell constructs, exploring ad-

ditional immune checkpoints, and enhancing strategies to modulate the tumor microenvironment can contribute to improved outcomes. Further, the microbiome's impact on treatment response needs to be understood and harnessed for enhancing therapeutic efficacy and overcoming resistance. The development of next-generation targeted therapies that address resistance mutations, exploit synthetic lethal interactions, and target alternative pathways can expand the therapeutic options for patients. Patients-centric approaches need more focused research. It involves considering individual patient characteristics, preferences and quality of life in treatment decisions, ensuring a holistic and personalized cancer care experience. Ongoing innovation in clinical trial design can expedite the translation of scientific discoveries into clinically meaningful advancements.

In conclusion, the future of cancer treatment holds great promise, driven by a commitment to unraveling the intricacies of resistance, harnessing the power of the immune system, and advancing personalized therapeutic strategies. Through continuous research, collaboration, and the integration of cutting-edge technologies, immunotherapy aims to redefine the paradigm of cancer care, offering hope for improved outcomes and a brighter future for patients facing this challenging disease.

Acknowledgement
The author recognizes and appreciates the support of colleagues in the Department of Clinical Biochemistry, College of Medicine, King Khalid University.

Conflict of Intrest
There is no conflict of interest.

Consent for publications
After reading the completed manuscript, the author gave it the go-ahead to publish.

Ethics approval and consent to participate
The current study used neither humans nor animals.

Author contribution:
Ayyub A. Patel to design the concept and write the manuscript draft.

Funding
Non.

References

1. Tourang M, Fang L, Zhong Y, Suthar RC (2021) Association between Human Endogenous Retrovirus K gene expression and breast cancer. Cell Mol Biomed Rep 1:7-13. doi:Https://doi.org/10.55705/cmbr.2021.138810.1008.
2. Ali Salman R (2023) Prevalence of women breast cancer. Cell Mol Biomed Rep 3:185-196. doi:https://doi.org/10.55705/cmbr.2023.384467.1095.
3. Saravani K, Saravani S, Dadras F (2021) Investigating attitudinal barriers to breast cancer mammography screening among women in Zabol city. Cell Mol Biomed Rep 1:158-167. doi:https://doi.org/10.55705/cmbr.2023.411556.1167.
4. Arabestanino AR, Naghibi Irvani SS, Ai A, Dinarvand B (2024) Structural carcinoma overall process: a systematic review. Cell Mol Biomed Rep 4:88-99. doi:10.55705/cmbr.2023.410370.1164.
5. Alsaedy HK, Mirzaei AR, Alhashimi RAH (2022) Investigating the structure and function of Long Non-Coding RNA (LncRNA) and its role in cancer. Cell Mol Biomed Rep 2:245-253. doi:Https://doi.org/10.55705/cmbr.2022.360799.1062.
6. Kanwal N, Al Samarrai OR, Al-Zaidi HMH, Mirzaei AR, Heidari MJ (2023) Comprehensive analysis of microRNA (miRNA) in cancer cells. Cell Mol Biomed Rep 3:89-97. doi:Https://doi.org/10.55705/cmbr.2022.364591.1070.
7. Li X, Mohammadi MR (2023) Combined Diagnostic Efficacy of Red Blood Cell Distribution Width (RDW), Prealbumin (PA), Platelet-to-Lymphocyte Ratio (PLR), and Carcinoembryonic Antigen (CEA) as Biomarkers in the Diagnosis of Colorectal Cancer. Cell Mol Biomed Rep 3:98-106. doi:Https://doi.org/10.55705/cmbr.2023.374804.1088.
8. Alhashimi RAH, Mirzaei AR, Alsaedy HK (2021) Molecular and clinical analysis of genes involved in gastric cancer. Cell Mol Biomed Rep 1:138-146. doi:Https://doi.org/10.55705/cmbr.2021.355860.1056.
9. Alavi M, Rai M, Martinez F, Kahrizi D, Khan H, Rose Alencar de Menezes I, Douglas Melo Coutinho H, Costa JGM (2022) The efficiency of metal, metal oxide, and metalloid nanoparticles against cancer cells and bacterial pathogens: different mechanisms of action. Cell Mol Biomed Rep 2:10-21. doi:Https://doi.org/10.55705/cmbr.2022.147090.1023.
10. Fazeli-Nasab B, Bidarnamani F (2022) Medicinal Plants and Herbal Compounds: Cancer Prevention and Treatment. Plant Biotechnology Persa 4:25-35.
11. Fazeli-Nasab B, Sayyed RZ, Sobhanizadeh A (2021) In Silico Molecular Docking Analysis of α-Pinene: An Antioxidant and Anticancer Drug Obtained from Myrtus communis. Int J Cancer Manag 14:e89116. doi:https://doi.org/10.5812/ijcm.89116.
12. Borgers J S W, Heimovaara J H, Cardonick E, Dierickx D, Lambertini M, Haanen J B A G, Amant F (2021) Immunotherapy for cancer treatment during pregnancy. Lancet Oncol 22(12):e550-e561.doi: 10.1016/S1470-2045(21)00525-8.
13. Rusch T , Bayry J, Werner J, Shevchenko I , Bazhin AV (2018) Immunotherapy as an option for cancer treatment. Arch Immunol Ther Exp (Warsz);66(2):89-96.DOI: 10.1007/s00005-017-0491-5.
14. Trapani JA and Darcy PK, (2017) Immunotherapy of cancer. Aust Fam Physician, 46(4):194-199.
15. Zaidi N, Jaffee EM, (2019) Immunotherapy transforms cancer treatment. J Clin Invest, 2;129(1):46-47. doi: 10.1172/JCI126046.
16. Murata K, Tsukahara T, Torigoe T (2016), Cancer immunotherapy and immunological memory. Nihon Rinsho Meneki Gakkai Kaishi. 39(1):18-22.doi: 10.2177/jsci.39.18.
17. Kruger S , Ilmer M, Kobold S, Cadilha BL, Endres S, Ormanns S, Schuebbe G, Renz BW , D'Haese JG, Schloesser H, Heinemann V, Subklewe M, Boeck S, Werner J, Bergwelt-Baildon MV (2019), Advances in cancer immunotherapy 2019–latest trends. J Exp Clin Cancer Res.19;38(1):268. doi: 10.1186/s13046-019-1266-0.
18. Cann S A H, Netten J P V, Netten C V (2003) Dr William Coley and tumour regression: a place in history or in the future. Postgrad Med J. 79(938):672-80.
19. Schreiber H, Ward P L, Rowley D A, Stauss H J (1988) Unique tumor-specific antigens. Annu Rev Immunol.6:465-83.doi: 10.1146/annurev.iy.6.040188.002341.
20. Rivoltini L, Carrabba M, Huber V, Castelli C, Novellino L, Dalerba P, Mortarini R, Arancia G, Anichini A, Fais S, Parmiani G (2002) Immunity to cancer: attack and escape in T lymphocyte–tumor cell interaction. Immunol Rev.188:97-113.doi: 10.1034/j.1600-065x.2002.18809.x.
21. Diefenbach A, Raulet DH (2002) The innate immune response to

tumors and its role in the induction of T-cell immunity. Immunol Rev.188:9-21.doi: 10.1034/j.1600-065x.2002.18802.x.

22. AM, Allison JP, Wolchok JD (2012) Monoclonal antibodies in cancer therapy. Cancer Immun.12:14.Epub 2012 May 1.
23. Grillo-López AJ, White CA, Dallaire BK, Varns CL, Shen CD, Wei A, Leonard JE, McClure A, Weaver R, Cairelli S, Rosenberg J (2000) Rituximab the first monoclonal antibody approved for the treatment of lymphoma. Curr Pharm Biotechnol.1(1):1-9. doi: 10.2174/1389201003379059.
24. Celeste Bello C, Sotomayor EM (2007) Monoclonal antibodies for B-cell lymphomas: rituximab and beyond. Hematology Am Soc Hematol Educ Program. 233-42. doi: 10.1182/asheducation-2007.1.233.
25. Postow MA, Harding J, Wolchok JD (2012) Targeting immune checkpoints: releasing the restraints on anti-tumor immunity for patients with melanoma. Cancer J. 18(2):153-9.
26. Rosenberg S A, and Lotze M T (1986) Cancer immunotherapy using interleukin-2 and interleukin-2-activated lymphocytes. Annu Rev Immunol. 4:681-709. doi: 10.1146/annurev.iy.04.040186.003341.
27. Rosenberg S A, Lotze M T, Yang J C, Aebersold P M, Linehan W M, Seipp C A, White D E (1989) Experience with the use of high-dose interleukin-2 in the treatment of 652 cancer patients. Ann Surg. 210(4):474-84; discussion 484-5.doi: 10.1097/00000658-198910000-00008.
28. Hughes T, Klairmont M, Broucek J, Iodice G, Basu S, Kaufman HL (2015) The prognostic significance of stable disease following high-dose interleukin-2 (IL-2) treatment in patients with metastatic melanoma and renal cell carcinoma. 2 Cancer Immunol Immunother. 64(4):459-65.doi: 10.1007/s00262-014-1652-6.015. **64**: p. 459-465.
29. Krummel M F and Allison J P (1995) CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. J Exp Med. 1;182(2):459-65.doi: 10.1084/jem.182.2.459.
30. Okazaki T and Honjo T (2007) PD-1 and PD-1 ligands: from discovery to clinical application. Int Immunol. 19(7):813-24.doi: 10.1093/intimm/dxm057.
31. Weber, J. (2010) Immune checkpoint proteins: a new therapeutic paradigm for cancer-preclinical background: CTLA-4 and PD-1 blockade. in Seminars in oncology. Semin Oncol. 37(5):430-9. doi: 10.1053/j.seminoncol.2010.09.005.
32. Hodi FH, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, Akerley W, Eertwegh AJMVD, Lutzky J, Lorigan P, Vaubel JM, Linette GP, Hogg D, Ottensmeier CH, Lebbé C, Peschel C, Quirt I, Clark JI, Wolchok JD, Weber JS, Tian J, Yellin JM, Nichol GM, Hoos A, Urba WJ (2010) Improved survival with ipilimumab in patients with metastatic melanoma. 2010. **363**(8): p. 711-723. N Engl J Med. 19;363(8):711-23.doi: 10.1056/NEJMoa1003466.
33. Sadelain M (2017) Cd19 Car T cells. Cell. 14;171(7):1471.doi: 10.1016/j.cell.2017.12.002.
34. Ballas, Z.K. (2018) The 2018 Nobel Prize in Physiology or Medicine: an exemplar of bench to bedside in immunology. J Allergy Clin Immunol.142(6):1752-1753. doi: 10.1016/j.jaci.2018.10.021.
35. Imai Y, Hasegawa K, Matsushita H , Fujieda N, Sato S, Miyagi E, Kakimi K, Fujiwara K(2018) Expression of multiple immune checkpoint molecules on T cells in malignant ascites from epithelial ovarian carcinoma. Oncol Lett.15(5):6457-6468. doi: 10.3892/ol.2018.8101.
36. Torphy RJ, Schulick RD, Zhu Y (2017) Newly emerging immune checkpoints: promises for future cancer therapy. Int J Mol Sci. 6;18(12):2642.doi: 10.3390/ijms18122642.
37. Riva A, and Chokshi S (2018) Immune checkpoint receptors: homeostatic regulators of immunity. Hepatol Int. 12(3):223-236.doi: 10.1007/s12072-018-9867-9.
38. Nair VS, Elkord E (2018) Immune checkpoint inhibitors in cancer therapy: a focus on T-regulatory cells. Immunol Cell Biol. 96(1):21-33.doi: 10.1111/imcb.1003. Epub 2017 Nov 17.
39. Mahoney KM, Freeman GJ, McDermott DF (2015) The next immune-checkpoint inhibitors: PD-1/PD-L1 blockade in melanoma. Clin Ther.1;37(4):764-82.doi: 10.1016/j.clinthera.2015.02.018.
40. Ivashko IG, and Kolesar JM (2016) Pembrolizumab and nivolumab: PD-1 inhibitors for advanced melanoma. Am J Health Syst Pharm. 15;73(4):193-201.doi: 10.2146/ajhp140768.
41. Byeon S, Cho JH, Jung HA, Sun JM, Lee SH, Ahn JS, Park K , Ahn MJ (2020) PD-1 inhibitors for non-small cell lung cancer patients with special issues: real-world evidence. Cancer Med. 9(7):2352-2362.doi: 10.1002/cam4.2868. Epub 2020 Feb 6.
42. Lee HT, Lee JY, Lim H, Lee SH , Moon YJ, Pyo HJ, Ryu SE, Shin W, Heo YS (2017) Molecular mechanism of PD-1/PD-L1 blockade via anti-PD-L1 antibodies atezolizumab and durvalumab. Sci Rep.17;7(1):5532. doi: 10.1038/s41598-017-06002-8.
43. Nimmagadda, S.J.C., (2020) Quantifying PD-L1 expression to monitor immune checkpoint therapy: opportunities and challenges. Cancers (Basel). 29;12(11):3173. doi: 10.3390/cancers12113173.
44. Yi M, Jiao D, Xu H, Liu Q, Zhao W, Han X, Wu K (2018) Biomarkers for predicting efficacy of PD-1/PD-L1 inhibitors. Mol Cancer. 23;17(1):129.doi: 10.1186/s12943-018-0864-3.
45. Meng X, Huang Z, Teng F, Xing L, Yu J (2015) Predictive biomarkers in PD-1/PD-L1 checkpoint blockade immunotherapy. Cancer Treat Rev. 41(10):868-76. doi: 10.1016/j.ctrv.2015.11.001.
46. Van Coillie S, Wiernicki B, Xu J (2020) Molecular and cellular functions of CTLA-4. Adv Exp Med Biol. 1248:7-32. doi: 10.1007/978-981-15-3266-5_2.
47. Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, Linsley PS, Thompson CB, Riley JL (2005) CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol. 25(21):9543-53. doi: 10.1128/MCB.25.21.9543-9553.2005.
48. Sobhani N, Tardiel-Cyril DR, Davtyan A , Generali D, Roudi R, Li Y (2021) CTLA-4 in regulatory T cells for cancer immunotherapy. Cancers (Basel) 22;13(6):1440. doi: 10.3390/cancers13061440.
49. Rotte, A. (2019) *Combination of CTLA-4 and PD-1 blockers for treatment of cancer.* J Exp Clin Cancer Res. 13;38(1):255. doi: 10.1186/s13046-019-1259-z.
50. Vanderwalde A, Spetzler D, Xiao N, Gatalica Z, Marshall J (2018) Microsatellite instability status determined by next-generation sequencing and compared with PD-L1 and tumor mutational burden in 11,348 patients. Cancer Med. 7(3):746-756. doi: 10.1002/cam4.1372.
51. Huang RSP, Haberberger J, Severson E, Duncan DL, Hemmerich A, Edgerly C, Ferguson NL, Williams E, Elvin J, Vergilio JA, Killian JK, Lin DI, Tse J, Hiemenz M, Owens C, Danziger N, Hegde PS, Venstrom J, Alexander B, Ross JS, Ramkissoon S (2021) A pan-cancer analysis of PD-L1 immunohistochemistry and gene amplification, tumor mutation burden and microsatellite instability in 48,782 cases. Mod Pathol. 34(2):252-263. doi: 10.1038/s41379-020-00664-y.
52. Ruffo E, Wu RC, Bruno TC, Workman CJ, Vignali DAA (2019) Lymphocyte-activation gene 3 (LAG3): The next immune checkpoint receptor. Semin Immunol. 42:101305. doi: 10.1016/j.smim.2019.101305.
53. He Y, Rivard CJ, Rozeboom L, Yu H, Ellison K, Kowalewski A, Zhou C, Hirsch FR (2016) Lymphocyte-activation gene-3, an important immune checkpoint in cancer. Cancer Sci 107(9):1193-7.

doi: 10.1111/cas.12986.

54. SA, Rehman AU, Gabr MT (2023) Discovery of First-in-Class Small Molecule Inhibitors of Lymphocyte Activation Gene 3 (LAG-3). ACS Med Chem Lett. 11;14(5):629-635.doi: 10.1021/acsmedchemlett.3c00054.
55. Mohsenzadegan M, Bavandpour P, Nowroozi MR, Amini E, Kourosh-Arami M, Momeni SA, Bokaie S, SharifiL (2021) The potential of T cell immunoglobulin and mucin-domain containing-3 (Tim-3) in designing novel immunotherapy for bladder cancer. Endocr Metab Immune Disord Drug Targets. 21(12):2131-2146. doi: 10.2174/1871530321666210310142141.
56. Cazzato G, Cascardi E, Colagrande A, Lettini T, Filosa A, Arezzo F, Lupo C, Casatta N, Loizzi V, Pellegrini C, Fargnoli MC, Maiorano E, Cicco G, Tamma R, Ingravallo G (2023)T Cell Immunoglobulin and Mucin Domain 3 (TIM-3) in Cutaneous Melanoma: A Narrative Review. Cancers (Basel).10;15(6):1697. doi: 10.3390/cancers15061697.
57. AL , Cerdá S, Miguel MD (2022) New checkpoint inhibitors on the road: Targeting TIM-3 in solid tumors. Curr Oncol Rep. 24(5):651-658. doi: 10.1007/s11912-022-01218-y.
58. Muller S, Lai WV, Adusumilli PS, Desmeules P , Frosina D, Jungbluth A, Ni A, Eguchi T, Travis WD, Ladanyi M, Zauderer MG, Sauter JL (2020) V-domain Ig-containing suppressor of T-cell activation (VISTA), a potentially targetable immune checkpoint molecule, is highly expressed in epithelioid malignant pleural mesothelioma. Mod Pathol. 33(2):303-311. doi: 10.1038/s41379-019-0364-z. Epub 2019 Sep 19.
59. Zong L, Mo S, Sun Z, Lu Z, Yu S, Chen J, Xiang Y (2022) Analysis of the immune checkpoint V-domain Ig-containing suppressor of T-cell activation (VISTA) in endometrial cancer. Mod Pathol. 35(2):266-273.doi: 10.1038/s41379-021-00901-y. Epub 2021 Sep 7.
60. Ait Boujmia OK (2021) V-domain Ig suppressor of T cell activation (VISTA) inhibition is a new approach to cancer therapy: a Bibliometric study. Naunyn Schmiedebergs Arch Pharmacol. 394(6):1057-1065. doi: 10.1007/s00210-021-02068-4.
61. Wu C, Cao X, Zhang X (2021) VISTA inhibitors in cancer immunotherapy: a short perspective on recent progresses. RSC Med Chem. 6;12(10):1672-1679. doi: 10.1039/d1md00185j.
62. Harjunpää H, and Guillerey C (2020)TIGIT as an emerging immune checkpoint. Clin Exp Immunol. 200(2):108-119.doi: 10.1111/cei.13407.
63. Takei J, Asano T, Nanamiya R, Nakamura T, Yanaka M, Hosono H, Tanaka T, Sano M, Kaneko MK, Harada H, Kato Y (2021) Development of anti-human T cell immunoreceptor with Ig and ITIM domains (TIGIT) monoclonal antibodies for flow cytometry. Monoclon Antib Immunodiagn Immunother. 40(2):71-75. doi: 10.1089/mab.2021.0006.64.
64. Li X, Xu Z, Cui G, Yu L, Zhang X (2020) BTLA expression in stage I–III non–small-cell lung cancer and its correlation with PD-1/PD-L1 and clinical outcomes. Onco Targets Ther. 9:13:215-224. doi: 10.2147/OTT.S232234. eCollection 2020.
65. Chen YL, Lin HW, Chien CL, Lai YL, Sun WZ, Chen CA, Cheng WF (2019) BTLA blockade enhances Cancer therapy by inhibiting IL-6/IL-10-induced CD19high B lymphocytes. J Immunother Cancer. 21;7(1):313. doi: 10.1186/s40425-019-0744-4.
66. Tang TT, Cheng X, Truong B, Sun L, Yang XF, Wang H (2019) Molecular basis and therapeutic implications of CD40/CD40L immune checkpoint. Pharmacol Ther. 219:107709. doi: 10.1016/j.pharmthera.2020.107709.
67. Bojadzic D, Chen J, Alcazar O, Buchwald P (2018) Design, synthesis, and evaluation of novel immunomodulatory small molecules targeting the CD40–CD154 costimulatory protein-protein interaction. Molecules. 11;23(5):1153.doi: 10.3390/molecules23051153.
68. Deng J, Zhao S, Zhang X, Jia K, Wang H, Zhou C, He Y (2019) OX40 (CD134) and OX40 ligand, important immune checkpoints in cancer. Onco Targets Ther. 6:12:7347-7353. doi: 10.2147/OTT.S214211.
69. Aspeslagh S, Postel-Vinay S, Rusakiewicz S, Soria JC, Zitvogel L, Marabelle A (2016) Rationale for anti-OX40 cancer immunotherapy. Eur J Cancer. 52:50-66. doi: 10.1016/j.ejca.2015.08.021.
70. Chen X, Mo S, Zhang Y,Ma H, Lu Z, Yu S, Chen J (2022) Analysis of a novel immune checkpoint, Siglec-15, in pancreatic ductal adenocarcinoma. J Pathol Clin Res. 8(3):268-278. doi: 10.1002/cjp2.260.
71. He F [1] , Wang N, Li J, He L Yang Z, Lu J, Xiong G, Yu C, Wang S (2021) High affinity monoclonal antibody targeting Siglec-15 for cancer immunotherapy. J Clin Transl Res. 6;7(6):739-749.
72. Melero I, Sanmamed MF, Glez-Vaz J, Luri-Rey C, Wang J, Chen L (2023) CD137 (4-1BB)-Based cancer immunotherapy on its 25th anniversary. Cancer Discov. 1;13(3):552-569. doi: 10.1158/2159-8290.CD-22-1029.
73. Etxeberria I, Glez-Vaz J, Teijeira A , Melero I (2019) New emerging targets in cancer immunotherapy: CD137/4-1BB costimulatory axis. ESMO Open 4(Suppl 3):e000733. doi: 10.1136/esmoopen-2020-000733.
74. Claus C, Ferrara-Koller C, Klein C (2023) The emerging landscape of novel 4-1BB (CD137) agonistic drugs for cancer immunotherapy. MAbs 15(1):2167189. doi:10.1080/19420862.2023.2167189.
75. Shiravand Y, Khodadadi F, Kashani SMA, Hosseini-Fard SR, Hosseini S, Sadeghirad H, Ladwa R, O'Byrne K, Kulasinghe A (2022) Immune checkpoint inhibitors in cancer therapy. Curr Oncol. 24;29(5):3044-3060.doi: 10.3390/curroncol29050247.
76. Willsmore ZN, Coumbe BGT, Crescioli S, Reci S, Gupta A, Harris RJ, Chenoweth A, Chauhan J, Bax HJ, McCraw A, Cheung A, Osborn G, Hoffmann RM, Nakamura M, Laddach R, Geh JLC, MacKenzie-Ross A, Healy C, Tsoka S, Spicer JF, Josephs DH, Papa S, Lacy KE, Karagiannis SN (2021) Combined anti-PD-1 and anti-CTLA-4 checkpoint blockade: Treatment of melanoma and immune mechanisms of action. Eur J Immunol 51(3):544-556. doi: 10.1002/eji.202048747.
77. Puri S, Shafique M (2020) Combination checkpoint inhibitors for treatment of non-small-cell lung cancer: an update on dual anti-CTLA-4 and anti-PD-1/PD-L1 therapies. Drugs Context 13:9:2019-9-2. doi: 10.7573/dic.2019-9-2.
78. Daly RJ, Scott AM, Klein O, Ernst M (2022) Enhancing therapeutic anti-cancer responses by combining immune checkpoint and tyrosine kinase inhibition. Mol Cancer. 29;21(1):189.doi: 10.1186/s12943-022-01656-z.
79. Yan Y, Kumar AB, Finnes H, Markovic SN, Park S, Dronca RS, Dong H (2018) Combining immune checkpoint inhibitors with conventional cancer therapy. Front Immunol. 27:9:1739. doi: 10.3389/fimmu.2018.01739.
80. Pottier C, Fresnais M, Gilon M, Jérusalem G, Longuespée R, Sounni NE (2020) Tyrosine kinase inhibitors in cancer: breakthrough and challenges of targeted therapy. Cancers (Basel) 20;12(3):731.doi: 10.3390/cancers12030731.
81. Wu Z, Cui P , Tao H, Zhang S, Ma J, Liu Z, Wang J, Qian Y, Chen S, Huang Z, Zheng X, Huang D, Hu Y (2021) The synergistic effect of PARP inhibitors and immune checkpoint inhibitors. Clin Med Insights Oncol. 25:15:1179554921996288. doi: 10.1177/1179554921996288.
82. Stewart RA, Pilié PG, Yap TA (2018) Development of PARP and immune-checkpoint inhibitor combinations. Cancer Res. 15;78(24):6717-6725. doi: 10.1158/0008-5472.CAN-18-2652.
83. Torres ETR, Emens LA (2022) Emerging combination immu-

notherapy strategies for breast cancer: dual immune checkpoint modulation, antibody–drug conjugates and bispecific antibodies. Breast Cancer Res Treat. 191(2):291-302. doi: 10.1007/s10549-021-06423-0.

84. Klein C, Schaefer W, Regula JT, Dumontet C, Brinkmann U, Bacac M , Umaña P (2019) Engineering therapeutic bispecific antibodies using CrossMab technology. Methods. 1:154:21-31. doi: 10.1016/j.ymeth.2018.11.008.
85. Huang S, Duijnhoven SMJV, Sijts AJAM, Elsas AV (2020) Bispecific antibodies targeting dual tumor-associated antigens in cancer therapy. J Cancer Res Clin Oncol. 146(12):3111-3122.
86. Warwas KM, Meyer M, Gonçalves M, Moldenhauer G, Bulbuc N, Knabe S, Luckner-Minden C, Ziegelmeier C, Heussel CP, Zörnig I, Jäger D, Momburg F (2021) Co-Stimulatory bispecific antibodies induce enhanced T cell activation and tumor cell killing in breast cancer models. Front Immunol. 16:12:719116. doi: 10.3389/fimmu.2021.719116.
87. Goebeler M-E, Bargou RC (2020) T cell-engaging therapies-BiTEs and beyond. Nat Rev Clin Oncol. 17(7):418-434. doi: 10.1038/s41571-020-0347-5.
88. Su T, Zhang Y, Valerie K, Wang X-Y, Lin S, Zhu G (2019) STING activation in cancer immunotherapy. Theranostics. 15;9(25):7759-7771.doi: 10.7150/thno.37574. eCollection 2019.
89. Gong y, Chang C, Liu X, He Y, Wu Y, Wang S, Zhang C (2020) Stimulator of interferon genes signaling pathway and its role in anti-tumor immune therapy. Curr Pharm Des 26(26):3085-3095. doi: 10.2174/1381612826666200610183048.
90. Hu Y, Manasrah BK, McGregor SM, Lera RF, Norman RX , Tucker JB, Scribano CM, Yan RE, Humayun M, Wisinski KB, Tevaarwerk AJ, O'Regan RM, Wilke LG, Weaver BA, Beebe DJ, Jin N, Burkard ME (2021) Paclitaxel induces micronucleation and activates pro-inflammatory cGAS–STING signaling in triple-negative breast cancer. Mol Cancer Ther. 20(12):2553-2567.doi: 10.1158/1535-7163.MCT-21-0195.91.
91. Mougel A, Terme M, Tanchot C (2019) Therapeutic cancer vaccine and combinations with antiangiogenic therapies and immune checkpoint blockade. Front Immunol. 14:10:467. doi: 10.3389/fimmu.2019.00467
92. Liao J-Y, Zhang S (2021) Safety and efficacy of personalized cancer vaccines in combination with immune checkpoint inhibitors in cancer treatment. Front Oncol. 28:11:663264. doi: 10.3389/fonc.2021.663264.
93. Gulijk MV, Dammeijer F, Aerts JGJV, Vroman H (2018) Combination strategies to optimize efficacy of dendritic cell-based immunotherapy. Front Immunol. 5:9:2759. doi: 10.3389/fimmu.2018.02759.
94. Sadeghzadeh M, Bornehdeli S, Mohahammadrezakhani H, Abolghasemi M, Poursaei E , Asadi M, Zafari V, Aghebati-Maleki L, Shanehbandi D (2020) Dendritic cell therapy in cancer treatment; the state-of-the-art. Life Sci. 1:254:117580.doi: 10.1016/j.lfs.2020.117580.
95. Ghorbaninezhad F, Asadzadeh Z, Masoumi J, Mokhtarzadeh A, Kazemi T, Aghebati-Maleki L, Shotorbani S, Shadbad MA, Baghbanzadeh A, Hemmat N, Bakhshivand M, Baradaran B (2022) Dendritic cell-based cancer immunotherapy in the era of immune checkpoint inhibitors: From bench to bedside. Life Sci. 15:297:120466. doi: 10.1016/j.lfs.2022.120466.
96. Ruella M, Kenderian SS (2017) Next-generation chimeric antigen receptor T-cell therapy: going off the shelf. BioDrugs. 31(6):473-481.doi: 10.1007/s40259-017-0247-0.
97. Jayaraman J, Mellody MP, Hou AJ, Desai RP, Fung AW, Pham AHT, Chen YY, Zhao W (2020) CAR-T design: Elements and their synergistic function. EBioMedicine. 58:102931. doi: 10.1016/j.ebiom.2020.102931.
98. Yu H, Pan J, Guo Z, Yang C, Mao L (2019) CART cell therapy for prostate cancer: status and promise. Onco Targets Ther. 3:12:391-395.doi: 10.2147/OTT.S185556.
99. García-Poutón N, Peyrony O, Chumbita M, Aiello F, Monzo P, Gallardo-Pizarro A, Garcia-Vidal C (2023) Post-CART-T Cell Infection: Etiology, pathogenesis, and therapeutic approaches. Rev Esp Quimioter. 36 Suppl 1:52-53. doi: 10.37201/req/s01.12.2023.
100. Ma W, Pham W, Li T (2022) Cancer neoantigens as potential targets for immunotherapy. Clin Exp Metastasis. 39(1):51-60. doi: 10.1007/s10585-021-10091-1.
101. Blass E, Ott PO (2021) Advances in the development of personalized neoantigen-based therapeutic cancer vaccines. Nat Rev Clin Oncol. 18(4):215-229. doi: 10.1038/s41571-020-00460-2.
102. Liu Z, Lv J, Dang Q, Liu L, Weng S, Wang L, Zhou Z, Kong Y, Li H, Han Y, Han X (2022) Engineering neoantigen vaccines to improve cancer personalized immunotherapy. Int J Biol Sci. 1;18(15):5607-5623.doi: 10.7150/ijbs.76281.
103. Buonaguro L, Tagliamonte M (2020) Tagliamonte, Selecting target antigens for cancer vaccine development. Vaccines (Basel). 17;8(4):615.doi: 10.3390/vaccines8040615.
104. Larocca CA, LeBoeuf NR, Silk AW, Kaufman HL (2020) An update on the role of talimogene laherparepvec (T-VEC) in the treatment of melanoma: best practices and future directions. Am J Clin Dermatol. 21(6):821-832.doi: 10.1007/s40257-020-00554-8.
105. Ferrucci PF, Pala L, Conforti F, Cocorocchio E (2021) Talimogene laherparepvec (T-VEC): an intralesional cancer immunotherapy for advanced melanoma. Cancers (Basel). 18;13(6):1383. doi: 10.3390/cancers13061383.
106. Greenbaum U, Dumbrava EI, Biter AB, Haymaker CL, Hong DS (2021) Engineered T-cell receptor T cells for cancer immunotherapy. Cancer Immunol Res. 9(11):1252-1261. doi: 10.1158/2326-6066.CIR-21-0269.
107. Sun Y, Li F, Sonnemann H, Jackson KR, Talukder AH, Katailiha AS, Lizee G (2021) Evolution of CD8+ T cell receptor (TCR) engineered therapies for the treatment of cancer. Cells. 10;10(9):2379. doi: 10.3390/cells10092379.
108. Shafer P, Kelly LM, Hoyos V (2022) Cancer therapy with TCR-engineered T cells: Current strategies, challenges, and prospects. Front Immunol. 3:13:835762. doi: 10.3389/fimmu.2022.835762.
109. Zhou C-B, Zhou Y-L, Fang J-Y (2021) Gut microbiota in cancer immune response and immunotherapy. Trends Cancer. 7(7):647-660. doi: 10.1016/j.trecan.2021.01.010.
110. Lu Y, Yuan X, Wang M, He Z, Li H, Wang J, Li Q (2022) Gut microbiota influence immunotherapy responses: Mechanisms and therapeutic strategies. J Hematol Oncol. 29;15(1):47. doi: 10.1186/s13045-022-01273-9.
111. Baldi S, Mundula T, Nannini G, Amedei A (2021) Microbiota shaping—The effects of probiotics, prebiotics, and fecal microbiota transplant on cognitive functions: A systematic review. World J Gastroenterol. 21;27(39):6715-6732. doi: 10.3748/wjg.v27.i39.6715
112. Takáčová M, Bomba A, Tóthová C, Michaľová A, Turňa H (2022) Any future for faecal microbiota transplantation as a novel strategy for gut microbiota modulation in human and veterinary medicine? Life (Basel). 12;12(5):723. doi: 10.3390/life12050723.
113. Wu J, Mayer AT, Li R (2022) Integrated imaging and molecular analysis to decipher tumor microenvironment in the era of immunotherapy. in Seminars in cancer biology. Semin Cancer Biol. 84:310-328. doi: 10.1016/j.semcancer.2020.12.005.
114. Jin W, Luo Q (2022) When artificial intelligence meets PD-1/PD-L1 inhibitors: population screening, response prediction and efficacy evaluation. Comput Biol Med. 145:105499. doi: 10.1016/j.compbiomed.2022.105499.
115. Gao Q, Yang L, Lu M, Jin R, Ye H, Ma T The artificial intelligence

and machine learning in lung cancer immunotherapy. J Hematol Oncol. 24;16(1):55.doi: 10.1186/s13045-023-01456-y.

116. Shao J, Ma J, Zhang Q, Li W, Wang C (2023) Predicting gene mutation status via artificial intelligence technologies based on multimodal data integration to advance precision oncology. in Seminars in Cancer Biology. Semin Cancer Biol. 91:1-15. doi: 10.1016/j.semcancer.2023.02.006.
117. Bai R, Chen N, Li L, Du N, Bai L, Lv Z , Tian H, Cui J (2020) Mechanisms of cancer resistance to immunotherapy. Front Oncol. 6:10:1290. doi: 10.3389/fonc.2020.01290.
118. Aldea M, Andre F, Marabelle A, Dogan S, Barlesi F, Soria J-C (2021) Overcoming resistance to tumor-targeted and immune-targeted therapies. Cancer Discov. 11(4):874-899. doi: 10.1158/2159-8290.CD-20-1638.
119. Raguz S, Yagüe E (2008) Resistance to chemotherapy: new treatments and novel insights into an old problem. Br J Cancer. 5;99(3):387-91.doi: 10.1038/sj.bjc.6604510.
120. Bukowski K, Kciuk M, Kontek R (2020) Mechanisms of multidrug resistance in cancer chemotherapy. Int J Mol Sci. 2;21(9):3233. doi: 10.3390/ijms21093233.
121. Rocha CRR, Silva MM, Quinet A, Cabral-Neto JB, Menck CFM (2018) DNA repair pathways and cisplatin resistance: an intimate relationship. Clinics (Sao Paulo). 6;73(suppl 1):e478s. doi: 10.6061/clinics/2018/e478s.
122. Dagogo-Jack I, Shaw AT (2018) Tumour heterogeneity and resistance to cancer therapies. Nat Rev Clin Oncol. 15(2):81-94. doi: 10.1038/nrclinonc.2017.166.
123. Lim Z-F, Ma PC (2019) Emerging insights of tumor heterogeneity and drug resistance mechanisms in lung cancer targeted therapy. J Hematol Oncol. 9;12(1):134. doi: 10.1186/s13045-019-0818-2.
124. Crucitta S, Cucchiara F, Mathijssen R, Mateo J, Jager A, Joosse A, Passaro A, Attili I, Petrini I, Schaik RV, Danesi R, Re MD (2022) Treatment-driven tumour heterogeneity and drug resistance: Lessons from solid tumours. Cancer Treat Rev. 104:102340. doi: 10.1016/j.ctrv.2022.102340.
125. Zhu S, Zhang T, Zheng L, Liu H, Song W, Liu D, Li Z, Pan C-X (2021) Combination strategies to maximize the benefits of cancer immunotherapy. J Hematol Oncol. 27;14(1):156. doi: 10.1186/s13045-021-01164-5.
126. Kim E, Brown JS, Eroglu Z, Anderson ARA (2021) Adaptive therapy for metastatic melanoma: predictions from patient calibrated mathematical models. Cancers (Basel). 16;13(4):823. doi: 10.3390/cancers13040823.
127. West J, You L, Zhang J, Gatenby RA, Brown JS, Newton PK, Anderson ARA (2020) Towards multidrug adaptive therapy. Cancer Res. 1;80(7):1578-1589. doi: 10.1158/0008-5472.CAN-19-2669.
128. Lindström HJG, and Friedman R (2022) Rotating between ponatinib and imatinib temporarily increases the efficacy of imatinib as shown in a chronic myeloid leukaemia model. Sci Rep. 25;12(1):5164. doi: 10.1038/s41598-022-09048-5.
129. Bratman SV, Yang SYC, Iafolla MAJ, Liu Z, Hansen AR, Bedard PL, Lheureux S, Spreafico A, Razak AA, Shchegrova S, Louie M, Billings P, Zimmermann B, Sethi H, Aleshin A, Torti D, Marsh K, Eagles J, Cirlan I, Hanna Y, Clouthier DL, Lien SC, Ohashi PS, Xu W, Siu LL, Pugh TJ (2020) Personalized circulating tumor DNA analysis as a predictive biomarker in solid tumor patients treated with pembrolizumab. Nat Cancer. 1(9):873-881. doi: 10.1038/s43018-020-0096-5.