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Review Article

Immune Checkpoint Inhibitors for Cancer Therapy: Status and Future Directions

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ABSTRACT

Among various treatment modalities available for the treatment of cancer, immunotherapy is one of the important strategies used for the management of different malignancies. Immune checkpoint inhibitors are used for the treatment of cancers based on immunotherapy. Immune checkpoints are implicated when the proteins on the immune cells identify and bind to the ligand on the surface of other cells. These proteins are referred as immune checkpoint proteins. As soon as the checkpoint protein and ligand combine, they convey an "off" signal to the immune cells and prevent the immune system from killing the cancerous cells. Thus, immunotherapy drugs such as immune checkpoint inhibitors act by inhibiting the checkpoint protein molecules. This act stops the "off" signal, permitting the immune cells to destroy the cancerous cells. Programmed Death Ligand-1 (PD-L1) and Programmed Death-1 (PD-1) inhibitors have achieved clinical success with good overall survival rates in solid tumors. Considering remarkable outcomes in clinical investigations, various PD-L1 and PD-1 inhibitors have gained significant attention as onco-immunotherapeutic agents to treat various malignancies effectively. The present review aimed to explain the fundamentals of cancer immunotherapy, basics of checkpoints, inhibitors implicated in immune checkpoints, chemistry, clinical status, adverse events, resistance to checkpoint inhibitors and future scope.

Keywords: Immune checkpoint inhibitors, PD-1, PD-L1, Cancer, Immunotherapy.

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INTRODUCTION

Cancer is a devastating illness that affects so many people worldwide. Fortunately, several treatment methods are available to help manage the condition. Some of the most common methods include chemotherapy, surgical removal and radiation therapy. However, in recent years, immunotherapy has emerged as a significant therapeutic option that has shown great promise in treating cancer.[1-4] Cancer immunotherapy uses the immune system, particularly T cells, to destroy cancer cells. Cancer vaccines, oncolytic viruses, cytokine treatment, adoptive cell therapy and Immune Checkpoint (IC) inhibition are few of the many methods that fall under this category.[5-8] The first cancer therapy using the immune system was developed toward the end of the 19th century.[9] Since then, various findings have clarified the immune system's crucial function in the regulation of malignantly altered cells. By extending the survival of patients with fast-growing cancers, immunotherapeutic methods have contributed tremendous milestones in cancer therapy.

The immune system is a primary defense line against the development and spread of tumors. Inability of the defense system to recognize tumor cells is a major factor involved in the pathogenesis and etiology of cancer development. Tumor cells have immune-evading ability due to the immuno-suppressive characteristics of the tumor microenvironment. Therefore, immunotherapy acts by enhancing the body's defense mechanisms and producing anticancer effects.[10] Among various immunotherapeutic approaches, IC inhibition is gaining popularity for the treatment of cancer (Figure 1). IC pathways that maintain immune responses to withstand self-tolerance are stimulatory or inhibitory in nature. Recently, Cytotoxic T-Lymphocyte-Associated antigen 4 (CTLA4), PD-1 receptor and PDL-1 inhibitory checkpoints have received remarkable attention from medicinal chemists. Consequently, in immunotherapy, molecules that can disrupt these pathways to increase host immune responses against tumors proved to be efficient in the management of cancer. IC inhibitors (ICIs) act by inhibiting the checkpoint protein molecules from linking with the ligand. Thus, this act stops the "off" signal, permitting the immune cells to destroy the cancerous cells. Among ICIs, Programmed Death Ligand-1 (PD-L1) and Programmed Death-1 (PD-1) proteins have continued to achieve substantial success clinically with good Overall Survival (OS) rates in solid tumors.

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The cancer immunity cycle can be targeted and controlled to induce tumor rejection at numerous crucial levels. This cycle produces effector T-cells, which can recognize the tumor antigens *in vivo* with excellent acuity, leading to invasion and trafficking into the tumors by overcoming the inhibitory networks of the tumor microenvironment. This phenomenon results in the direct identification of tumor antigens and production of an anti-tumor effector response and enduring anti-tumor T-cell efficacy.[11] PD-1/PD-L1 antibodies with dual focus are also known to induce significant antitumor activity. This combination eliminates immunosuppressive brakes, promotes various activities in the cycle of cancer and immunity and creates an immune-supportive tumor microenvironment.[12] The discovery of CTLA4 and PD-L1 inhibitors as immunotherapeutic agents provided major advancements in developing novel cancer treatment strategies.

A thorough consideration of the molecular substructures of the immune system and preclinical and clinical drug development processes is necessary for rational combination strategies to increase anticancer benefits of immunotherapies.[13] In less than a decade, among 57 new immune-oncology-related FDA approvals, 17 were successfully indicated for solid tumor treatment.[14] Six out of these compounds were identical PD-1/PD-L1 antibodies accounting for 82% of the total immune-oncology-related approvals. Recently, anti-PD-L1 monoclonal Antibodies (mAbs) such as durvalumab, avelumab and atezolizumab demonstrated potential outcomes against various cancers including bladder, non-small cell metastatic lung cancers and melanoma.[15-18] An assessment of these drugs and patient outcomes would result from recognizing distinctive characteristics of immune-oncology-related therapies and considering them in clinical studies.[14] As a result of their effectiveness against various hematologic and solid malignancies, these therapies have considerably changed the treatment approaches for distinct tumors.[19] The current manuscript aimed to discuss the basics of immunotherapy implicated in cancer, fundamentals of checkpoints, checkpoint inhibitors implicated in cancer therapy, chemistry of ICs, clinical status, adverse events related to checkpoint inhibitors, resistance to checkpoint inhibitors and future viewpoint.

Immune checkpoints: regulators of unrestrained immune response

ICs are characteristic integral constituents of the immune system and they play an important role by inhibiting the response of immune cells toward healthy cells to avoid the killing of healthy cells. ICs are watchdogs over the immune system, as IC conduits are imperative for self-tolerance. Moreover, IC pathways inhibit the immune response from attacking cells indiscriminately. Fundamentally, IC systems are activated as the protein molecules present on the T-cell surface identify and adhere to the attachment protein molecule on the surface of cells. Similarly, ICs are implicated in the cancer cell and leave the cancer cells undestroyed, leading to the growth and progression of malignancies. A multitude of genetic changes that are features of all types of malignancies offer a variety of antigens that help the immune system differentiate cancerous cells from healthy cells. The magnitude and quality of the immune reaction are instigated via recognition of antigen by the T Cell Receptor (TCR) and synchronized by an equilibrium between inhibitory and co-stimulatory signals (that is, ICs).[20,21] However, some tumors prevent the T-cell response by overexpressing PDL-1. PD-1 and PD-L1, also named CD279, are proteins found on the cell surface that suppress the immune system and prevent autoimmune disorders by lowering the inflammation-causing potential of T-cells and promoting self-tolerance. However, they can prevent the immune system from functioning by eliminating carcinogenic cells.[22,23]

Monocytes, dendritic cells, natural killer cells and stimulated T-cells and B-cells all express PD-1 on their surface. PD-1 often shows interaction with two proteins or ligands: PD-L1 (B7-H1 and CD274) suppresses the adaptive immune system during conditions such as hepatitis, pregnancy and autoimmune disorders.[22-24] The binding affinity of PD-L1 for PD-1 is found to be three times greater than that of PD-L2. The PD-1/PD-L1 complex (1:1) was structurally characterized in 2015 and the crystalline structure of the trans-membrane glycoproteins PD-1 and PD-L1 was proposed, which showed seven strands being systematized into two sheets coupled through a disulfide bridge.[24,25] Other co-inhibitory agents that target the PD-1 and PD-L1 checkpoint receptors are companions of the immune system. Moreover, the influence of immunological reactions on the tumor microenvironment can be increased by activating stimulatory ICs. The increased activation, proliferation and activity of CD4+ T-cells, CD8+ T-cells, natural killer cells and macrophages can enhance the production of inflammatory molecules.[26] Two agonistic checkpoint agents, namely, inducible T-cell co-stimulatory and CD28, belong to the B7-CD28 superfamily, whereas stimulatory checkpoint agents, including CD27, GITR, CD40, CD137, OX40 and TNFR, are members of the TNFR superfamily.[27]

Immune checkpoint pathway

Protein molecules involved in immunotherapy preserve tolerance and protect against immune system-related pathology in a healthy state; however, their continuous expression impairs T-cell functions. Recent advancements in the immunotherapy of lung cancer and metastatic squamous cell carcinoma include blockage of CTLA-4 and PD-1/PD-L1 to restore immunity and minimize T-cell exhaustion.[28] The immune system is adversely controlled by the PD-1/PD-L1 complex, which also keeps T-cell homeostasis in check. However, oncogenic cells may take advantage of this mechanism by upregulating PD-L1 as a strategy to undermine the immune system's effectiveness in fighting cancers.[29,30] First, the T-cell responses are dependent on the ability of Antigen-Presenting Cells (APCs) to recognize MHC/peptide

complexes via the T-cell receptor. Additional involvement of co-inhibitory and co-stimulatory molecules ensures the initiation or constrain of T-cell functions to support the functions of immunological checkpoints.

The PD-1/PD-L1 complex disrupts the contact between oncogenic cell and T-cell and restores lymphocytic activity, which is thought to be an attractive target for the design and discovery of therapeutic agents. By avoiding ICs that neutralize tumors, PD-1 and PD-L1 play crucial roles in the tumor microenvironment during the growth of the tumor. Even though oncogenic cells and APCs express PD-L1, their binding to PD-1 leads to T-cell malfunction, fatigue, neutralization and production of IL-10. As a result, tumor cells are protected from being destroyed by cytotoxic T-cells (CD8+ killer T-cells) when PD-L1 is overexpressed. Moreover, activated T-cells and APCs create the B7-1 (CD80) protein, which interacts with PD-L1 and inhibits the activation and proliferation of effector T-cells. Oncogenic cells are extremely harmful, release various pro-inflammatory cytokines such as IFN-γ, IL-2 and TNF-α due to the death of cytotoxic T-cells. The consistent expression of PD-1 is maintained by regulatory T-cells to provide an extremely immunosuppressive tumor environment.[31]

PD-1 is responsible for the conversion of helper T-cells to control regulatory T-cells and subsequently reduce the immunological responses with the help of multifunctional cytokines, such as TGF and CD3.[32] Consequently, PD-1 expression enhances the proliferation of immune-suppressive regulatory T-cells and

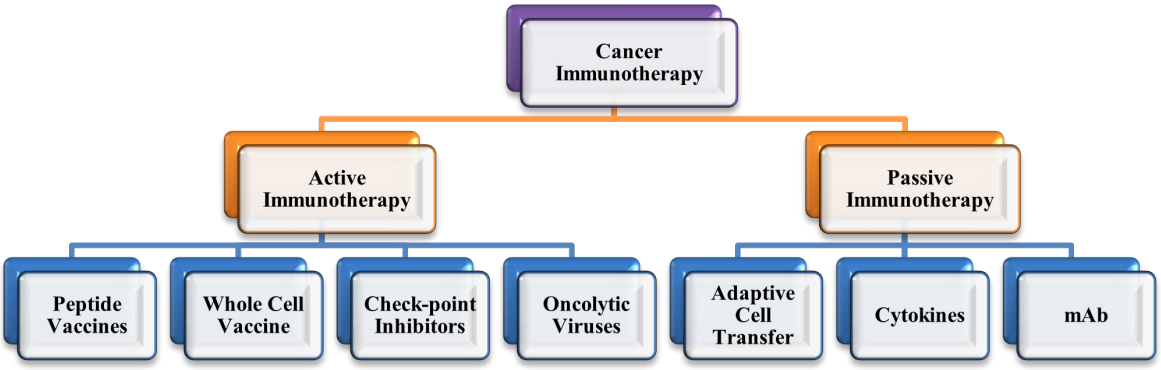

Figure 1: Approaches for cancer treatments in immunotherapy.

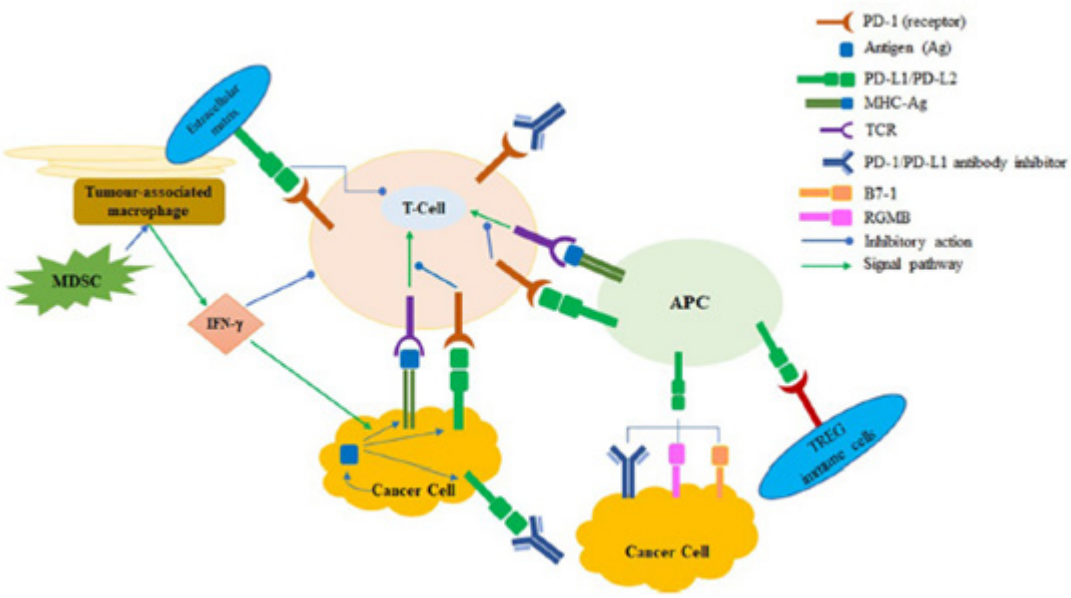

Figure 2: Mechanism of action of PD-1/PD-L-1 inhibitors.[34]

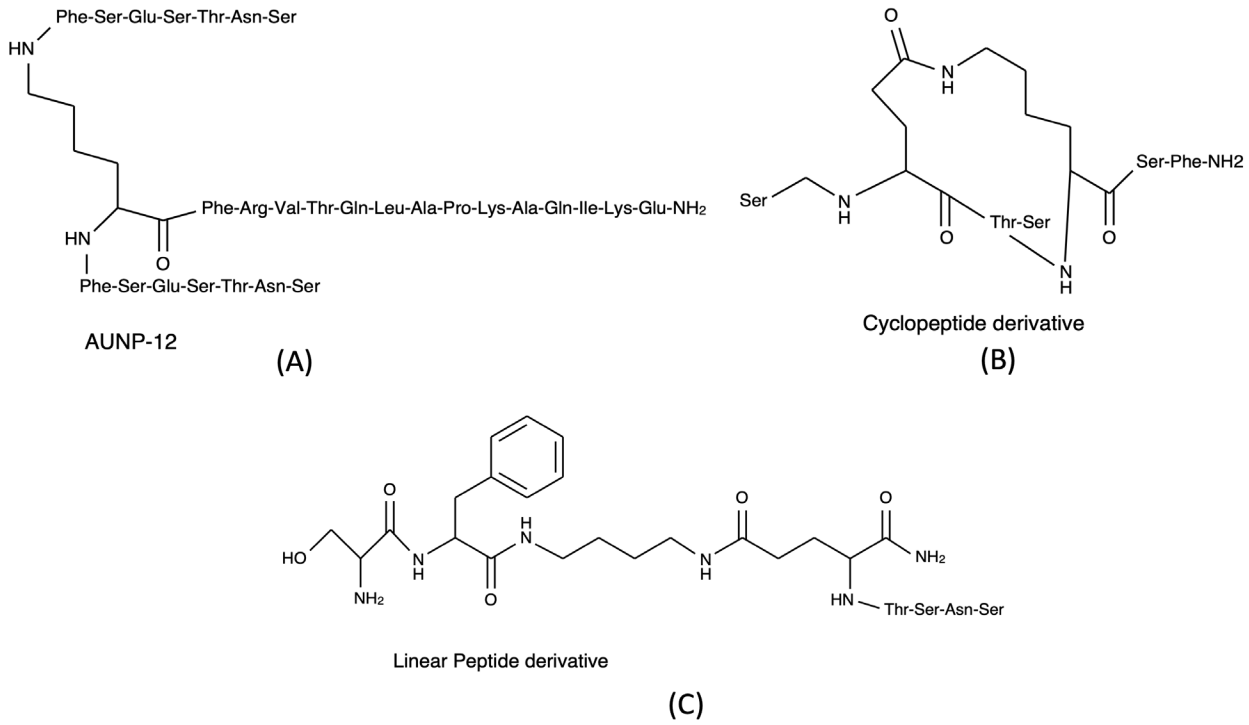

Figure 3: Structures of (A) AUNP-12, (B) cyclopeptide derivative and (C) linear peptide derivative.

suppresses the effector T-cell. Despite low levels in the initial stages of B-cell maturation and development, PD-1 is associated with the immune deficiency of B-cell malignancies because its activation is controlled during B-cell differentiation. By triggering TLR9 agonists, PD-1 prevents B-cell-assisted T-cell activation. Thus, it encourages B-cell expansion and enhances antigen-specific immune reactions. Moreover, PD-L1 modulates immunological processes linked to oncogenic tumors and hematopoietic cells invigorated by cytokines such as IFN-γ and TNF-α. APCs excite the T-Cell Receptor (TCR) and MHC interaction by attaching to the antigen from neoplastic cells and T-cells to achieve MHC binding and TCR activation (Figure 2).[26,31,33]

Early research on immunosuppressive activity was achieved through the mutual activation of PD-1 and CTLA-4 ligands. Activated regulatory T-cells express CTLA-4, which competes with stimulating CD28 protein molecule (CD80/CD86) for interaction.[35] The CD80/CD86 and stimulatory CD28 ligands compete for binding with CTLA-4, as shown by activated regulatory T-cells. Once PD-1 binds to the ligands, PD-L1 and PD-L2, TCR signaling is directly inhibited by SHP2-mediated de-phosphorylation of proximal signaling components. Activated and tattered T-lymphocytes express the PD-1 protein. PD-1 controls intra-tumoral T-cell trafficking, whereas CD28 works as a convergence regulatory substrate for CTLA-4 and PD-1. Moreover, the amount and configuration of inhibitory receptors produced by T-cells are expected to be influenced by various chronic viral infections and malignancies, which can influence checkpoint antibody-blocking mechanisms.[26]

In summary, immunotherapy target characterization might benefit the patients from ICIs, as the co-inhibitory proteins are reduced, resulting in exceptional success in the management of several malignancies.

PD-1/PDL-1 checkpoint inhibitors: agents unleashing the immune responses

As a result of complicated multi-target networks, inflammatory immune reactions are frequently challenging to be used selectively as therapeutic targets. Currently, remarkable research is being conducted on three important IC receptors including PD-1/PD-L1 and CTLA-4 as anticancer targets. The best medicines currently available are mAbs that act by interacting with these targets. Against tumor cells, the immune system can be strengthened through utilization of appropriate antibodies, which might act via interaction with the receptors. Apart from the above-mentioned ones, the ICs are also being investigated as promising anticancer treatments.[36-38]

In recent times, several pharmaceutical companies have paid significant attention toward research involving the development of checkpoint inhibitors for the treatment of cancer. ICIs are being tested for several forms of malignancies such as liver and bowel cancer and some of the agents are currently in the clinical research stage. The first checkpoint blocker examined clinically was against CTLA-4 and the resulting outcome included extended survival in patients with metastatic cancer. Anti-PD-1 antibodies, the second-generation checkpoint blockers, raised potency in various carcinomas. Two CTLA-4 antibodies, namely,

Table 1: PD-1/PD-L1 inhibitors for the treatment of carcinoma.

Agent	Category	Intervention	Disease	Study type	Phase	Sponsor	NCT Number
Nivolumab	PD-1	Single	Hodgkin Lymphoma.	Interventional	Phase 2	SCRI Development Innovations, LLC.	NCT03436862
		Single	Head and neck squamous cell carcinoma.	Observational	Phase 2	Chang Gung Memorial Hospital.	NCT03917537
		Single	Metastatic Pancreatic Cancer.	Interventional	Phase 2	University Hospital, Basel, Switzerland.	NCT04212026
Pembrolizumab	PD-1	Single	Multiple Myeloma	Interventional	Phase2A	Canadian Myeloma Research Group.	NCT04258683
		Single	HER2-Negative Breast Cancer.	Interventional	Phase 2	University of Malaya.	NCT03989089
		With paclitaxel	Lung Cancer	Interventional	Phase 2	Seoul National University Hospital.	NCT02551432
Atezolizumab	PD-L1	with Bevacizumab	Lung Cancer	Interventional	Phase 2	Fundación GECP	NCT03836066
		single	Cutaneous Melanoma	Interventional	Phase 1	The Methodist Hospital Research Institute.	NCT04020809
		single	Non-small Cell Lung Cancer.	Interventional	Phase2	Hoffmann-La Roche.	NCT05171777

ipilimumab and tremelimumab and four PD-1/PD-L1 antibodies (i.e., nivolumab, pembrolizumab, atezolizumab and avelumab) have been approved by the US-FDA.[36-38] After chemotherapy, nivolumab is also accepted to treat squamous non-small cell lung carcinoma in localized or distant metastasis cases. Apart from the abovementioned ICs, other checkpoints have also been identified. For instance, lymphocyte-activation gene 3 (LAG-3) is an important immunological checkpoint that functions *in vivo* and regulates the human immune system in a balanced manner. LAG-3 negatively controls T-lymphocytes, through attachment on the outer cell surface of the ligand, preventing the onset of autoimmunity brought on by excessive T-cell activation. Currently, 12 new molecules targeting LAG-3 are under clinical trials. Among these Molecules, eftilagimod alpha (IMP321), developed by Prima BioMed/Immutep, is being tested for the management of stage IV breast cancer and it was found to show the fastest clinical research advancement among other tested agents.[35,39]

New IC-based therapeutic techniques are now being applied to the foundation of this breakthrough in cancer therapy. The variable regions of therapeutic IC-blocking mAbs stick to immune inhibitor-epitopes, while the "Fragment crystallizable" (Fc) part initiates specified cell damage due to reaction with the supplement entity C1q and the Fc region on the inborn ligand cells. Currently, IgG1s and IgG4s, two approved IC-mAbs can kill the target cells, depending on the mioenvironment.[40] IgG1s including ipilimumab and tezolizumab are likely to deplete regulatory T-cells (Treg) and tumor cells, respectively.[35] On the other hand, nivolumab and pembrolizumab are modified IgG4 antibodies with minimal effector capabilities that work primarily by stopping the PD-1 from interacting with its ligands. Combined with anti-PD-1/PD-L1 and anti-CTLA4 antibodies, these ICI mAbs enhance effector the T-cell activation and increase survival. Moreover, ICs are activated when tumor cells are not fully eliminated, evolving in the disappearance of cancer cells through rejection from immune system.[41-44]

Agent	Category	Intervention	Disease	Study type	Phase	Sponsor	NCT Number
Cemiplimab	PD-1	Biological: RP1	Advanced Squamous Skin Cancer.	Interventional	Phase 2	Replimune Inc.	NCT04050436
		With Rwlc	Stage I-II Merkel Cell Carcinoma.	Interventional	Phase 1	H. Lee Moffitt Cancer Center and Research Institute.	NCT04975152
		Single	Secondary Angiosarcomas.	Interventional	Phase 4	Radboud University Medical Center.	NCT04873375
Avelumab	PD-L1	Single	Refractory Testicular Germ Cell Cancer.	Interventional	Phase 2	National Cancer Institute, Slovakia.	NCT03403777
		Single	Metastatic AR+ Triple Negative Breast Cancer.	Interventional	Phase 1b	Royal Marsden NHS Foundation Trust.	NCT04360941
		MRx0518	Urothelial Carcinoma	Interventional	Phase 2	4D pharma plc	NCT05107427
Dostarlimab	PD-1	Niraparib Biological: Pembrolizumab.	Non-Small Cell Lung Cancer.	Interventional	Phase 2	Tesaro, Inc.	NCT03308942
		Niraparib Pegylated, liposomal doxorubicin, Paclitaxel, Gemcitabine, Topotecan, Bevacizumab.	Recurrent, Ovarian, Fallopian Tube or Primary Peritoneal Cancer.	Interventional	Phase 3	Fondazione Policlinico Universitario Agostino Gemelli IRCCS.	NCT04679064
		Niraparib	Lung Cancer and Neuroendocrine Carcinomas.	Interventional	Phase 2	M.D. Anderson Cancer Center.	NCT04701307
		With Carboplatin-Paclitaxel.	Endometrial Cancer.	Interventional	Phase 3	ARCAGY/ GINECO GROUP.	NCT05201547
		With Niraparib	BRCA-Mutated Unresectable or Metastatic Breast, Pancreas, Ovary, Fallopian Tube, or Primary Peritoneal Cancer.	Interventional	Phase 1	University of Washington.	NCT04673448

Agent	Category	Intervention	Disease	Study type	Phase	Sponsor	NCT Number
Durvalumab	PD-L1	PD-L1 imaging (Diagnostic)	HNSCC	Interventional	Phase 2	Radboud University Medical Centre.	NCT03829007
			Extensive Small-cell Lung Cancer.	Interventional	Phase 2	Henan Cancer Hospital.	NCT04660097

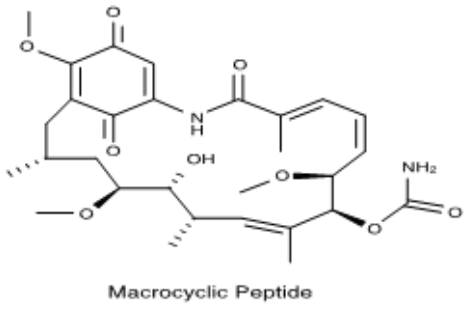

Figure 4: Macrocyclic peptide as PD-1/PD-L1 inhibitor.

The preliminary investigations on PD-1 were carried out in 1992 by Tasuku and colleagues, who found that the PD-1 is upregulated during apoptosis.[45] Later it was found that the apoptosis was not directly linked to the PD-1; rather T-cells were responsible for the control of negative T-cell and immunological responses.[45] Different types of PD-1 receptors are widely distributed and found to be present on the surface of B-cells, activated T-cells, monocytes, CD4+, CD8+ cells, dendrimer cells and natural killer cells. The expression of PD-1 in T-cells is controlled by IL-2, IL-7, IL-15 and IL-21 interleukin receptors and different other T-cell modulators.[46] The role of PD-1 protein signaling is to promote TCR inhibition through direct or indirect blocking of signaling cascades. PDL-1 (CD274 and B7-H1) and PDL-2 (CD273 and B7-DC) have distinct cell distribution profiles and are about 38% homologous to each other. By using the CD80 and CD86 sequences on hematological and few non-hematopoietic cells, Chen and co-workers discovered the first PDL-1 in 1999. In general, PDL-1 is expressed mainly on monocytes and macrophages, whereas PDL-2 is mainly expressed on dendritic cells.[33,47-49]

Small peptides

Small peptides are promising candidates that interrupt binding between PD-1 and its ligand PD-L1. Synthetic peptides with low molecular weight have several advantages, including simplicity of synthesis, reduced immunogenicity, improved kinetics and absence of negative consequences linked to Fc receptors.[50-53] Additionally, increased inhibition of PD-1/PD-L1 both near and far from the tumor vasculature is provided by effective tumor penetration. Moreover, low-molecular-weight peptides offer a nano-delivery choice with simple coupling to a targeted ligand or encapsulating system. Peptide-based checkpoint inhibitors appear to be advantageous for cancer immunotherapy, offering all the benefits that have been demonstrated for them.[54,55]

To interrupt the PD-1/PD-L1 interplay, researchers synthesized AUNP-12, a branched peptide consisting of 29 amino acids, in 2011 (Figure 3A). According to previous reports, AUNP-12 might inhibit the growth and spread of tumors while maintaining the antitumor immune response for 24 hr with minimal side effects. Given the molecule's short half-life, PD-1/PD-L1 can control the frequency of unfavorable immune-related events. Binding experiments on human HEK293 (Human Embryonic Kidney) cells that express PD-L2 and PD-1/PD-L2 revealed that binding might be disrupted by AUNP-12.[56-59] As a prototype, AUNP-12 prompted scientists to develop small peptides for the management of cancer. In 2015, Aurigene Discovery Technologies Limited developed various linear and cyclic peptides[60] (Figures 3B and 3C). A *de novo* drug design methodology was used in 2016 to create four short peptide ligands for the PD-1 protein. The newly created peptides' binding affinities to PD-1 were measured through a surface plasmon resonance test. The peptide had the highest affinity (KD=1.380±0.39 μM), whereas the KD values for the three other peptides were 2.68-4.24 μM. This striking outcome proved that the *de novo* design approach can produce peptide ligands for PD-1 with observable affinity.

To determine the peptide's *in vitro* activity, combinations of the PD-1 protein and various concentrations of the peptide were pre-incubated. Decreasing surface plasmon resonance signals with increasing concentrations of the peptide molecule indicated that the peptide can effectively prevent the interaction between PD-L1 to PD-1. Furthermore, ELISA revealed that the addition of peptide (at 250 μM) might recover 67% of Jurkat T-cells co-cultured with IFN-γ pre-treated colon cancer cell line HCT116 to generate IL-2 and consequently, restore the inhibited function of Jurkat T-cells by blocking the PD-1/PD-L1 interactions.[61] In 2018, Li and colleagues revealed that TPP-1, a PD-L1 targeting peptide, has a significant affinity for the PD-L1 protein, as shown by the bacterial surface display technique and the ability to disrupt PD-1/PD-L1 *in vitro* interactions. Thus, peptides can inhibit tumor growth in mice to a larger degree than PD-L1 antibody (56% vs. 71%). Furthermore, the KD value of the peptides to PD-L1 was determined to be 74 nM. TPP-1 increased

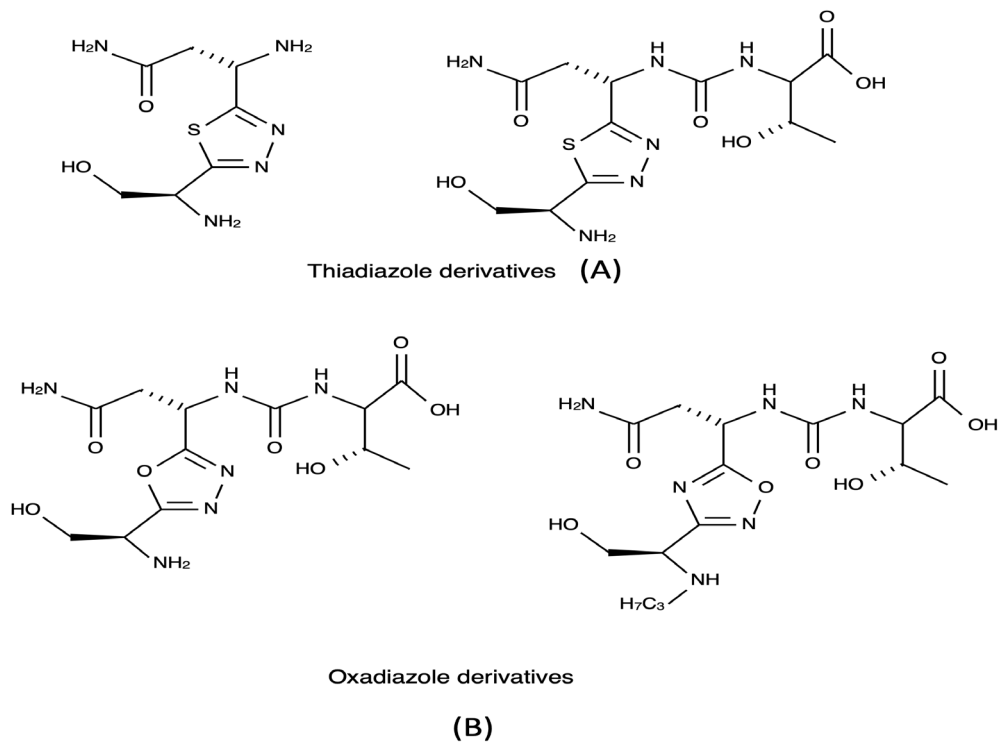

Figure 5: (A) Thiadiazole derivatives and (B) oxadiazole derivatives as modulators of PD-1.

IFN-γ release and granzyme-B expression, lowering the size of tumors in a lung cancer xenograft mice model (H460).[62]

Macrocyclic peptides

Most macrocyclic peptides consist of several amino acid residues and contain one or more rings. A popular method for enhancing the pharmacological characteristics and bioactivity of peptides is macrocyclization. Macrocyclic peptides, comprising monocyclic and bicyclic peptides, are favored molecular modalities that can be exploited for drug administration for the treatment of diseases (like cancer), diagnosis (e.g., biosensors) and drug delivery.[63,64] Macrocyclization, a property shared by molecules with various structural characteristics, often enhances a peptide's pharmacological properties, suggesting its potential for a novel approach to enhance bioactivity.[65] Compared with the linear form, macrocyclic peptides exhibit superior qualities, encompassing improved affinity, specificity and enhanced proteolytic resistance toward the target protein.[66-70] Thus, the design and development of macrocyclic peptides have become an important strategy for the management of cancer. A number of reactions have been designed for macrocyclization of peptides, include sidechain and backbone cyclization; however, backbone cyclization offers most conformational constraint.[71-73] In 2014, researchers from Bristol-Myers-Squibb (BMS) revealed two distinct strategies that aimed to block immunomodulation by interfering with PD-1/PD-L1 binding. The newly synthesized PD-1/PD-L1 macrocyclic inhibitors showed good efficacy in the homogeneous time-resolved-fluorescence binding experiment (Figure 4).[74]

Small Molecule Inhibitors

Small-Molecule Inhibitors (SMIs), which may be used in immunotherapy, have generated extensive attention in the field of cancer-related research. Increased permeability of cells, tissue selectivity, smaller biological half-lives, less expensive manufacturing and potential for oral administration are but a few of the benefits that SMIs have over large-molecule inhibitors, such as mAbs.[75,76] When juxtaposed with traditional drugs, small-molecule inhibitors are linked to a broad variety of potential targets and pathways for reducing the expression of oncogenes.[75,76] Greater stability and improved tumor penetration are two additional benefits of SMIs over currently available mAbs.[77] According to preclinical research, SMIs show promise in suppressing tumors by preventing the PD-1/PD-L1 interaction.[78,79] The relatively flat and hydrophobic surfaces where these proteins interact make it difficult for these inhibitors to come into contact with those surfaces, so employing SMIs for targeting the PD-1/PD-L1 interaction is challenging.[75,80] SMIs that target the PD-1/PD-L1 axis have recently emerged, showing encouraging cellular inhibitory efficacy and the possibility to mitigate the drawbacks of mAbs. SMIs that successfully suppress the PD-1/PD-L1 interaction were found by structure-based virtual screening.[81]

Sulfamethizole derivatives were the first novel small-molecule PD-1 modulators identified by Harvard University researchers in 2011 and their oxadiazole analogues were prepared by replacing sulfur with oxygen.[82-84] Following this development, considerable research was carried out by scientists worldwide for preparing peptides and small molecules that can combat a variety of tumors.

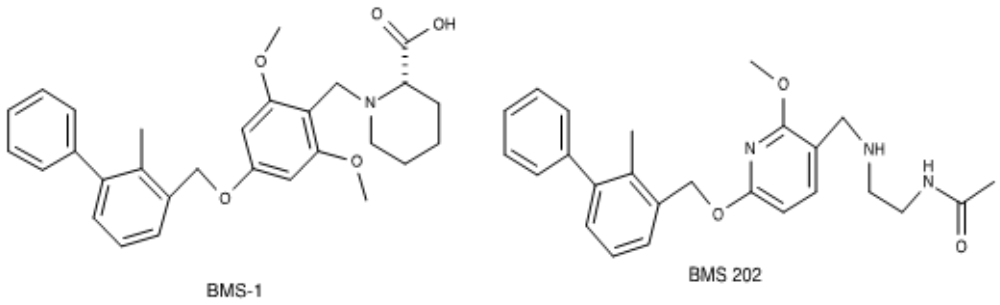

Figure 6: BMS molecules showing *in vitro* interference with the PD-1/PD-L1 complex.

Many thiadiazole and oxadiazole derivatives were later identified as modulators of the PD-1 signaling pathways[82-84] (Figures 5A and 5B). Decitabine, a DNA methyltransferase inhibitor, which is routinely used to treat myelodysplastic syndrome, has also been investigated. The results proved the *in vitro* interference with the PD-1/PD-L1 complex after discovering BMS molecules and validated the direct interaction with PD-L1 before binding to the PD-1 protein[82-84] (Figures 6 and 7).

Clinical Status on PD-1/PDL-1 Inhibitors: Lab to Bedside Journey

Patients with carcinoma clinically benefit from PD-1/PDL-1 inhibitors that have been available on the market since 2014. Some novel molecules acting as PD-1/PD-L1 blockers, which are being utilized to treat carcinoma, are enlisted in Table 1. These therapeutic agents are probably one of the first choices for the treatment of carcinoma and prove to be clinically effective in improving OS as compared with other drugs such as dacarbazine. Thus, the ICI pembrolizumab shows significantly low toxicity while improving the OS of patients suffering from advanced metastatic melanoma. Besides melanoma, PD-1 blockers also show clinical applicability in liquid and solid malignancies, together with non-Hodgkin lymphoma, bladder, pancreatic, follicular B cell and Non-Small Cell Lung Cancer (NSCLC).[85]

Compared with other medications such as docetaxel, both nivolumab and pembrolizumab showed encouraging outcomes in terms of improved safety, potency and survival chances in patients with NSCLC.[86] Tumors with high mutagenicity and antigenicity such as those with high tumor mutation load, Mismatch Repair deficit (dMMR) and microsatellite instability can also be treated with PD-1 inhibitors. However, biomarkers cannot fully differentiate tumors that respond well to PD-1/PD-L1 inhibitors. Compared with other antitumor treatment modalities, immunotherapy is superior because of the capacity of the immune system to adapt and target specific cancer cells. Moreover, established immunotherapy induces a long-lasting memory of similar antigenic stimuli and uses PD-1 blockers, which are further related to overall improved survival rates compared with other IC blockers, including anti-CTLA-4 mAbs and BRAF/MEK blockers.[85] It can also be utilized to treat a range of malignancies. In addition, PD-1 inhibitors such as pembrolizumab are currently accepted as a novel treatment strategy and first-line therapy for melanomas resistant to ipilimumab.[87,88]

The outcomes from several trials revealed that PD-1 blockers produce lesser toxicity than other immunotherapies such as CTLA-4. Considering that they are non-invasive and all-natural, immunotherapy based on PD-1/PDL-1 inhibitors is often considered safer than other cancer treatment approaches such as radiation, chemotherapy and surgery.[89,90] The therapeutic process enables self-reactive immune cells to combat cancers. Checkpoint immunotherapy features few harmful side effects because it is highly selective to the target cells and it maintains a memory of the cancer antigen.[87,91,92] Immunodeficient individuals are at great risk of cancer development and a large population of patients with immune deficiencies is undergoing immunotherapy.[93] Administering immunotherapeutic remedies to patients with cancer and concomitant primary immunodeficiency diseases, such as hereditary angioedema and other antibody deficiency syndromes, remains a major challenge. Additionally, individuals with autoimmune illnesses are typically not viewed as viable subjects for these therapies because of ICI drug-related adverse events. Thus, ICI-based therapy might be beneficial for patients with autoimmune disorders; however, the incidences of immune-related adverse events can result in low survival rates[93,94]

In comparison with the CTLA-4 inhibitors, PD-1 inhibitors display a greater tendency to enhance the rate of recurrent disease. Although approximately 18% of the patients who receive treatment with checkpoint inhibitors may exhibit oligoprogression, most patients eventually develop progressive disease. Local therapy might offer some of these patients with long-term progression-free survival.[91,92] The PD-1 inhibitor-based monotherapies are typically costlier than other immunotherapies and typical cancer treatments. Age is believed to be a substantial factor for the development and progression of cancer, which might explain the age-related atrophy of the primary immunogenic organs and a general drop in immune cell production.[88] Selecting precise biomarkers would increase both the cost-effectiveness of therapy and the use of checkpoint blockade. Additionally, the cost-effectiveness of ICI combination therapy versus monotherapy is still up for dispute.[95,96]

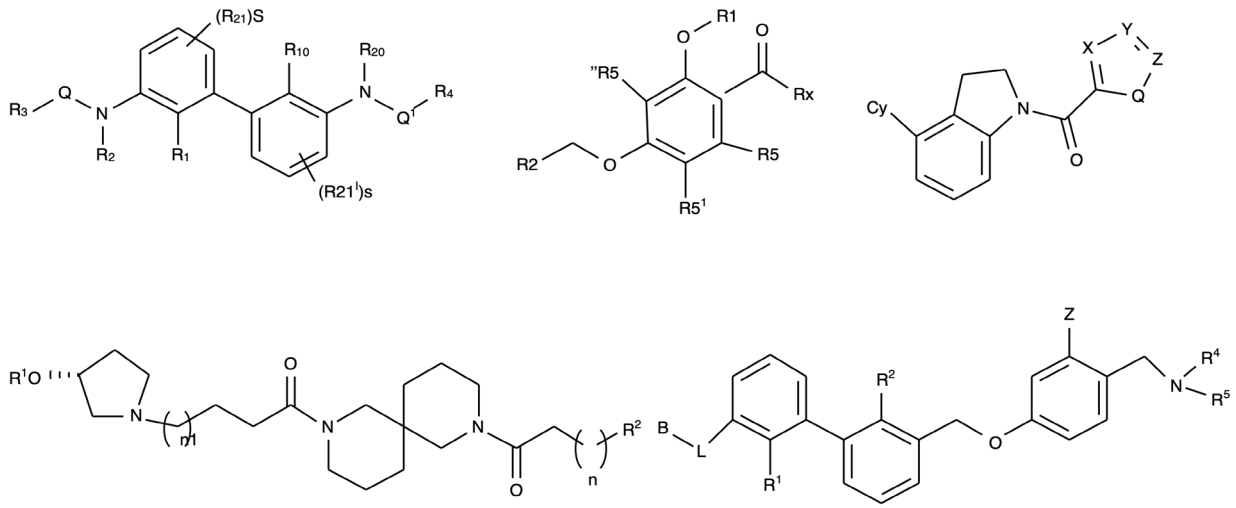

Figure 7: General structures of small molecules as immune checkpoint blockers.

Adverse effects of PD-1/PDL-1 blockers

Immune system-related adverse effects

With the breakthroughs in the use of checkpoint inhibitors against cancer, patients receiving ICI-based treatment may face several side effects due to increased T-cell activation and immune system inhibition. These side effects of ICI treatment are commonly referred to as immunotherapy-related adverse events. Adverse effects associated with checkpoint inhibitors may occur during treatment, although they frequently arise during 3-6 months of commencement of therapy and typically affect systems that have elevated turnover of cells including renal, endocrine, dermatologic and gastrointestinal systems.[97] Experiments using a mouse animal model indicated that long-term use of PD-1/PDL-1 antibodies in breast cancer resulted in serious xenogenic hypersensitivity events in contrast to anti-CTLA-4 agents. Anti-PD-1 antibodies might have adverse effects on tissues and organ systems, including GIT, liver, skin, pancreas, renal and endocrine system associated with the immune system.

Anti-CTLA-4 antibodies are generally known to have higher levels of toxicity than PD-1/PDL-1 blocking agents, whereas some organ-specific adverse effects, including pneumonitis, are observed when PD-1 inhibitors are used.[98] Pneumonitis caused by PD-1 inhibition is a significant adverse effect observed in patients with NSCLC. Other serious adverse effects such as abrupt cardiac failure due to myocarditis were also observed with the PD-1 inhibitor pembrolizumab.[99-102] The thymus plays a critical function in the tolerance of healthy organs including the heart, as well as during the majority of autoreactive T-cell removal.[103] Immunological tolerance is induced by the PD-1 and PDL-1 proteins, which also stop immune responses to cardiac antigens. Both proteins were found to be strongly activated in cardiac tissues in preclinical experiments and their dysregulation led to dilated cardiomyopathy and potentially fatal myocarditis.

Additionally, the unique reactions between PD-1 and PDL-1 produce exceptional immune modulation, detrimental cardiac immune-mediated consequences during ischemia-reperfusion injury and myocardial infarction.[104-108] Subjects with specific diseases, such as diabetes mellitus and thyroid disorders, are highly likely to experience B-cell auto-reactivity. In contrast to *de novo* immune-related adverse events caused by anti-CTLA-4 medicines, subjects with pre-existing autoimmune disorders experience higher blazes of disease when treated with PD-1/PDL-1 inhibitors than their counterparts. Globally, CTLA-4 inhibitors activate memory and naive T-cells from lymph nodes, as opposed to anti-PD-1/PDL-1 agents, which affect T cell activity locally in the outlying tissues; greater adverse effects are observed with CTLA-4 blockers than with anti-PD-1/PDL-1 agents.[109,110] Some systemic side effects associated with PD-1/PDL-1 therapy have been reported, including cardiac arrhythmia, polyradiculitis, meningoradiculitis, paresis and asystole.

Organ-specific adverse effects

With the diversity in symptoms, such as headaches, sleep problems, or mental symptoms, identifying neurologic consequences of ICI therapy remains difficult.[111] However, information on the precise occurrence of neurologic sequelae is limited and research has indicated that percentages vary from 1% to 6%.[111] Meanwhile, severe neurologic problems (e.g., non-infectious encephalitis, myasthenia gravis, Guillain-Barre Syndrome [GBS], transverse myelitis and aseptic meningitis) linked with ICI therapy are substantially less common.[111,112] Non-infectious encephalitis and myasthenia gravis are more common after PD-1/PD-L1-based treatment, but GBS or aseptic meningitis of the brain are more common after CTLA-4-mediated treatment. The precise

causes of these difficulties are unknown, but one possibility is that the blood-brain barrier and sensitization of T-cells for neuronal antigen are compromised.[112] With the expansion of ICI applications and monitoring, the incidence of ICI-linked cardiac adverse reaction has increased; however, the exact prevalence of such problems has been hard to assess.

The incidence of heart-related immunotherapy-related adverse events associated with ICI-mediated treatment is minimal, affecting fewer than 1% of individuals treated. Heart failure, pericarditis, myocarditis, arrhythmias and coronary artery disease are all examples of cardiovascular problems. Salem *et al*. discovered that adverse events related to the heart are more prevalent in men than in women, affecting all age categories and often occurring within a month of starting immunotherapy.[113] In addition, individuals with lung cancer under ICI treatment have a high chance of pericardial illness, but individuals with melanoma under ICI medication have a low risk of myocardial condition. Myocarditis and pericarditis appear frequently with PD-1-based treatment in comparison with CTLA-4-based treatment, with myocarditis having a 50% fatality risk.[113] Respiratory problems may develop in as many as 19% of ICI-treated individuals, resulting in a 1%-2% death risk.

However, pneumonitis is among the highly prevalent pulmonary problems, as well as the leading factor in mortality associated with immunotherapy-related adverse events. Individuals usually report cough, chest discomfort, hypoxia, reduced exercise tolerance and dyspnea, with manifestations appearing 3 months after starting immunotherapy. Productive coughing is unusual and could indicate another etiology. Although the evidence is inconsistent, patients receiving CTLA-4 treatment are at greater risk than the subjects taking PD-1/PD-L1 treatment. Pulmonary toxicity, such as adverse events related to other organ systems, is caused by uncontrolled T-cell stimulation to host antigens, leading to widespread parenchymal inflammatory conditions.[114-116] Moreover, renal toxicity, which may involve glomerulonephritis, acute kidney damage, IgA nephritis and interstitial nephritis, was documented in as many as 29% of patients undergoing immunotherapy.[116] The prevalent type of ICI-related kidney damage is interstitial nephritis.[117]

Additionally, ICI-associated damage to the kidneys often manifests as pyuria, hematuria, rising creatinine in the blood and increased blood pressure, with most patients presenting during the initial 2-3 months.[116] Major impairment occurs in 0.6% of the total ICI-based therapies and could be identified with uremic encephalopathy, mineral imbalances and volume overload. The combined use of nivolumab and ipilimumab induces more renal damage than individual ICI drug.[118] Creatinine values are graded according to their surge: >0.3 mg/100 mL (1.5-2.0-fold beyond the baseline (grade 1); creatinine level increase from 2.0-fold to 3.0-fold over the baseline (grade 2); creatinine level more than 3.0-fold beyond the baseline, creatinine levels of >4.0 mg/100 mL (grade 3); as well as any of the serious side effects or require dialysis therapy (grade 4). The specific cause of ICI-linked kidney failure is uncertain; however, it is thought to result from the invasion and proliferation of T cells in the kidneys, followed by exposure to local antigens.[116,119]

Hormonal imbalance was reported in up to 17% of patients receiving ICI treatment and is caused by excessive stimulation of T-cells functions toward antigen.[114,120,121] The toxicological profile comprises inflammation of the pituitary gland, hypophysitis, hypothyroidism and adrenal dysfunction.[121] The frequency of these types of adverse effects changes with hypothyroidism, hyperthyroidism and hypophysitis, affecting 6.6%, 2.9% and 17% of subjects taking ICI treatment, respectively.[114,120] Adrenal dysfunction and diabetes mellitus are notably less prevalent, occurring in only 1% of patients.[114,121] The development of signs and symptoms differ extensively. Thyroid impairment lasts 2-20 weeks, hypophysitis lasts 8-12 weeks and diabetes lasts 1-52 weeks following the start of ICI medication. Combination treatment tends to raise the possibility of hypophysitis, thyroid impairment and adrenal dysfunction, whereas the PD-1/PD-L1 treatment strategy increases the chances of diabetes mellitus.[121] Remarkably, individuals who show endocrine dysfunction might have a higher chance of ICI therapeutic efficacy in terms of treating malignancies than their counterparts.[122]

Adverse reactions related to the skin are prevalent and they usually appear 15-20 days following the start of ICI therapy.[116,123] Adverse effects associated with the skin occur in as many as 50% of individuals receiving CTLA-4 treatment and in about 40% of subjects receiving PD-1/PD-L1 therapies.[116,123,124] Less serious dermatitis (such as eczematous, lichenoid, maculopapular and psoriasiform), vitiligo and pruritus are the most common skin-related adverse effects. Bullous responses and serious dermatological adverse effects, such as severe epidermal necrolysis, Stevens-Johnson syndrome and drug reactions with eosinophilia and systemic symptoms, are uncommon.[116,123,124] The range of disease might be challenging to assess because of the broad and often imprecise symptoms of skin reactions. The form of adverse drug reactions influences grading. Non-serious dermatitis is classified as follows: signs and symptoms that do not impair quality of life (grade 1), signs that impair quality of life and necessitate treatment (grade 2), therapy failure for grade 2 toxicity (grade 3) and uncontrollable or unbearable toxic effects (grade 4).[123] Bullous disorders are classified principally by the percentage of the body's surface area impacted: grade 1 (less than 10%), grade 2 (10%-30%), grade 3 (more than 30%), or impairing the overall quality of life with electrolyte or fluid imbalance (grade 4).

Liver impairment and colitis are the two most common side effects associated with the gastrointestinal tract, after the onset of ICI treatment. Clinical manifestations of ICI-related colitis comprise stomach discomfort, diarrhea and gastrointestinal

tract inflammations, as seen by radiography or endoscopy. Gastrointestinal toxicities, such as other organ systems, are caused by the proliferation and excessive stimulation of T-cells toward the antigen. Liver toxicity is typically characterized by an asymptomatic modest increase in liver function tests, although individuals may also present with weakness, jaundice and fever. Signs often appear 2-3 months after therapy begins. Fulminant liver failure is uncommon.[123,125] Hepatotoxicity is a common side effect of ICI single-drug treatment, although it is substantially more prevalent among individuals receiving combination treatment, affecting as much as 30% of individuals.

Adverse effects related to the blood tend to be an uncommon side effect of ICI treatment, with about 100 instances recorded annually. These adverse effects include hemolytic uremic syndrome, thrombocytopenic purpura, thrombocytopenia, lymphopenia, hemophilia and ICI-induced hemolytic anemia. However, prevalent hematological consequence is thrombocytopenia, which is accompanied with ICI-induced hemolytic anemia, whereas reports of the other adverse effects are considerably few.[123,126,127] Individuals commonly experience these problems about 1-3 months after the start of an ICI, with CTLA-4 therapy having a faster median start of symptoms as compared with PD-1/PD-L1 treatment. Reduced tolerance to exercise, jaundice, drowsiness, pallor and urine that is dark in color are the signs that frequently coexist. Physicians should order a complete blood count in addition to activated partial thromboplastin time, prothrombin, reticulocyte count, total bilirubin, haptoglobin, fibrinogen and lactate dehydrogenase if patients have concerns about these disorders. A complete drug list and tests related to infection should be carried out to evaluate non-ICI causes of hematological problems.[123,126-128]

Development of resistance to IC blockers

Approximately 30%-60% of patients do not respond to PD-1/PDL-1 blockers, even though they can improve the anticancer response, cause a prolonged clinical effect and occasionally extend survival rates.[129] The Wnt/-catenin pathway, deficiencies in interferon signaling and class-I antigen presentation are some of the IC blockade resistance mechanisms that have been studied so far.[130] The adaptive resistance has also been developed against PD-1/PDL-1 inhibitory drugs in a few cases. A study revealed that the blockade of the PD-1/PDL-1 pathway leads to overexpression of mucin domain-containing molecule-3 and T-cell immunoglobulin, resulting in resistance to anti-PD-1 therapy.[131]

Adapted resistance to anticancer drugs may be broken down into mechanisms that occur through population-level alterations and modifications at the cellular level of a single cancer cell. A group of innately "fit" subpopulations of cells respond to a particular cancer treatment by expanding, whereas less "fit" cells are efficiently eliminated upon exposure to the treatment course, resulting in adapted resistance at the population level. The cells in question were part of the primary populations before treatment; however, they had the necessary traits to withstand it. In reaction to specific pressure placed on them via treatment for cancer, such types of cells survived, multiplied and overtook the original group of cells. In the aftermath of anticancer treatment, single-cell adaptation, also known as "homeostatic resistance," activates intracellular signaling pathways and modifies transcription.[131]

Adapted drug resistance to cancer treatments can be categorized into mechanisms that result from modifications at the community and individual levels. The inhibition of the presentation of the antigen mechanism represents one among the best validated and defined processes. In a study of 4,512 cancers throughout 11 different types of tumors, omissions and harmful changes in HLA-alleles and B2M, elements of the MHC-I molecules necessary for antigen presentation, have been shown to be linked to the gene expression signatures of cytotoxic immune cells. This result is in accordance with cancer downregulating antigen presentation to avoid a cytotoxic T-cell antigen-specific immune system reaction. A late-progressing tumor from a melanoma subject who had initially responded to PD-1 treatment was revealed to have adapted detrimental mutations in B2M.[132] The loss of or harmful mutation in B2M has been identified in growing tumors in three individuals via an initial reaction to treatment and two individuals with inherent resistance within an overall longitudinal cohort group of 17 subjects with melanoma receiving ICI with subsequent development.[133]

Future Directions

Some of the most important immune system regulators are ICs. ICs are currently equal to immune system inhibitor controllers. In addition to PD-1 and PD-L1, other IC proteins include SIGLEC7, HO-1, NOX2, A2AR, KIR and BTLA. Additionally, the stimulatory ICs, including GITR, OX40, CD137, CD122 and CD40, are attractive targets for immune treatment. T cells can identify and obstruct prospective challenges by depending on neoantigen produced on cells in tumors. Tumor cells seek for inhibitory chemicals to attach and mute immune system cells to bypass the immune system of the host. Immune blockade of checkpoints was demonstrated to be a useful adjunct therapy in the management of tumors. Some cancers, however, have minimal immunogenicity and do not efficiently react to IC blockage. Given the heterogeneity of cancers and the choice of low immunogenic clones, non-responders-whose percentage ranges between 4% and 29%-will experience numerous recurrences and potentially high progression.[134]

Resistance is a term used to describe this phenomenon.[135] The inherent mechanisms include overexpression of additional ICs, modification of several suppressive pathways of signaling and absence of tumor presentation of antigens. In the tumor microenvironment, external processes are commonly referred

to as different elements.[136] Scientists are working to reduce the incidence of resistance and treat individual problems. When implementing a basic concept, many techniques must be used, including modulating the tumor microenvironment, activating T-cell stimulation, enhancing costimulatory signals and decreasing the amount of suppressive immunological signals.[137,138] The process of drug development is not an easy task. Multiple research efforts to create novel therapies aimed at ICs were abandoned because of poor response and deadly immunotherapy-related adverse events. Immunotherapy-related adverse events brought on by ICI are a major challenge we have yet to overcome, with mortality as the most serious repercussion. A clinical study (NCT03489369) about Sym022 (anti-LAG-3 mAb) in patients including cancer with metastatic tumors that are solid or lymphomas showed an unfavorable result with high recurrence and spread and immunotherapy-related adverse event rate. Additional information must be provided about the mechanics of ICI. Further research is required to better understand specific pathways, accomplish promising goals and mitigate negative consequences for individuals with cancers and other disorders.

CONCLUSION

The PD-1/PD-L1 blocking antibodies have been successfully utilized as immunotherapeutic agents to treat several malignancies. This review addresses the growing interest in developing immunotherapy that utilizes primarily PD-1/PD-L1 as a potential target for antitumor therapy. Developing small molecules and peptides targeting ICs will improve the prospects of cancer-related medical care. Understanding the advancements in scientific research directed toward the development of chemical frameworks, preparation of novel compounds and cytotoxic chemotherapy is essential to maximize the benefits of this new emerging field of cancer therapy. Immunotherapeutic drugs are expected to play a crucial function in cancer management, mainly by enhancing the sensitivity of cancer cells to PD-1/PD-L1 interactions. Therefore, IC inhibition is a promising method for treating cancer, despite its limitations.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

PD-L1: Programmed death ligand-1; **PD-1:** Programmed death-1; **OS:** Overall survival; **ICI:** Immune checkpoint inhibitor; **mAbs:** Monoclonal antibodies; **CTLA4:** Cytotoxic T-lymphocyte-associated antigen 4; **APCs:** Antigen-presenting cells; **TCR:** T-cell receptor; **M:** Monocyte; **irAEs:** Immune-related events; **HEK:** Human embryonic kidney; **ADTL:** Aurigene Discovery Technologies Limited; **NSCLC:** Non-small cell lung cancer; **dMMR:** Mismatch repair deficit; **PFS:** Progression-free survival.

SUMMARY

Immune checkpoint inhibitors are used to treat cancer by blocking checkpoint proteins that prevent the immune system from attacking cancerous cells. PD-L1 and PD-1 inhibitors have shown clinical success in treating solid tumors. This review covers the basics of cancer immunotherapy, immune checkpoints, inhibitors, chemistry, clinical status, adverse events, resistance and future prospects.

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