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Review Article

Pharmacological targeting of immune checkpoints: Advances and challenges in cancer immunotherapy

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Abstract

Utilizing the body's immune system to precisely target and eradicate cancerous cells, cancer immunotherapy has become a ground-breaking method of treating the disease. Pharmacologically targeting immunological checkpoints—regulatory pathways that cancer cells use to elude immune monitoring and destruction—is a key tactic in this treatment approach. With an emphasis on their methods of action, clinical uses, and the difficulties they faced throughout research and clinical deployment, this article examines current developments in immune checkpoint inhibitors (ICIs). CTLA-4, PD-1, and PD-L1 are examples of immune checkpoint proteins that are essential for regulating immune responses in the tumor microenvironment. By boosting anti-tumor immunity, blocking these check points has shown significant therapeutic benefit, especially in malignancies like melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma. Notwithstanding the encouraging results, a number of issues still exist, such as resistance development, immune-related side effects, and restricted effectiveness in specific tumor types. Combination treatments, new biomarkers for patient classification, and methods to get around resistance mechanisms are all being investigated in ongoing research. The present state of clinical studies, possible pharmacological combinations to maximize therapeutic success, and the developing knowledge of immune checkpoint pharmacology are all reviewed in this study. Integrating immune checkpoint inhibitors with other therapeutic modalities, like targeted medicines and chemotherapy, is one intriguing way to get around present restrictions and enhance clinical results.

Keywords: Cancer immunotherapy, Immune checkpoints, PD-1/PD-L1, CTLA-4 inhibitors, Combination therapies.

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1. Introduction

Because of its exceptional capacity to elude the body's immune monitoring, cancer has long been considered one of the most pernicious and difficult diseases to cure. Cancer treatments have historically concentrated on direct methods that attack the tumour directly, such as radiation, chemotherapy, and surgery. Nevertheless, these therapies frequently have serious adverse effects and little long-term efficacy, particularly when it comes to recurrent and metastatic tumours. Immunotherapy, which uses the body's natural defences to identify and eliminate cancer cells, has become a viable alternative as our knowledge of the immune system and its connection to cancer cells has grown. Immunocheckpoint inhibitors (ICIs) stand out as a ground-breaking strategy among the novel medicines that have emerged as a result of this paradigm shift in cancer treatment.[1-2]

The foundation of cancer immunotherapy is the notion that cancerous cells can be specifically targeted and destroyed by mobilising the immune system. In an ideal world, immunological surveillance—the process by which immune cells, particularly T cells, identify and target cancer cells—occurs. But in order to prevent immune system destruction, cancer cells have evolved complex defences against immune detection. The activation of immunological checkpoints, which are regulatory pathways that serve as

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restraints on immune responses, is one of the most important of these processes.[3-4] When activated, these checkpoints stop the immune system from overreacting and harming healthy tissues. Tumours have figured out how to take advantage of these checkpoints to shield themselves from immune attack, which enables them to flourish in an immunologically hostile environment, even though this mechanism is crucial for preventing autoimmune disorders.[5-6]

Immune checkpoints are essential for preserving immunological tolerance and averting autoimmunity, but tumours have developed ways to circumvent immune monitoring by taking over these pathways. Important immune checkpoint proteins have been found to be crucial regulators of tumour immune evasion, including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and its ligand PD-L1. When the T cell surface receptor PD-1 binds to the tumour cell-expressed PD-L1, it delivers an inhibitory signal that lessens the T cell's capacity to attack the tumour. Likewise, another checkpoint receptor that inhibits T cell activation in the early phases of immunological responses is CTLA-4. Important elements of the immunological checkpoints that tumours use to evade immune destruction are CTLA-4 and PD-1/PD-L1.[7]

Immuno checkpoint inhibitors (ICIs) were developed as a result of the identification of immune checkpoint pathways, which created new treatment options for cancer. By preventing immune checkpoint proteins and their ligands from interacting, these biologic drugs effectively deactivate the immune system and allow T cells to target and eliminate tumour cells. Monoclonal antibodies that target PD-1 (e.g., pembrolizumab, nivolumab), PD-L1 (e.g., atezolizumab, durvalumab), and CTLA-4 (e.g., ipilimumab) are the most well-known immune checkpoint inhibitors. These ICIs have shown impressive clinical performance, especially in malignancies such as head and neck squamous cell carcinoma, renal cell carcinoma, non-small cell lung cancer (NSCLC), and melanoma. Patients have frequently demonstrated long-lasting improvements, with some going on to experience permanent remission.[8-9]

The introduction of ICIs has transformed cancer treatment and given people with illnesses that were thought to be incurable a new lease on life. But the success of ICIs has also brought attention to a number of issues. The effectiveness of ICIs varies greatly among patients, with a considerable proportion of patients either not responding or gradually developing resistance, despite the encouraging outcomes in some tumour types. Additionally, there are dangers associated with immune checkpoint inhibition, and immune-related adverse events (irAEs) are becoming a major worry. These negative consequences arise when the immune system, which has been awakened, targets healthy tissues, causing inflammation and possible harm to organs like the liver, lungs, intestines, and skin.[10-12] Understanding the underlying mechanisms governing the effectiveness and limitations of immune checkpoint inhibitors is becoming more and more important as they continue to transform the landscape of cancer treatment. This entails figuring out the intricate biology of immune checkpoints, finding predictive indicators to help choose patients, and creating plans to get beyond resistance mechanisms. To improve therapeutic results and increase the range of tumours that can benefit from immunotherapy, combination therapies—which combine ICIs with additional treatment modalities like chemotherapy, targeted treatments, or radiation—are also being intensively investigated.[13-14]

With an emphasis on the most recent developments in immune checkpoint inhibition, the obstacles that still prevent it from reaching its full potential, and the prospective avenues for future research and development, this study attempts to investigate the pharmacological targeting of immune checkpoints in cancer therapy. We can better comprehend the justification for their pharmacological targeting and the increasing significance of these inhibitors in contemporary cancer treatment by looking at the biological mechanisms underlying immunological checkpoint-mediated immune evasion. In the end, knowing the advantages and disadvantages of ICIs will help us better understand how cancer immunotherapy will develop in the future and how it can change to meet the unmet needs of patients around the globe.[15-16]

2. Immune Checkpoints and Their Role in Cancer Immunology

The immune system's complex architecture protects the body from infections, cancers, and aberrant cellular activity. T lymphocytes, which identify and target aberrant cells, including cancer cells, are essential to this defence mechanism. To ensure their survival and growth, cancer cells have evolved complex strategies to elude immune surveillance. The manipulation of immunological checkpoints, which are molecules that control the immune response and prevent excessive activation that could result in autoimmunity, is one of the main ways tumours avoid the immune system. Tumours use immunological checkpoints to decrease immune activity and evade immune cell identification, despite the fact that these pathways are essential for immune homeostasis and tolerance.[17] The function of immunological checkpoints in cancer immunology will be discussed in this section, with particular attention paid to the main immune checkpoint pathways—PD-1/PD-L1, CTLA-4, and other newly discovered immune checkpoints including TIM-3, LAG-3, and TIGIT—that have been found to be important contributors to immune evasion. We may learn more about how tumour cells influence the immune system and why focussing on these checkpoints has become a key component of contemporary cancer immunotherapy by comprehending the mechanisms by which these checkpoints function.[18]

2.1 Overview of the immune system's role in cancer defense

Through a process called immunological surveillance, the immune system is essential in locating and destroying cancer cells. T cells are essential to this defence, especially cytotoxic T lymphocytes (CTLs). An immunological response is triggered when a malignant cell releases aberrant proteins that the immune system may identify as "non-self." T cells are then stimulated to eliminate the cancerous cells. Nonetheless, tumours frequently create defences against immune detection or immune activation suppression, which promotes tumour growth and spread.

Increasing immunological checkpoints, which operate as biochemical restraints on T cell activation, is one of the most popular ways tumours circumvent the immune system. Tumours stop immune cells from fully activating and fighting the malignant tissue by interfering with these routes. The immune system's capacity to identify and eradicate cancer cells has been revitalised by the development of immune checkpoint inhibitors (ICIs) in recent years, which block these pathways. The effectiveness of these treatments has transformed the way cancer is treated, but more progress in cancer immunotherapy will require a better understanding of the underlying immune checkpoint processes.[19-21]

One of the most extensively researched immune checkpoint pathways, the PD-1/PD-L1 pathway is essential for controlling the immune system's reaction to cancer. T cells, especially active or tired T cells, express the receptor known as programmed cell death protein 1 (PD-1). The T cell receives an inhibitory signal from PD-1 when it attaches to its ligand, PD-L1, which is produced on tumour cells and other immune cells in the tumour microenvironment (TME). This effectively reduces the immunological response by inhibiting T cell activation and proliferation [22-23] In order to take advantage of this inhibitory mechanism and stop immune cells from attacking the tumour, cancer cells commonly upregulate PD-L1 expression. The tumour can grow unnoticed and withstand immune-mediated elimination thanks to this immune evasion mechanism. Crucially, the PD-1/PD-L1 axis affects not just T cell suppression but also the activity of other immune cells, such as macrophages and dendritic cells, which helps to create a more extensive immune suppressive environment. Immune checkpoint drugs that block PD-1, including pembrolizumab (Keytruda) and nivolumab (Opdivo), have shown great clinical success by reviving T cell activation and improving their ability to target and eliminate cancer cells.[24]

2.2. PD-1/PD-L1 pathway: Mechanism of action and roles in immune evasion

Another immunological checkpoint that controls T cell activation, especially in the early phases of immune responses, is cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). T cells express CTLA-4, which binds to antigen-presenting cells' (APCs') CD80 and CD86 to function as a negative regulator of T cell activation. T cell activation and function are effectively suppressed by this interaction, which stops T cells from being co-stimulated. CTLA-4 overexpression in tumours impairs T cell initial activation, which hinders the immune system's ability to mount a successful anti-tumor response.[25-26]

2.3 CTLA-4 Pathway: Limiting t-cell activation and its relevance in tumors

T cells in the tumour microenvironment frequently express more CTLA-4 in cancer, which reduces the immune response against tumour cells. Because of this, CTLA-4 is an important immunotherapy target. The first immune checkpoint inhibitor to show clinical effectiveness in the treatment of cancer was the anti-CTLA-4 monoclonal antibody Ipilimumab (Yervoy). Ipilimumab increases T cell activation and fosters a stronger immune response against tumours by inhibiting CTLA-4, particularly in malignancies like melanoma.[27]

2.4 Other immune checkpoints: TIM-3, LAG-3, TIGIT, and their potential therapeutic targeting

Several other immune checkpoint receptors have been found to be important regulators of immune evasion in cancer, in addition to PD-1, PD-L1, and CTLA-4. These consist of:

1. TIM-3 (T-cell immunoglobulin and mucin-domain containing-3): T cells and macrophages are among the immune cells that express TIM-3. It contributes significantly to T cell fatigue, especially in tumours and chronic infections. Exhausted T lymphocytes in the tumour microenvironment exhibit TIM-3 expression, which inhibits their activation and aids in immune suppression. In preclinical and clinical trials, targeting TIM-3 with certain antibodies has demonstrated promise as a means of enhancing cancer immunity and restoring T cell function.[28-29]

2. LAG-3 (Lymphocyte-activation gene 3):.Another inhibitory receptor on T cells and regulatory T cells (Tregs) is LAG-3 (Lymphocyte-activation gene 3). It suppresses T cell activation and fosters immunological tolerance in concert with PD-1. Numerous malignancies have elevated LAG-3, which is linked to a bad prognosis. LAG-3-targeting clinical trials have shown promising outcomes when used either alone or in conjunction with other immune checkpoint inhibitors.[30-31]

3. TIGIT (T cell immunoreceptor with immunoglobulin and ITIM domains): TIGIT, or T cell immunoreceptor with immunoglobulin and ITIM domains, is a receptor that is expressed on T cells and natural killer (NK) cells. It reduces immune cell function when it interacts with its ligand, the poliovirus receptor (PVR). TIGIT expression on T cells aids in immune suppression inside the tumour microenvironment. Clinical trials

are investigating novel treatments that target TIGIT as a possible means of boosting anti-tumor immunity.[32]

2.5. Tumor microenvironment and immune suppression mechanisms

By establishing a suppressive environment that prevents immune cell activation, the tumour microenvironment (TME) plays a crucial part in immune evasion. Immunosuppressive cytokines (such as TGF-β and IL-10), immunological checkpoint proteins, and regulatory cells like Tregs and myeloid-derived suppressor cells (MDSCs) are all present in greater amounts, and they all aid in immune suppression. Effective immune responses are hampered by the expression of immunological checkpoints in the TME, such as PD-L1 on tumour cells and other immune cells. This immune-suppressive environment promotes the growth of cancer by assisting tumours in evading immune surveillance. Hypoxia and the accumulation of metabolic waste products are two physical characteristics of the TME that further impede immune cell function and make it more difficult for immune cells to target and kill tumour cells. An intriguing field of study aimed at overcoming these obstacles is the combination of immune checkpoint inhibitors with treatments that alter the TME, such as immune modulators, targeted therapies, or chemotherapy.[33-34] The overview of Immune Checkpoint Inhibitors (ICIs) approved for clinical use are enlisted in (**Table 1**).

Table 1: Overview of immune checkpoint inhibitors (ICIs) approved for clinical use [33-34]

Immune Checkpoint Inhibitor	Targeted Immune Checkpoint	Approved Cancer Types	Mechanism of Action
Pembrolizumab (Keytruda)	PD-1	Melanoma, NSCLC, head and neck cancer, urothelial carcinoma, Hodgkin lymphoma, others	Blocks PD-1 receptor on T cells, preventing its interaction with PD-L1 and PD-L2 on tumor cells, thereby activating T cells to attack cancer cells.
Nivolumab (Opdivo)	PD-1	Melanoma, NSCLC, renal cell carcinoma, head and neck cancer, others	Similar to pembrolizumab, blocks PD-1, enhancing the immune system's ability to recognize and destroy tumor cells.
Atezolizumab (Tecentriq)	PD-L1	NSCLC, urothelial carcinoma, triple-negative breast cancer, others	Binds to PD-L1 on tumor cells and immune cells, preventing its interaction with PD-1 and reactivating the immune response.
Durvalumab (Imfinzi)	PD-L1	NSCLC, urothelial carcinoma	Similar to atezolizumab, blocks PD-L1 and enhances T-cell-mediated immune response against tumors.
Ipilimumab (Yervoy)	CTLA-4	Melanoma, NSCLC, renal cell carcinoma, others	Binds to CTLA-4 on T cells, preventing its interaction with CD80/CD86 on antigen-presenting cells, thus promoting T-cell activation and tumor destruction.
Tremelimumab (Imjudo)	CTLA-4	NSCLC, mesothelioma, others	Inhibits CTLA-4, enhancing the activity of T cells and promoting immune responses against cancer.
Cemiplimab (Libtayo)	PD-1	Cutaneous squamous cell carcinoma, NSCLC	Blocks PD-1, preventing immune suppression by tumor cells and stimulating an immune response to fight the cancer.
Carboplatin + Atezolizumab	PD-L1 and other immune pathways	NSCLC, small cell lung cancer	Combination therapy that combines platinum-based chemotherapy with immune checkpoint inhibition to enhance both the cytotoxic and immune-mediated response.
Nivolumab + Ipilimumab	PD-1 and CTLA-4	Melanoma, NSCLC, renal cell carcinoma	Combination of PD-1 and CTLA-4 inhibitors, allowing dual blockade of immune checkpoints for more robust T-cell activation and tumor destruction.

3. Advances in Immune Checkpoint Inhibition: Development of Immunotherapies

Immunocheckpoint inhibitors (ICIs) have transformed the treatment of cancer and given patients with previously incurable tumours fresh hope. Regulatory molecules known as immunological checkpoints stop the immune system from targeting healthy cells. Cancer cells, however, take advantage of these routes to evade immune monitoring. By blocking these pathways, immune checkpoint inhibitors—which specifically target PD-1/PD-L1 and CTLA-4—have made it possible to reactivate the immune system to target and destroy cancer cells. The development and clinical use of these inhibitors will be covered in this section, with particular attention paid to the main monoclonal antibodies that have been authorised by regulatory organisations including the FDA and EMA.[8-10]

3.1 Monoclonal Antibodies as Immune Checkpoint Inhibitors

Because monoclonal antibodies may selectively target immune checkpoint molecules and neutralise their inhibitory signals, they have emerged as a key component of cancer immunotherapy. Among the checkpoint inhibitors that are most frequently utilised are:

1. Pembrolizumab (Keytruda) and Nivolumab (Opdivo): Monoclonal antibodies called pembrolizumab (Keytruda) and nivolumab (Opdivo) target the PD-1 receptor, a crucial immunological checkpoint on T cells. PD-1 suppresses T-cell activation and function when it binds to its ligands, PD-L1 or PD-L2. This connection is blocked by pembrolizumab and nivolumab, which keeps T cells active and enables them to attack cancer cells. Melanoma, non-small cell lung cancer (NSCLC), and head and neck malignancies are among the tumours for which these inhibitors have demonstrated notable therapeutic effect.

2. Atezolizumab (Tecentriq) and Durvalumab (Imfinzi): The PD-L1 inhibitors durvalumab (Imfinzi) and atezolizumab (Tecentriq) disrupt the inhibitory signal that inhibits T-cell activation by preventing PD-L1 from binding to PD-1. The usage of durvalumab plus atezolizumab has been authorised for the treatment of triple-negative breast cancer, urothelial carcinoma, and non-small cell lung cancer. These treatments improve immune identification and tumour destruction by blocking PD-L1 on immune and tumour cells.

3. Ipilimumab (Yervoy): This medication targets CTLA-4, another important immune checkpoint receptor, in contrast to PD-1/PD-L1 inhibitors. By vying with the co-stimulatory receptor CD28 for binding to CD80/CD86 on antigen-presenting cells, CTLA-4 prevents T-cell activation. Ipilimumab increases anti-tumor immunity and strengthens T-cell activation by inhibiting CTLA-4. For synergistic effects, it is frequently used in conjunction with PD-1 inhibitors and has shown especially good results in treating melanoma.[10-35]

3.2 Mechanisms of action

Blocking the immunological inhibitory signals that cancer cells utilise to avoid immune monitoring is the therapeutic advantage of immune checkpoint inhibitors. These inhibitors keep T cells from receiving the "off" signal when they connect with tumour cells by blocking PD-1/PD-L1 interactions. This keeps T cells activated and enables them to continue attacking cancer cells. Likewise, CTLA-4 inhibitors stop T cell activation from being suppressed, which is important in the early phases of the immunological response. T cell reactivation has the potential to eradicate cancer cells and, in certain situations, produce enduring anti-tumor immunity.[8,36]

3.3. Clinical trials and FDA approvals

The development of immune checkpoint inhibitors from preclinical research to clinical use has been rapid and revolutionary. The earliest human clinical trials followed early preclinical research showing that suppressing immunological checkpoints in mouse models was effective. In 2014, the FDA approved ipilimumab for melanoma after approving pembrolizumab and nivolumab, two of the first PD-1 inhibitors. Since then, these medications have been used to treat a wider variety of tumours, such as kidney, head and neck, and lung cancers. Numerous checkpoint inhibitors for different types of cancer have recently received approval from regulatory bodies such as the FDA and EMA. The remarkable outcomes of early clinical trials, where patients who had not responded to conventional therapy before saw substantial tumour shrinking and, in several cases, total remission, accelerated the approval procedure.[37-38]

3.4. Indications and approved cancer types

Immune checkpoint inhibitors have shown effective in treating a variety of malignancies, particularly those with substantial immune evasion or mutational loads. These treatments have shown therapeutic benefits for a number of malignancies, including:

1. Melanoma: PD-1 inhibitors pembrolizumab and nivolumab, which provide long-lasting effects in a subgroup of patients, have emerged as conventional therapies for metastatic melanoma.

2. Non-Small Cell Lung Cancer (NSCLC): PD-1 and PD-L1 inhibitors, pembrolizumab and durvalumab, respectively, have been authorised for the treatment of advanced NSCLC. These drugs are frequently used alone or in conjunction with chemotherapy. Renal Cell Carcinoma: Nivolumab has been licensed for advanced renal cell carcinoma, and combo treatments containing ipilimumab have shown better overall survival rates.

3. Head and Neck Squamous Cell Carcinoma (HNSCC):PD-1 inhibitors, particularly pembrolizumab, are licensed for the treatment of head and neck squamous cell carcinoma (HNSCC) and have been shown to have higher survival rates than conventional chemotherapy[8,10,37-38]

3.5 Combination treatments

Combining immune checkpoint inhibitors with additional treatments like chemotherapy, targeted therapy, and radiation is one of the most promising strategies in cancer immunotherapy. By breaking through the immune-suppressive tumour microenvironment and boosting the quantity of tumor-reactive T cells, combination treatment may improve the effectiveness of checkpoint inhibitors. For instance, when compared to monotherapy, the combination of nivolumab (a PD-1 inhibitor) and ipilimumab (a CTLA-4 inhibitor) has demonstrated synergistic effects in melanoma, greatly increasing response rates and survival outcomes. Immune checkpoint inhibitors are frequently used in conjunction with traditional treatments such as radiation and chemotherapy. Chemotherapy can promote immune cell infiltration into tumours, release tumour antigens, and cause tumour cell death, all of which increase the tumours' vulnerability to checkpoint inhibition. Likewise, it has been

demonstrated that radiation therapy increases tumour immunogenicity, which increases the tumor's responsiveness to checkpoint inhibitors.[39-40]

4. Clinical Efficacy of Immune Checkpoint Inhibitors

With their high clinical efficacy in many tumours, immune checkpoint inhibitors (ICIs) have made significant progress in the treatment of a variety of cancers. These treatments improve immune surveillance and tumour killing by inhibiting the immune suppression systems that tumours use. ICIs have demonstrated significant responses in a number of malignancies, and for certain reasons, PD-1/PD-L1 and CTLA-4 inhibitors are now considered conventional treatments.[8,10]

4.1. Melanoma

Immunocheckpoint inhibitors have significantly increased the survival rates of melanoma, a very aggressive kind of skin cancer. Both PD-1 inhibitors, pembrolizumab (Keytruda) and nivolumab (Opdivo), have demonstrated notable improvements in overall survival (OS) and progression-free survival (PFS) in metastatic melanoma. Response rates increase when ipilimumab (Yervoy), a CTLA-4 inhibitor, is added, leading to even better therapeutic results.[41].

4.2. NSCLC, or non-small cell lung cancer

One of the main causes of cancer-related death globally is non-small cell lung cancer (NSCLC). As PD-1 inhibitors, pembrolizumab and nivolumab have considerably increased survival in patients with metastatic or advanced non-small cell lung cancer, particularly in those with elevated PD-L1 expression. Treatment options for untreated metastatic non-small cell lung cancer have been further expanded with the approval of atezolizumab (Tecentriq), a PD-L1 inhibitor, for use in conjunction with chemotherapy.[42]

4.3. RCC or renal cell carcinoma

Historically, RCC has resisted conventional chemotherapy. The effectiveness of treatment has significantly increased after the advent of immune checkpoint inhibitors, especially nivolumab and pembrolizumab. When compared to standard therapy, combination medicines, such nivolumab and ipilimumab, have demonstrated higher PFS and OS, which represents a revolutionary shift in the management of RCC.[43]

4.4. Other cancers

ICIs have proven effective in treating a number of additional cancers in addition to melanoma, NSCLC, and RCC, such as urothelial carcinoma, head and neck squamous cell carcinoma, and microsatellite instability-high tumours. The potential of ICIs in these and other cancer types is still being investigated in ongoing clinical trials, which points to a hopeful future for immunotherapy in oncology as well as wider application.[44]

5. Mechanisms of Resistance to Immune Checkpoint Inhibitors

Even though immune checkpoint inhibitors (ICIs) have drastically changed the way cancer is treated, resistance to these medications is still a big problem. The overall effectiveness of ICIs has been limited by the observation of both acquired (evolutionary) and primary (intrinsic) resistance mechanisms. Developing solutions to overcome resistance and enhance patient outcomes requires an understanding of these mechanisms. Extrinsic factors like the tumour microenvironment and systemic immune responses, as well as tumor-intrinsic factors including genetic mutations, loss of tumour antigens, or changes in immune signalling pathways, might result in resistance to ICIs.[45]

5.1. Primary resistance

The term "primary resistance" describes some tumours' innate capacity to fend off the therapeutic effects of ICIs right away. The loss or downregulation of tumour antigens, which hinders the immune system's capacity to identify and destroy the tumour cells, is one of the main mechanisms of primary resistance. By changing the way antigens are presented, tumour cells frequently evade immune detection. For example, tumour cells that have lost or mutated their major histocompatibility complex (MHC) molecules may not properly display tumor-associated antigens to T-cells, so making them imperceptible to immune surveillance. Resistance may also result from mutations in the interferon (IFN)-gamma signalling system, which is essential for increasing MHC expression. Low mutational loads in tumours can result in fewer neoantigens being produced for the immune system to identify and combat. Since they produce fewer neoantigens to elicit an immune response, cancers with low tumour mutational burden (TMB) are less likely to benefit from ICIs. Even PD-L1 expression or the use of checkpoint inhibitors might not be enough to activate T cells in certain situations.[46]

5.2. Acquired resistance

Resistance that develops throughout treatment, frequently following an initial period of therapeutic benefit, is referred to as acquired resistance. Through a variety of strategies, such as epigenetic modifications, activation of alternative immune checkpoint pathways, or mutations in important immune signalling pathways, tumours can develop and adapt over time to evade immune-mediated elimination. The development of mutations that enable cancer cells to evade the effects of immune checkpoint inhibitors is one of the most frequent causes of acquired resistance. For example, lack of sensitivity to PD-1/PD-L1 inhibition may result from alterations in the JAK-STAT signalling system, which controls immune cell activation. Similarly, changes in genes that encode immune-related receptors or their ligands, including mutations in the PD-1 receptor or amplification of PD-L1, can reduce the effectiveness of ICIs. PD-1/PD-L1 inhibitors may be less effective against tumours that use

alternative immune checkpoint pathways, such as TIM-3, LAG-3, and TIGIT, to decrease T-cell activation. By modifying immune-related pathways and gene expression patterns, epigenetic modifications such as DNA methylation and histone modifications can also lead to acquired resistance. Tumour escape can occur, for instance, when immune modulators, costimulatory molecules, or antigen-presenting molecules are epigenetically silenced. This will lessen the immunological response that ICIs cause.[47-48] The mechanisms of Resistance to Immune Checkpoint Inhibitors are enlisted in **Table 2**.

Table 2: Mechanisms of resistance to immune checkpoint inhibitors [45-48]

Type of Resistance	Mechanisms	Potential Strategies to Overcome Resistance
Primary Resistance	Loss or downregulation of tumor antigens, insufficient T-cell activation	Development of vaccines, targeting additional immune checkpoints (e.g., TIM-3, LAG-3)
Acquired Resistance	Mutations in immune signaling pathways, epigenetic changes	Combination therapies with other immune-modulatory agents or chemotherapy
Tumor Microenvironment	Presence of Tregs, MDSCs, and immune suppressive factors	Targeting the tumor microenvironment with small molecules or cytokine therapies

5.3. Immunosuppressive tumor microenvironment

The tumour microenvironment (TME) can have a major impact on the efficacy of ICIs and is essential in determining immune responses to cancer. T-cell activation and activity are hampered by the immunosuppressive environment created by immune-suppressive cells such as tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and regulatory T-cells (Tregs) present in the TME. By inhibiting effector T-cell function and creating an immunosuppressive milieu, tregs in particular aid in immune evasion. Signalling chemicals like TGF-beta and IL-10, which are both prevalent in the TME, can attract these cells to the tumour site. T-cell activity is inhibited by cytokines released by MDSCs, another type of immune-suppressive cell that builds up in tumours. Additionally, they have the ability to directly stimulate Treg differentiation, which would strengthen the immunosuppressive response. Immune tolerance and resistance to checkpoint suppression are facilitated by the TME's high amounts of immune checkpoint ligands, such as PD-L1, metabolic stress, and hypoxia. immunological checkpoints may be upregulated in the TME in hypoxic conditions, which reduces the immunological response. The resistance to ICIs is made worse by the presence of immune-suppressive cytokines such TGF-beta and IL-10.[49]

5.4. Targeting resistance pathways

A number of tactics are being investigated to combat immune evasion and boost the effectiveness of ICIs in response to the problem of resistance. In order to get around resistance, combination therapies that target several immune pathways or combine ICIs with other forms of treatment such radiation, chemotherapy, and targeted therapies show promise. For instance, treating tumours like melanoma and non-small cell lung cancer (NSCLC) has demonstrated increased efficacy when PD-1/PD-L1 inhibitors are combined with CTLA-4 inhibitors, such as ipilimumab (Yervoy), potentially overcoming the resistance observed with monotherapy. Furthermore, preclinical and clinical research is increasingly focussing on alternative immune checkpoints including TIM-3, LAG-3, and TIGIT; preliminary findings indicate that these treatments may be able to overcome resistance mechanisms associated with PD-1/PD-L1 suppression. [8,10]

Targeting the tumour microenvironment itself, for example, by employing substances that reduce Tregs, stop MDSCs, or undo immune-suppressive signalling, is another intriguing strategy. Agents that normalise blood arteries, target the TME's metabolic pathways, or lower hypoxia may also boost immunity and increase the efficacy of ICIs. Even though immune checkpoint inhibitor resistance is a major problem, novel approaches and combination therapies that potentially improve the longevity and effectiveness of immunotherapy in the treatment of cancer are being made possible by further study into the molecular underpinnings of resistance.[50]

6. Challenges in Cancer Immunotherapy with Immune Checkpoint Inhibitors

Immunocheckpoint inhibitors (ICIs) have transformed the treatment of cancer, but in order to fully realise their therapeutic promise, a number of issues must be resolved before they can be used in clinical settings. These difficulties include tumour heterogeneity, high treatment costs, patient stratification, immune-related adverse events (irAEs), and response durability.[51]

6.1. Immune-related adverse events (irAEs)

The development of immune-related adverse events (irAEs), which are caused by the immune system becoming activated against healthy tissues, is one of the main difficulties with utilising ICIs. Colitis, dermatitis, pneumonitis, hepatitis, and endocrinopathies are some of the adverse effects that might range in intensity. irAEs happen when the immune system attacks healthy organs and tissues in addition to tumour cells.

Immunosuppressive medications like corticosteroids are frequently needed to manage irAEs, which can reduce the efficacy of ICIs and make the entire treatment plan more difficult. To lessen these side effects, patients receiving ICI therapy must be identified early and closely monitored.[52]

6.2. Patient stratification

Finding the patients who will benefit most from ICI therapy requires efficient patient stratification, which presents another major obstacle. Although they offer some direction, indicators such as tumour mutational burden (TMB) and PD-L1 expression are not always indicative of clinical outcomes. To create more accurate biomarkers, a deeper comprehension of the immunological and molecular characteristics of tumours, including the tumour microenvironment (TME), is required. Based on these profiles, tailored treatment plans may aid in better patient selection and raise ICIs' overall effectiveness.[53]

6.3. Cost and accessibility

One major obstacle to the widespread adoption of immunotherapies is their high cost, especially in environments with low resources. Both individuals and healthcare systems may be severely impacted financially by the expense of ICIs and the lengthy course of treatment that some patients must endure. Improving access to these life-saving therapies globally depends on initiatives to lower costs, make ICIs more affordable, and look into other affordable options.[54].

6.4. Tumor heterogeneity

Another difficulty is tumour heterogeneity, which refers to the variations in phenotype and genetic makeup among tumour cells within a single patient. Treatment results can vary since not all tumour cells in a particular patient will react to ICIs. Especially in tumours with low mutational burden or those that have evolved immune evasion mechanisms, this variability may lead to resistance or insufficient responses. Improving the effectiveness of treatment requires an understanding of how tumour heterogeneity affects the response to ICIs.[55]

6.5. Durability of response

One of the biggest obstacles to cancer immunotherapy is the persistence of responses. Many individuals either do not respond or relapse following an initial favourable response, however some people enjoy long-lasting remission. In diseases like melanoma and non-small cell lung cancer (NSCLC), where initial responses to ICIs may be followed by progression, the problem of relapse is especially prevalent. Research is continuously being done on ways to extend results, like combo treatments or new medicines.[56]

7. Novel Approaches to Overcome Challenges and Enhance Immunotherapy

Current developments in cancer immunotherapy are concentrating on methods to improve the efficacy of immune checkpoint inhibitors (ICIs) and get past their drawbacks. These strategies seek to address tumour microenvironmental problems as immunological suppression, resistance, and heterogeneity.[8]

7.1. Combination therapies

Combining ICIs with other treatment modalities like immune-modulatory drugs, targeted therapies, or chemotherapy is one promising tactic. By causing tumour cell death and releasing tumour antigens, chemotherapy can boost the immune response and perhaps improve the effectiveness of ICIs. Tyrosine kinase inhibitors and other targeted medicines can be used in conjunction to stop the signalling pathways that tumours utilise to evade the immune system. Furthermore, it has been demonstrated that using cytokines or vaccines in addition to ICIs may help prime the immune system and encourage a stronger immunological response.[57-58]

7.2. Next-generation checkpoint inhibitors

In addition to PD-1, PD-L1, and CTLA-4, next-generation immune checkpoint medicines are being developed to target other checkpoint pathways. For individuals who do not respond to existing ICIs, inhibitors that target novel targets like TIM-3, LAG-3, and TIGIT may offer more potent treatment alternatives. These targets are being investigated for their role in immune evasion.[10]

7.3. Cancer vaccines and adoptive cell therapy

ICIs are being studied in conjunction with cancer vaccines, which are intended to boost the immune system's ability to identify and combat tumour cells, in order to maximise their therapeutic impact. In order to strengthen the immune response against tumours, adoptive cell therapies—such as T-cell and CAR-T cell therapies—are also being investigated in combination with ICIs.[8]

7.4. Personalized immunotherapy

Another line of research is personalised immunotherapy, which makes use of transcriptomic and genomic data. Clinicians can customise treatments to increase the chance of a positive response and decrease side effects by discovering patient-specific biomarkers.[59]

8. Regulatory and Ethical Considerations in the Use of Immune Checkpoint Inhibitors

Although there are several clinical advantages to using immune checkpoint inhibitors (ICIs) in cancer immunotherapy, there are also a number of ethical and regulatory issues that need to be properly resolved to guarantee patient safety and fair access.[8]

8.1. Regulatory approvals

New immune checkpoint inhibitors must pass stringent preclinical and clinical trials to prove their safety, effectiveness, and long-term advantages before being approved. Before approving a product for general use, regulatory bodies such as the FDA and EMA assess the data from these trials. Furthermore, thorough information on synergistic effects, possible toxicities, and patient selection criteria is necessary for the approval process of combination therapies, such as those that combine ICIs with chemotherapy or targeted medicines. Regulators must modify approval processes to satisfy the rising need for individualised and efficient immunotherapy options as ICIs are used more frequently in different forms of cancer.[10]

8.2. Ethical considerations

Cost-effectiveness, patient access, and off-label use are among the ethical challenges pertaining to the use of ICIs. Even while ICIs can save lives, access to them is sometimes restricted by their expensive costs, especially in environments with limited resources. Additionally, when ICIs are used more frequently outside of recognised indications—sometimes without adequate evidence of benefit—the ethical ramifications of off-label usage become apparent, posing questions regarding informed consent and patient safety.[60]

8.3. Global disparities

Access to ICIs is further impacted by differences in regulatory procedures around the world. Patients in various nations may experience delays or lack access to potentially life-saving medicines due to differences in approval timelines and healthcare infrastructure. Reducing these differences is essential to guaranteeing that cancer patients everywhere gain from immunotherapy advancements.[61]

9. Future Directions and Emerging Trends in Immune Checkpoint Therapy

Immunocheckpoint therapy has a bright future thanks to new targets and next-generation treatments. To overcome resistance to existing treatments and expand the use of immunotherapy, new checkpoint inhibitors that target TIM-3, LAG-3, and TIGIT are being investigated. With the help of genomic profiling and biomarkers, personalised immunotherapy will increasingly direct treatment plans, guaranteeing that patients receive the most efficient, customised treatments. In order to improve efficacy, ongoing clinical trials are still looking into these novel strategies, such as combination medicines. There will be a global push to increase accessibility as immunotherapy develops, making these life-saving medicines more widely available, and particularly in environments with limited resources.[62-62]

10. Conclusion

With significant therapeutic improvements in a range of cancers, immune checkpoint inhibitors (ICIs) have revolutionised cancer immunotherapy. Targeting important immunological checkpoints including CTLA-4, PD-1, and PD-L1, these treatments have effectively stimulated the immune system to identify and destroy tumour cells. But issues including tumour heterogeneity, resistance mechanisms, immune-related side effects, and the requirement for improved patient classification continue to be major roadblocks to maximising their effectiveness. Immunotherapy's future depends on overcoming these obstacles by creating novel combination treatments, next-generation checkpoint inhibitors, and individualised treatment plans based on molecular and genomic analysis. To improve the therapeutic results of ICIs, more study into overcoming resistance mechanisms and better patient selection is essential. Furthermore, increasing access to these treatments globally is still crucial to guaranteeing that all patients can take advantage of these developments, irrespective of financial or geographic constraints. It seems obvious that immune checkpoint inhibition will continue to be a key component of cancer treatment as the field develops. Immunotherapy has the potential to further improve patient outcomes and turn cancer into a chronic, manageable illness for a large number of individuals.

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12. Conflict of Interest

None.

References

1. Amjad MT. Cancer Chemotherapy. In: StatPearls . Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK564367/
2. Finn O.J., Immuno-oncology: understanding the function and dysfunction of the immune system in cancer, *Ann Oncol*, 2021;23(8):26-9.
3. Waldman, A.; Fritz, J.; Lenardo, M. A Guide to Cancer Immunotherapy: From T Cell Basic Science to Clinical Practice. *Nat Rev Immunol.* 2020;20(20):1–18.
4. Mateusz Kciuk. Recent Advances in Molecular Mechanisms of Cancer Immunotherapy. *Cancers.* 2023;15(10):2721.
5. Pardoll D. M. The Blockade of Immune Checkpoints in Cancer Immunotherapy. *Nat Rev Cancer.* 2012;12(4):252–64.
6. Weigmann K. Releasing the Brakes to Fight Cancer. *EMBO Rep.* 2016;17(9):1257–60.
7. Lidy Vannessa Mejía-Guarnizo. The Role of Immune Checkpoints in Antitumor Response: A Potential Antitumor Immunotherapy. *Front Immunol*. 2023;14;1298571.
8. Lao Y., Shen D., Zhang W., He R., Jiang M. Immune Checkpoint Inhibitors in Cancer Therapy-How to Overcome Drug Resistance? *Cancers* 2022;14(15):3575.
9. Marei H. E., Hasan A., Giacomo Pozzoli C. Cancer Immunotherapy with Immune Checkpoint Inhibitors (ICIs): Potential, Mechanisms of Resistance, and Strategies for Reinvigorating T Cell Responsiveness When Resistance Is Acquired. *Cancer Cell Int.* 2023;23(1):64.

10. Shiravand, Y, A. Immune Checkpoint Inhibitors in Cancer Therapy. *Curr Oncol (Toronto, Ont.)* 2022;29(5):3044–60.
11. Baxevanis C. N. Immune Checkpoint Inhibitors in Cancer Therapy—How Can We Improve Clinical Benefits?, *Cancers* 2023;15(3):881.
12. Wei J. Current Trends in Sensitizing Immune Checkpoint Inhibitors for Cancer Treatment. *Mol Cancer.* 2024;23(1):64.
13. Havel J. J., Chowell D., Chan T. A. The Evolving Landscape of Biomarkers for Checkpoint Inhibitor Immunotherapy. *Nat Rev Cancer.* 2019;19(3):133–50.
14. Santiago-Sánchez. Landscape of Checkpoint Blockade Resistance in Cancer: Underlying Mechanisms and Current Strategies to Overcome Resistance. *Cancer Biol Ther.* 2024;25(1):2308097
15. Koster B. D.; de Gruijl T. D., Van den Eertwegh AJM, Recent Developments and Future Challenges in Immune Checkpoint Inhibitory Cancer Treatment. *Curr Opin Oncol*. 2015;27(6):482–8.
16. Wei J. Current Trends in Sensitizing Immune Checkpoint Inhibitors for Cancer Treatment. *Mol Cancer.* 2024;23(1):279.
17. Gonzalez H., Hagerling C., Werb Z. Roles of the Immune System in Cancer: From Tumor Initiation to Metastatic Progression. *Genes Dev.* 2018;32(9):1267–84.
18. Dong Y. Sun Q., Zhang X. PD-1 and Its Ligands Are Important Immune Checkpoints in Cancer. *Oncotarget.* 2016;8(2):2171-86.
19. Anisha Singha Deo; None Shrijana; Sruthika S.U; Shreya Karun; Kashish Bisaria; Sarkar, K. Participation of T Cells in Generating Immune Protection against Cancers. *Pathol Res Pract.* 2024;262:155534
20. Hamaï A. Immune Surveillance of Human Cancer: If the Cytotoxic T-Lymphocytes Play the Music, Does the Tumoral System Call the Tune?. *Tissue Antigens*. 2010;75(1):1–8.
21. Vinay D.S., Ryan E.P., Pawelec G. Immune evasion in cancer: Mechanistic basis and therapeutic strategies. *Semin Cancer Biol.* 2015;35:S185–98.
22. Han Y., Liu D., Li L. PD-1/PD-L1 pathway: current researches in cancer. *Am J Can Res.* 2020;10(3):727–42.
23. Jiang Y., Chen M., Nie H., Yuan Y. PD-1 and PD-L1 in cancer immunotherapy: clinical implications and future considerations. *Hum Vaccines Immunotherapeutics.* 2019;15(5):1111–22.
24. Cha J. H. Mechanisms Controlling PD-L1 Expression in Cancer. *Molecular cell*. 2019;76(3):359–70.
25. Chikuma S. CTLA-4, an Essential Immune-Checkpoint for T-Cell Activation. *Curr Top Microb Immunol*. 2017;410:99–126.
26. Buchbinder, E. I., & Desai, A. CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition. *Am J Clin Oncol*. 2016;39(1):98–106.
27. Barrueto L. Resistance to checkpoint inhibition in cancer immunotherapy. Translational Oncology, 2020;13(3):100738.
28. Granier C. Mechanisms of action and rationale for the use of checkpoint inhibitors in cancer. ESMO Open, 2017, 2(2), e000213.
29. Qin S. Novel immune checkpoint targets: moving beyond PD-1 and CTLA-4. Molecular cancer, 2019;18(1):155.
30. Gertel S. Lymphocyte activation gene-3 (LAG-3) regulatory T cells: An evolving biomarker for treatment response in autoimmune diseases. *Autoimmunity Rev.* 2022;21(6):103085.
31. Ruffo E. Lymphocyte-activation gene 3 (LAG3): The next immune checkpoint receptor. *Sem Immu*. 2019;42:101305.
32. Bolm L. Gene of the month: T-cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT). *J Clin Pathol.* 2022;75(4):217–21.
33. Bilotta M. T., Antignani A., Fitzgerald D.J. Managing the TME to improve the efficacy of cancer therapy. *Front Immunol.* 2022;13;954992.
34. Tie Y., Tang F., Wei YQ, Wei X.W. Immunosuppressive cells in cancer: mechanisms and potential therapeutic targets. *J Hematol Oncol*, 2022;15(1):61.
35. Stark M. C., Joubert A. M., Visagie M. H. Molecular Farming of Pembrolizumab and Nivolumab. *Int J Mol Sci*. 2023;24(12):10045.
36. Sharma P. Immune checkpoint therapy—current perspectives and future directions. *Cell*, 2023;186(8):1652–69.
37. Ito A., Kondo S., Tada K., Kitano S. Clinical Development of Immune Checkpoint Inhibitors. *BioMed Res Int.* 2015; 605478.
38. Watson G.A., Doi J., Hansen A.R., Spreafico A. Novel strategies in immune checkpoint inhibitor drug development: How far are we from the paradigm shift?. *Brit J Clin Pharmacol.* 2020;86(9):1753–68.
39. Vanneman M., Dranoff, G. Combining immunotherapy and targeted therapies in cancer treatment. Nature reviews. *Cancer,* 2012;12(4):237–51.
40. Varayathu H. Combination Strategies to Augment Immune Check Point Inhibitors Efficacy - Implications for Translational Research. *Front Oncol.* 2021;11:559161.
41. Knight A. Immunotherapy in Melanoma: Recent Advances and Future Directions. *Cancers*, 2023;15(4):1106.
42. Malhotra J., Jabbour S. K., Aisner J. Current state of immunotherapy for non-small cell lung cancer. *Trans Lung Cancer Res*. 2017;6(2):196–211.
43. Larroquette M. Combining immune checkpoint inhibitors with chemotherapy in advanced solid tumours: A review. *Eur J Cancer.* 2021;158:47–62.
44. Okobi T. J. Immune Checkpoint Inhibitors as a Treatment Option for Bladder Cancer: Current Evidence. *Cureus.* 2023;15(6):e40031.
45. Tan S. Immune Checkpoint Inhibitor Therapy in Oncology: Current Uses and Future Directions: JACC: CardioOncology State-of-the-Art Review. JACC. CardioOncology, 2022, 4(5):579–97.
46. Wang F. The Resistance Mechanisms of Lung Cancer Immunotherapy. *Front Oncol*. 2020; 10:568059.
47. Schoenfeld A.J, Hellmann M. D. Acquired Resistance to Immune Checkpoint Inhibitors. *Cancer Cell.* 2020;37(4):443–55.
48. Bai R. Mechanisms of Cancer Resistance to Immunotherapy. Front oncology, 10; 1290.
49. Sadeghi Rad H. Understanding the tumor microenvironment for effective immunotherapy. Medicinal research Rev. 2021;41(3):1474–98
50. Bader J. E., Voss, K., & Rathmell, J. C. Targeting Metabolism to Improve the Tumor Microenvironment for Cancer Immunotherapy. *Molecular cell,* 2020;78(6):1019–33.
51. Marei H. E. Cancer Immunotherapy with Immune Checkpoint Inhibitors (ICIs): Potential, Mechanisms of Resistance, and Strategies for Reinvigorating T Cell Responsiveness When Resistance Is Acquired. *Cancer Cell Int.* 2023;23(1):64
52. Bardoscia L.; Pasinetti, N.; Triggiani, L.; Cozzi, S.; Sardaro, A. Biological Bases of Immune-Related Adverse Events and Potential Crosslinks with Immunogenic Effects of Radiation. Frontiers in Pharmacology 2021:12.
53. Fumet JD., Truntzer C., Yarchoan M., Ghiringhelli F. Tumour Mutational Burden as a Biomarker for Immunotherapy: Current Data and Emerging Concepts. *Eur J Cancer.* 2020;131;40–50.
54. Ventola C. L. Cancer Immunotherapy, Part 3: Challenges and Future Trends. P & T: a peer-reviewed J Formul Manag. 2017:42(8):514–21.
55. Zhu L., Jiang M., Wang H., Sun H., Zhu J., Zhao W., A Narrative Review of Tumor Heterogeneity and Challenges to Tumor Drug Therapy. *Ann Transl Med.* 2021;9(16):1351.
56. Restifo N.P., Smyth M.J., Snyder A. Acquired Resistance to Immunotherapy and Future Challenges. *Nat Rev Cancer.* 2016;16(2):121–6.
57. Li, B.; Jin, J.; Guo, D.; Tao, Z.; Hu, X. Immune Checkpoint Inhibitors Combined with Targeted Therapy: The Recent Advances and Future Potentials. Cancers 2023, 15 (10), 2858. https://doi.org/10.3390/cancers15102858.
58. Gholap A.D., Hatvate N.T, Khuspe P.R., Mandhare T.A. Pooja Kashid; Gaikwad, V. D. Proteomics in Oncology. *Retros Prosp*. 2023;243–69.
59. Krzyszczyk P. Acevedo A.; Davidoff E. J., Timmins L.M. The Growing Role of Precision and Personalized Medicine for Cancer Treatment. *Technol.* 2018;06(3-4):79–100.
60. Wesevich A. Interventional Pharmacoeconomics for Immune Checkpoint Inhibitors through Alternative Dosing Strategies. *Brit J Cancer*. 2023;129(9):1389–96.

61. Ndebele P., Blanchard-Horan C., Shahkolahi A., Sanne I., Regulatory Challenges Associated with Conducting Multicountry Clinical Trials in Resource-Limited Settings. *J Acqu Immun Def Synd.* 2014;65:S29–31
62. Cai L., Li Y., Tan J., Xu L., Li Y. Targeting LAG-3, TIM-3, and TIGIT for Cancer Immunotherapy. *J Hematol Oncol.* 2023;16(1):101.
63. LU C., Tan Y. Promising Immunotherapy. Targets: TIM3, LAG3 and TIGIT Joined the Party. *Del J.* 2024; 200773.

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