The Implications of Immunotherapy in Tumor through Targeting the Immune Checkpoints Inhibitors PD-1 /PD-L1.

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Abstract

In the last several years, immune checkpoint inhibitors (PD-1/PDL1) are currently looked at more positively to be a potential targeted treatment for cancer therapy for addressing tumor immune evasion. Specifically, checkpoint molecules such as programmed cell death protein 1 (PD-1) exhibit potent immunomodulatory properties by functioning as inhibitors of T-cell activation. Various forms of human cancer have been observed on the cell surface displaying the immune checkpoint known as programmed death-ligand 1 (PD-L1) (He et al., 2018), several kinds of cancer include kidney (Curran and Kopp, 2021), breast cancer (Erber and Hartmann, 2020), bladder (Eckstein et al., 2019), and ureter (Stenehjem et al., 2018), in addition to non-small cell lung cancer (NSCLC), (Pawelczyk et al., 2019), cancer of the pancreas (Liu et al., 2022b), esophageal cancer (Whooley et al., 2022), squamous cell carcinoma of the head and neck carcinomas (Crosta et al., 2021), and renal cell cancer (RCC) (Munhoz and Postow, 2018). Furthermore, Activated T cells are less effective at combating tumors when PD-L1 binds to its corresponding receptor, PD-1, blocking the transmission of signals designed to activate these cells. Following treatment with PD-1-PD-L1 inhibitor antibodies, there have been documented cases of tumor regression in patients with a variety of advanced cancer types. The findings of this study suggest that the presence of PD-L1 on tumor cells and other cellular elements in the tumor microenvironment has therapeutic implications. This review aims to investigate the structure and functions of the PD-1-PD-L1 axis within the framework of cancer. This study will primarily examine crucial elements including the therapies for PD-1 and PD-L1, the corresponding antibodies, and prospective innovative therapeutic strategies for future investigations. Extensive research is necessary in the coming years to determine the efficacy of immunotherapy, particularly PD-1 with PD-L1 immune checkpoint blockade, as a potential beneficial application in cancer treatment for specific cancer subtypes.

Keywords: Tumor; immunomodulatory treatment; the programmed cell death protein 1 (PD-1) and its ligand PD-L1.

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Introduction

Cancer is the uncontrollable development of cells in humans, and many forms of cancer currently lack treatment options. Delayed diagnosis of cancer performs a crucial role during the process of resistance to therapy. Nowadays, immunotherapy is recognized as can be a part of the most effective methods for cancer treatment, considered effective for tumors resistant to chemotherapy and/or radiotherapy, with fewer side effects compared to conventional therapies (Abdullah, 2019) (Wiersma et al., 2015).

In the past decades, surgical cancer treatment is generally followed by chemotherapy and/or radiation therapy(Abdullah et al., 2022). However, these therapies are unable to differentiate between healthy cells and malignant cells, posing an excessive danger. The immune system, on the other hand, can distinguish between regular cells in the body and foreign entities. Immunotherapy utilizes this ability by targeting foreign cells while sparing native cells (Nicholson, 2016). Consequently, many scientists have focused on identifying specific cancer antigens for the development of effective cancer vaccines and antigen-specific T lymphocytes, which form the basis of immunotherapy (Farkona et al., 2016) (Pandya et al., 2019). Immunotherapy works by inducing an immune response to eliminate cancer cells (Ventola, 2017).

As immunological expertise expanded, T-cells have emerged as crucial players in the immune system response to malignancy, effectively eliminating cancerous cells and combating external threats (Raskov et al., 2021). Dendritic cells located within lymph nodes perform a crucial function by facilitating the stimulation and activation of T-lymphocyte cells. This process ultimately allows for the infiltration of T-cells into the cancer microenvironment, which includes tumour cells as well as other immune cells that have infiltrated the cancerous area (Marciscano and Anandasabapathy, 2021). The activation of T-cells recognises, bind to, with eliminate tumors cells. Additional T-cells engage in interactions with dendritic cells and other MHC class II antigen-presenting cells by recognising antigens presented on MHC class II molecules (Marciscano and Anandasabapathy, 2021). The T-cell receptor (TCR) is essential for T-cell activation and so plays a crucial role in controlling this interaction (Shah et al., 2021). In addition to their primary receptors, T-cells also express other receptors such as CD28, which serves as a co-stimulatory receptor and engages with CD80 and CD86 molecules found on dendritic cells (Kennedy et al., 2022). This interaction elicits the secondary activation signal for T-cells. Furthermore, the activation of T-cells is facilitated by cytokine signalling, specifically through the action of Il-2, which serves as a third signal. (Disis, 2010).

In the last decade, the utilization of "checkpoints" for instance, the programmed death ligand-1(PDL-1), has gained significant attention. PDL-1 is among the inhibitory ligands that contribute to sustaining in the homeostasis of immune regulation under normal conditions; nevertheless, it is found to be present in many malignancies (Gutic et al., 2023). Abundant expression of PDL-1 in tumors can assist them in evading the immune system, particularly interferon-gamma is secreted as a result of T-cell activation, which triggers this process (Qian et al., 2018). This leads to an overexpression of PDL-1 on both invading immune cells and cancer cells (Han et al., 2020). The interaction between PDL-1 and its receptor B7-1 (also known as CD80), follow by T-cell activation surface PD-1 expression inhibits cytotoxic T-cell function, as illustrated in Figure 1. PDL-1 and PD-1 are critical components that need to be activated for proper immune cell functioning. PDL-1 is commonly located on the outer layer of cancer cells that have been stimulated by interferon-gamma, PD-1 is commonly observed membrane-expressed antigens to be produced by the immune system (Ghosh et al., 2021).

Utilising the immune checkpoint molecules known as PD-1 with PDL-1has been recognised as a crucial aspect influencing the outcomes of immune checkpoint inhibitors (Figure 1). This approach can be implemented through various strategies, including: (i) understanding the mechanism of PD-1 and PDL-1; (ii) elucidating how PD-1 immunotherapy suppresses the anti-tumors immune response; and (iii) exploring treatment strategies to stimulate the immune response for combating cancer. This review is aimed at highlighting the essential function that immunotherapy plays in the treatment various cancers. and to explore novel prospects for developing effective combination therapies based on immuno-oncology that target the protein that inhibits cell death 1 (PD-1) and its ligand, PD-L1 signalling in high cases of cancer. Consequently, these advancements pave the way for potentially revolutionizing

cancer therapy, with promising clinical applications in the future.

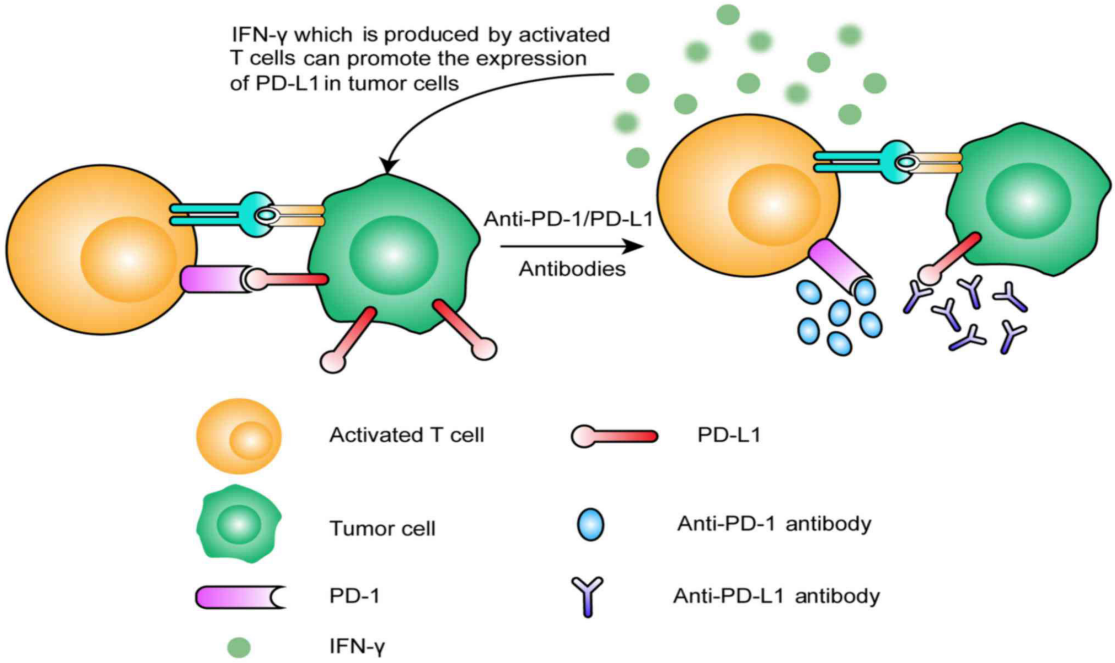

Figure 1. Outline of PDL-1 in the checkpoint immunity system. The immune checkpoints are regulators of immune activation (Fan et al., 2019). T-cells recognise tumour antigens presented by APCs to TCRs; however, the T-cell activation requires a second indication, known as the co-stimulatory signalling, following TCR binding; Co-stimulatory molecules bind to their ligands, such as B7 on APCs. Once these molecules bind to their ligands on the surface, T-cells stimulate immunological response. against cytotoxic antigens, simultaneously, when APCs come into contact with B7-1 or B7-2 (Abdullah, 2019), they also transmit suppressive messages. Furthermore, PDL-1 on activation of T-cells and tumour cells releases the cytokine interferon-gamma (IFN-), which may upregulate expression of programmed death ligand 1 (PD-L1) in malignant cells, allowing immunological escape (Fan et al., 2019).

The biological structure of PD-1 and its corresponding ligand.

PD-L1, also known as programmed cell death ligand 1 or CD274, is a protein that is produced by the PDCD1 gene. It is the protein that is responsible for the creation of CD274 (Kalim et al., 2020). The term CD274 is used to identify this molecule specifically (Wu et al., 2022). Its nomenclature as enhancement upregulation of PD-1 arises from its heightened presence in response to apoptotic stimuli observed in two distinct cell lines, namely 2B4.11 and LyD9t, which are involved in apoptosis (Fabrizio et al., 2018). In contrast to the T cell membrane, which expresses programmed cell death protein 1 (PD-1) at extremely high degrees, the B cell membrane only sometimes shows signs of expressing it (Han et al., 2020, Ishida et al., 1992). Structurally, PD-1 is characterised by its structural composition, which includes a type 1 transmembrane glycoprotein arrangement. This structure consists of a cytoplasmic tail and a single extracellular domain known as the immunoglobulin variable (IgV) domain. The IgV domain, containing a sequence of twenty amino acids, demonstrates a noteworthy characteristic of extending beyond the plasma membrane in the extracellular region (Patsoukis et al., 2020b). Additionally, the results show that 23 per cent of the sequence is identical to cytotoxic T lymphocyte antigen-4 (CTLA-4) (Chou et al., 2022). The PD-1 cytoplasmic domain indicates the existence of two tyrosine motifs. An acronym for tyrosine-based switch motif, ITSM stands for "immune receptor signalling inhibitor," and it is responsible for blocking immune receptor signalling (Qi et al., 2020). It represents an inhibitory motif that is frequently observed in immune receptors and is centred around the amino acid tyrosine

(Intlekofer and Thompson, 2013). Numerous Studies recently released data confirming the essential role that the intracellular tail of PD-1, also known as ITSM, plays in enhancing the immune-suppressive actions produced by PD-1 on activated T cells (Jiang et al., 2019b). Both programmed death ligand 2 (PD-L2 or B7-DC, also known as CD273) and programmed cell death protein l (PD-L1 or B7H1, commonly referred to as CD274) are members of the PD-1 ligand family and are categorised as class I glycoproteins (Jin et al., 2011). The ligands under consideration exhibit common structural features, such as The addition of immunoglobulin variable (IgV) and immunoglobulin constant (IgC) domains, as well as a transmembrane domain that is marked by hydrophobic characteristics, and a cytoplasmic tail (Li and Li, 2023). There is a significant amount of sequence conservation between the PD-L1 and PD-L2 molecules which are encoded by genes located on chromosome nine. Within the microenvironment of malignancy, an interaction between programmed cell death protein 1 (PD-1) and its ligand, programmed death-ligand 1 (PD-L1), is observed (Bolandi et al., 2021). The protein programmed death-ligand 1 (PD-L1) is expressed not only by antigen-presenting cells (APCs) but also by malignant cells. However, the appearance of PD-L1 is the major sign of T-cell activation (Liu et al., 2022a). Protein tyrosine phosphatase-2 (SHP-2) is attracted to phosphorylated tyrosine residues in the immunoreceptor tyrosine-based switch motif (ITSM) of PD-1 (Patsoukis et al., 2020a). The following signalling mechanisms are set off by this phosphorylation, which also inhibits the synthesis of cytokines and the cytotoxicity of T- cytotoxic lymphocytes (CTLs), among other biological activities of T-lymphocytes cells (Ross and Cantrell, 2018). It is possible that the interaction between the PD-1 receptor and its ligand, PD-L1, might result in a decline in the population of T-cells that are especially focused towards tumors. Eventually, more of these T-cells may die, which would allow tumor cells to avoid being attacked by T-lymphocyte cells. (Wang and Wu, 2020).

The role of PD-1/PDL-1 molecules and their respective functions in cancer cells.

Different types of immune cells express the PD-1 programmed cell death protein, including T-lymphocytes, B-lymphocytes, monocytes, dendritic cells, regulatory T-cells, and natural killer T cells (Zhang et al., 2020). The indicated evidence of a lack of T cells is notably observed in instances of protracted viral infections and malignancies (Wherry and Kurachi, 2015). A significant number of tumor-infiltrating lymphocytes (TILs) from a wide variety of tumors types have been shown to exhibit the protein PD-1 (Evangelou et al., 2020). Immunosuppression is present when tumor microenvironment (TME) contains activated Treg cells (Paluskievicz et al., 2019). Additionally, The activation status of CD4+ TILs can be detected by their increased PD-1 expression in Treg cells(Liu et al., 2021). Additionally, Increased PD-1 expression in CD8+ TILs may indicate cytotoxic T lymphocyte (CTL) exhaustion or dysfunction (Dolina et al., 2021). Recent studies have indicated that Macrophages that are associated with tumors (TAMs) express PD-1 in both mice and humans, impairing their ability to phagocytose malignancy cells (Peranzoni et al., 2018). However, the enhancement of phagocytosis can be achieved by blocking the interaction between PD-1 and PD-L1and reduces tumor growth. Programmed death-ligand 1 (PD-L1) exhibits a common occurrence of increased expression in neoplastic cells found in both solid tumors and hemangiomas (Jiang et al., 2019b). There exist various immune cell types, such as T cells, B cells, macrophages, dendritic cells (DCs), and mast cells, which originate from the bone marrow. However, it is worth noting that this specific characteristic is not limited solely to immune cell populations, but is also observed in certain non-immune cells (Patel et al., 2021). Cancer cells and antigen-presenting cells (APCs) can respond to type 1 and type 2 interferon stimulation by upregulating PD-L1. Activated macrophages and dendritic cells are where PD-L2 is most commonly found, despite the fact that PD-1 expression is ubiquitous (Dong et al., 2017). Furthermore, there is evidence that PD-L1 is expressed in the microenvironment of tumors, specifically in suppressor cells that are generated by myeloid cells, dendritic cells (DCs), and tumor cells (Peng et al., 2020). In colon cancer, myeloid-derived suppressor cells (MDSCs) with elevated levels of programmed death-ligand 1 (PD-L1) maintain an inhibitory role by dampening T cell activation (Weber et al., 2018). Additionally, Head and neck squamous cell cancers have been linked to high numbers of CD4+ and CD8+ tumor-infiltrating lymphocytes (TILs) and PD-L1 expression on tumor-associated macrophages (TAMs) (Li et al., 2021). The protein known as PD-L1 has been identified in plasma cells, as well as in specific sub-populations of dendritic cells, in instances of multiple myeloma (Ahn et al., 2021). Anti-PD-1/anti-PD-L1 antibody performance in stimulating anti-tumor T-cells can be compromised by the existence of PD-L1+ plasma cells and CD141+ mature

DCs (Costa et al., 2021). Consequently, the potential of this response as a therapy option that is both viable and effective for people suffering from multiple myeloma has become apparent (Kyle and Rajkumar, 2009). However, Autoimmune disorders, viruses, and their pathogenesis all depend heavily on the PD-1/PD-L1 pathway (Velu et al., 2015), organ transplantation immunology, and cancer immunity (Zhang et al., 2021). In healthy individuals, this pathway functions to prevent excessive tissue inflammation and autoimmune diseases by inducing and maintaining peripheral immunological tolerance(Qin et al., 2019). Tumor immune evasion takes place tumor-infiltrating lymphocytes (TILs) have their activation and programmed cell death inhibited when the programmed death 1 (PD-1) receptor interacts with PD-L1 (Vathiotis et al., 2021). Furthermore, this interaction has the effect of inhibiting the synthesis of cytotoxic T lymphocyte (CTL) granular enzymes and perforin, while also reducing the secretion of inflammatory mediators including interferon-gamma, interleukin-2, and tumor necrosis factor-gamma (Cunningham et al., 2021). Additionally, It promotes the synthesis of IL-10, an immunosuppressive cytokine that blocks the maturation of T-cell responses (Iyer and Cheng, 2012). In order to specifically target cancer cells, therapeutic approaches that make use of inhibitors of the PD-1/PD-L1 pathway have been used. It is essential to point out, however, that based on our present knowledge of the molecular mechanisms at play, it appears that only a small percentage of patients have experienced complete and long-lasting remission from their disease (Sun et al., 2020).

Checkpoint inhibitors that specifically target programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) in the context of cancerous cells.

Evidence suggests that tumor cells can produce highly abundant levels of inhibitory signalling molecules (Jiang et al., 2019a). Tumor-induced immune suppression, which acts as an immunological gate, is a critical checkpoint mechanism in this network(Kim and Cho, 2022). The proteins PD-1 and PD-L1, also known as programmed cell death 1 and its corresponding ligand, respectively, are responsible for the regulation of this process. PD-1 is also known as programmed cell death 1, while PD-L1 is known as programmed cell death-ligand 1 (Salmaninejad et al., 2019).

Many different types of malignant tumor cells express PD-L1 (Akhtar et al., 2021), nonetheless, PD-1 is highly expressed in lymphocytes that are actively involved in immune system responses, including T cells, B cells, dendritic cells, and natural killer cells. PD-L1 is also present in many different kinds of healthy cells (Han et al., 2020). According to the findings of a number of studies, decreasing the amount of interaction that occurs between PD/1 and PD/L1 results in a better immune response from T cells and greater antitumor effectiveness (Seifert et al., 2017). However, The extracellular receptor known as programmed cell death protein 1 (PD-1) acts as a regulatory control for the action of effector cells that are involved in the process of cell depletion. When The suppression of T-cell activation is the end result of the contact between the programmed death-1 (PD-1) receptor and its ligand, programmed death-ligand 1 (PD-L1). This connection plays a critical role in mediating signal transduction, which ultimately leads to the inhibition of T-cell activation (Hudson et al., 2020) (Figure 2). Since solid tumors and antigen-presenting cells within tumor tissues can maintain the viability of cancerous cells by increasing their expression of PD-L1, there is significant interest in developing anti-PD/1;/PD/L1 antibodies as a potential cancer treatment (Zanello et al., 2022). Malignant cells can sustain their survival mostly under conditions where the levels of PD-L1 are elevated (Balar and Weber, 2017). There have been significant developments in immunotherapy, particularly in the clinical testing and application of checkpoint inhibitors. These inhibitors include antibodies that target PD1 and CTLA-4 as immunological checkpoints (Wojtukiewicz et al., 2021). By blocking the interactions between these checkpoints and their ligands, these inhibitors help to enhance the immunological response against tumors and restore the immune cell activity against cancer cells. In contrast to the mechanism of action exhibited by anti-CTLA-4 antibodies, which function by inhibiting the function of CTLA-4 on T cells, anti-PD-1 antibodies specifically target PD-1 receptors on T cells (Seidel et al., 2018). Both classes of inhibitors have demonstrated encouraging outcomes in clinical tests and have received regulatory approval for the treatment of a variety of cancers (Naimi et al., 2022). The demonstrated capacity to improve overall survival rates and achieve solid responses in patients establishes their significance as viable therapeutic options in the fight against cancer (Shiravand et al., 2022). Melanoma, a highly mutated form of human cancer, has exhibited a remarkably high rate of response to anti-PD-1 therapy, ranging from 30 to 40%.

(Gellrich et al., 2020). Immunotherapy with ICI has also exhibited promising results in germ cells testicular cancer that is resistant to platinum-based treatments with the remarkable outcomes observed, immunotherapy drugs have the potential to emerge as the fundamental treatment approach for several different kinds of cancer (Kalavska et al., 2020). In contrast, the effectiveness of PD-1 pathway-blocking antibodies in treating cancers, such as pancreatic and prostate cancer, which have lower median mutational loads, has been limited. The receptor known as programmed cell death protein 1 (PD-1), also referred to as CD279, exhibits co-inhibitory characteristics. Following antigen stimulation, the presence of T-cell activation is discernible on the outer membrane (Figure 2) (Xu et al., 2021). Additionally, mast cells, dendritic cells, and macrophages have all been found to express PD-L2 (Topalian et al., 2016). The protein PD-L1 has been identified in various categories of hematopoietic cells (Leon et al., 2020).

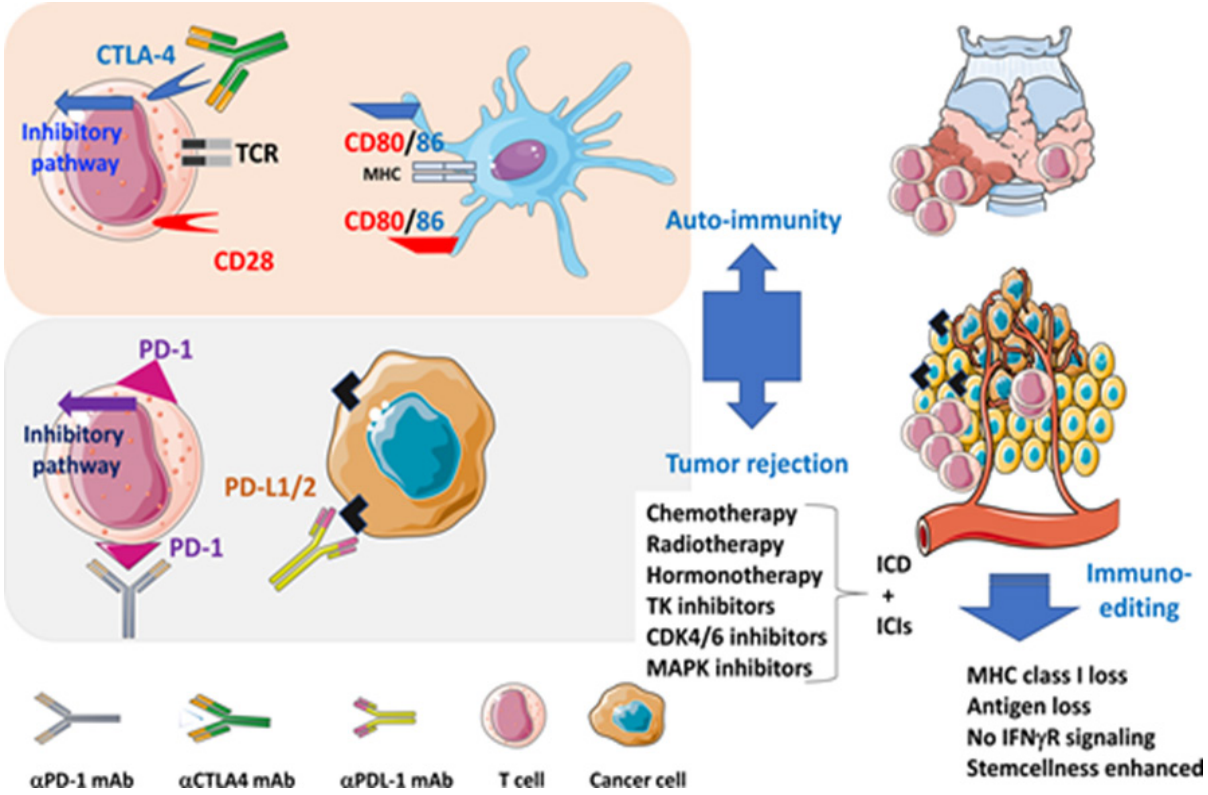

Figure 2. A diagrammatic image showing the primary tumour microenvironment, antigen-presenting cells known as dendritic cells are responsible for the processing of particular tumour peptides (TAA) and the subsequent association of those peptides with major histocompatibility complex (MHC) molecules. Dendritic cells are categorised as professional antigen-presenting cells (APCs). (Kroemer and Zitvogel, 2021).

Clinical applications of therapies targeting the blockade of PD-1 and PD-L1

PD-1 and PDL-1 blocking antibodies

Cancer immunotherapy induces the expansion of cancer-fighting T lymphocytes, which then eliminate malignant tumors by recognizing and targeting their presenting antigens (Abdullah et al., 2022). Monoclonal antibody molecules, commonly referred to as MAbs, have exhibited significant promise in the eradication of malignant tumors by selectively interacting with the programmed cell death protein 1 (PD-1) and its ligand, PD-L1 (Salmaninejad et al., 2019). Three anti-human PD-1 antibodies combine active immunization and nonspecific immune activation(Wang et al., 2018b). Nivolumab and pembrolizumab are representative examples of antibodies that have exhibited promising therapeutic capabilities about cancer therapy. The Food and Drug Administration (FDA) declined to issue their approval for the use of immunotherapy in the treatment of melanoma, non-small cell lung cancer, and other types of

malignancies until the year 2014 (Raedler, 2015b). In the year 2018, licensure was granted by the United States for the third-generation cemiplimab, which was designed to treat advanced or metastatic cutaneous squamous cell carcinoma (Migden et al., 2018). Pidilizumab, AMP-224, AMP-514, and PDR001 are not yet in clinical trials(Jiang et al., 2019b). Table 1 presents the indications of PD1/L1, antibody classes, and the side effects associated with FDA approval

Table-1

FDA-approved medications for immunotherapy of cancer

Target	Name of the medications	Route of administration	Purpose of using	Antibodies classes	Side effect
PDL-1	Avelumab (Bavencio)(Guo et (al., 2020	Intravenously (.(i.v	Malignant Merkel cell metastatic disease NSCLC cancer	IgG1	Body aches, swelling in the extremities, Bowel issues and a giant in weight
	Atezolizumab (Tecentriq)(Apo(lo et al., 2017	Intravenously (.(i.v	Urothelium, breast, bladder transitional cell cancers and carcinoma of the kidney	IgG1	Loss of appetite, dyspnea, dizziness .and coughing
	Duravulumab (Imfinzi)(Anto(nia et al., 2017	Intravenously (.(i.v	Cancer of the squamous cells of the head and .neck	IgG1κ	Bladder discomfort, oedema in the face, arms, hands, lower legs, or feet, tightness in the chest, shivers and sneeze
PD-1	Nivolumab(Overman et (al., 2017	Intravenously (.(i.v	NSCLC) cancer) .Liver cancer Lymphoma of the Hodgkin .type	IgG4	.Backache Skin blistering, peeling, or loos.ening Pain in the bones, joints, or .muscles Burning, numbness, tingling, or .unpleasant feelings are all possible .Taste changes or is lost Tightnetumour-associated
	Pembrolizumab(Robert et al., (2014	Intravenously (.(i.v	Metastatic melanoma	IgG4 kappa	They include a reduction in white blood cell count. and platelets in the bloodstream, diarrhoea and stomach ache
	Cemiplimab(Migden (et al., 2018	Intravenously (.(i.v	Cutaneous squamous cell carcinoma	IgG4	Hands or feet that are numb, muscle or bone pain; nausea, diar.rhoea, and lack of appetite

Nivolumab

The monoclonal antibody nivolumab is an IgG4 antibody that has been modified to have human-like properties and is targeted at the protein PD-1 (Opdivo, BMS-936558, MDX1106) inhibits the binding of PD/1 to its specific receptor, PD/L1 (Guo et al., 2017). The FDA granted Nivolumab approval in December 2014 for advanced cancer treatment or metastatic melanoma, marking an important milestone in its medical application(Robert et al., 2015a). Nivolumab was granted approval by the FDA in March 2015 for its use in the therapeutic management of metastatic squamous-cell non-small cell lung cancer. This term refers to the methods and treatments that are used to treat and control the spread of this type of cancer in addition to the lungs, and it provides patients who have this condition with an additional treatment option (Borghaei et al., 2015). Moreover, Nivolumab has exhibited notable effectiveness in combating a variety of cancers, including melanomas and non-small cell lung tumors (NSCLC), and hepatocellular cancer, indicating its broad potential in treating diverse malignancies (Lepik et al., 2020) (El-Khoueiry et al., 2017). The findings of the study indicate that Nivolumab exhibited promising outcomes in terms of cancer response and extended periods of disease remission in individuals diagnosed with non-small cell lung cancer (NSCLC) (Sundar et al., 2015). The overall response rate (ORR) was determined to be 23.7%, while the progression-free survival (PFS) was observed to be 91.1 days (Sato et al., 2018). Furthermore, it is important to note that around 80% of individuals diagnosed with Hodgkin's lymphoma experienced a minimum of three years of survival (Shanbhag and Ambinder, 2018). Moreover, the median duration of progression-free survival (PFS) fell within the range of 12 to 18 months (Goldkuhle et al., 2018) Adverse reactions such as pneumonia, colitis, and hepatitis, adrenal insufficiency, hypothyroidism, infusion reactions, cough, upper respiratory infection, peripheral edema, and fatigue have been reported (Ryder et al., 2014).

Pembrolizumab

Pembrolizumab (Keytruda, MK-3475) is The monoclonal antibody under consideration is designed to specifically target the programmed cell death protein 1 (PD-1) and has a significant binding affinity, as described by Longoria and Tewari (2016). Pembrolizumab is derived from lambrolizumab, which also targets PD-1. Pembrolizumab received FDA approval in 2014 (Keytruda, MK-3475, lambrolizumab) (Longoria and Tewari, 2016) specifically for addressing metastatic melanoma (Raedler, 2015a). The Phase I clinical trials conducted for melanoma provided evidence regarding the effectiveness and safety of pembrolizumab (Hamid et al., 2013), Additionally, the findings from Phase II clinical trials demonstrated a positive effect of pembrolizumab on metastatic melanoma, particularly when compared to ipilimumab, an antibody that specifically targets CTLA-4 (Robert et al., 2015a). The study findings revealed that Pembrolizumab was found to have a 33% objective response rate (ORR) in people with advanced melanoma (Robert et al., 2015b, Ribas et al., 2016). However, research on Pembrolizumab kinetics revealed that while its peak and trough levels remained essentially unchanged, over time, As doses were increased, the area under the plasma concentration-time curve increased (resulting in increased clearance and a wider AUC)(Longoria and Tewari, 2016).

Cemiplimab

The first checkpoint inhibitor that has received authorization from the FDA (Food and Drug Administration) was specifically developed for The primary therapeutic intervention employed for the management of advanced cutaneous squamous cell carcinoma (CSCC) involved the utilisation of cemiplimab (Libtayo), an anti-PD-1 antibody characterised by its high affinity (Fala, 2023). The results of a phase 1 clinical trial evaluating the efficacy of cemiplimab as a treatment for advanced cutaneous squamous cell carcinoma (CSCC) have demonstrated an extended response (Rischin et al., 2021), with no evidence of disease recurrence observed for a duration of up to 16 months following treatment (Naik, 2021) An expansion phase I study showed a 50% response rate and a durable impact, while a phase

II study revealed a 47% objective response, with adverse effects comparable to other PD-1 inhibitors (Migden et al., 2018). Common adverse effects of cemiplimab therapy include muscle or bone pain, rash, itching, nausea, and diarrhoea (LP, 2017). There are several anti-PD-L1 monoclonal antibodies available on the market. The FDA authorized atezolizumab, avelumab, and durvalumab in September 2014, May 2016, and May 2017, respectively. BMS-936559 and CK-301 are currently in the research and development stage (Akinleye and Rasool, 2019).

Atezolizumab

The monoclonal antibody atezolizumab (Tecentriq) is an Fc fragment of human IgG1 origin that was engineered using phage display technology (Alfaleh et al., 2020). It blocks tumor-surface PD-L1 and has shown potential for cancer treatment (Krishnamurthy and Jimeno, 2017). Since, the Fc portion of atezolizumab can undergo gene editing to reduce its antibody-dependent cell-mediated cytotoxicity (ADCC) effect (Powles et al., 2014). In May 2016, Atezolizumab is the first PD-L1 inhibitor to be approved by the Food and Drug Administration (FDA) for the therapeutic management of urothelial carcinoma. This authorization makes it possible for atezolizumab to take its place as the first PD-L1 inhibitor (Ning et al., 2017). Positive treatment responses with atezolizumab have been documented in various other malignancies, that includes renal cell carcinoma, transitional cell carcinoma of the urethra, and breast cancer (Balar et al., 2017). In a clinical trial, 62 people with renal cell carcinoma were given atezolizumab to test its efficacy and safety (Bosma et al., 2022). The results indicated an objective response rate (ORR) of 26% (Hodi et al., 2010). Additionally, The objective response rate (ORR) of treatment of advanced transitional cell bladder cancer with atezolizumab was found to be 26%, whereas for breast cancer treatment, the reported ORR was 10% (Bernard-Tessier et al., 2018) (Jiang et al., 2019b). Common adverse drug reactions associated with atezolizumab include fatigue, pneumonitis, colitis, inflammation of the thyroid, pituitary, and/or adrenal gland (0.4%), ocular inflammation, and infusion-related reactions (Corp., 2014).

Avelumab

Merck and Pfizer made an announcement in November 2014 regarding the development of avelumab, which is marketed as Bavencio and identified by its designation (MSB0010718C), is described as a monoclonal antibody of the IgG1 class that targets PD-L1 and is fully derived from human sources (gangolf.schrimpf, 2023). The intrinsic Fc region of Avelumab shows the ability to initiate antibody-dependent cell-mediated cytotoxicity (ADCC) by activating inactive T cells and inhibiting PD/L1. Furthermore, the administration of Avelumab demonstrated a notable objective response rate of 62.1% among patients diagnosed with metastatic Merkel cell carcinoma (D'Angelo et al., 2018). However, lung non-small cell carcinoma's overall response rate was only 12% (Gulley et al., 2017). Avelumab therapy is associated with the occurrence of exhaustion as a side effect, body aches, swelling in the extremities, bowel issues (both loose and hard stools), endocrinopathies, Crohn's disease, gastrointestinal and autoimmune disorders, as well as infectious diseases such as pneumonia and hepatic conditions. These results were published in 2018 (Bernard-Tessier et al., 2018).

Duravulumab

Imfinzi is a monoclonal antibody that targets immunoglobulin G1 kappa (also known as IgG1). Durvalumab (also known as Imfinzi) falls into this category that has undergone humanization to closely resemble endogenous human antibodies (Faiena et al., 2018). It inhibits the interaction between programmed death ligand 1 (PD-L1) and programmed death receptor 1 (PD-1), thereby preventing T-cell communication (Syed, 2017). Research investigating the administration of durvalumab therapy in individuals diagnosed with head and neck squamous cell carcinoma (HNSCC) resulted in an overall response rate (ORR) of 9.2% (Qiao et al., 2020) (BioIntron, 2021). Furthermore, it is currently being discussed what the progression-free survival rate is after six months for individuals who have been diagnosed and squamous cell carcinoma of the head and neck (HNSCC) was 20%, with a higher incidence of 25%

only in patients with a positive PD-L1 test result; progression-free survival rate (PFS) was not significantly different (Wise-Draper et al., 2022). However, In NSCLC patients, the ORR with durvalumab reached 66.3% (LP, 2017). Adverse reactions to durvalumab treatment include lethargy, urinary tract infections, muscle and joint discomfort, constipation, loss of appetite, peripheral oedema, infusion reactions, infections (such as pneumonia, hepatitis, colitis, hypothyroidism, and hyperthyroidism), and rashes(Lou et al., 2022).

Side effects of checkpoint inhibitors

antibodies of PD-1 generally exhibit reduced lethal and milder adverse effects in comparison to alternative therapeutic interventions (Wang et al., 2018a). However, they can still lead to significant adverse effects, including pneumonitis, which can occasionally result in death (Wu et al., 2017). Immune checkpoint inhibitors are commonly used for treating various types of cancer, but their potentially severe side effects pose a challenge (Ardolino and Joshua, 2019). Although combining two medications can enhance the effectiveness of cancer treatment such as melanoma, it is also associated with increased toxicity (Smalley et al., 2016). No evidence exists to indicate that managing toxicity through immune suppression compromises efficacy. Utilizing other checkpoint inhibitors can also be beneficial in boosting the patient's immune system, which performs a fundamental part in innate immunity (Achkar and Tarhini, 2017).

Promising advancements can be achieved through the utilisation of alternative checkpoint inhibitors that boost the immune system, a fundamental component of the body's natural immunological response within the patient (Darvin et al., 2018). The use of antibody-drug conjugates in combination with radiotherapy, either internal (via radioimmunotherapy) or external (through conventional beam radiotherapy), shows promise in cancer treatment (Dean et al., 2021). Prioritizing the management of suppurative symptoms is crucial, but it also carries risks for patients who choose this therapeutic approach. In conclusion, significant improvements can be achieved through the examination of multiple checkpoint inhibitors for enhancing the patient's immune response, with a simultaneous focus on wary toxicity monitoring and management, as well as the exploration of alternative therapeutic approaches.

Summary and future perspectives

The recent success of several immunotherapies, particularly checkpoint inhibitors, has brought immunotherapy to the forefront as a cancer treatment option. These therapeutic interventions have effectiveness in the treatment of a variety of different cancers based on clinical trials with demonstrate the capacity to contribute to the reduction of adverse effects associated with traditional chemotherapy. A number of recent researches have provided evidence supporting the effectiveness of cancer immune treatment that specifically targets the PD-1 as well as PDL-1 pathway can enhance sustained therapeutic immunity with reduced toxicity within multiple tumor types. While there is still much to learn about this signaling pathway, In the future years, the inhibition of the PD-1/PD-L1 signalling pathway represents a potentially important cancer immunotherapy strategy. The important questions remain unanswered in this field. Firstly, how do we select patients who are positive for PD-1and PD-L1? What traits are exhibited by individuals diagnosed with cancer? and which clinical detection method is the most effective? Secondly, what are the potential strategies that can be used to improve the infiltration of lymphocytes with CD8+ status into the tumor microenvironment (TME)? CD8+ T cells with tumor-reactive TCR repertoires have the potential to eliminate cancer cells, so understanding how to enhance their presence is crucial. Thirdly, how does PD-1 regulate CTLs and T-regulatory cells, and how does PD-L1 modulates the activity of cancer cells and antigen-presenting cells (APCs) within the tumor microenvironment (TME) is of interest? Can we develop more potent inhibitors based on these mechanisms? Fourthly, what is the effective treatment for PD-1and PD-L1-negative patients? Can these individuals take the advantage of alternative drugs or combination therapies that incorporate an anti-PD antibody strategy? Lastly, personalized indicators for guiding anti-PD therapy, alone or in combination with other targets, will be crucial for achieving clinical efficacy. Additional research is required to obtain a deeper comprehending of personal

genomic data to address these essential topics. Furthermore, the field of cancer treatment has recently undergone a transformative phase with the immunotherapy research and development, including PD-1 and PD-L1 pathway targeting. However, additional investigation is necessary to verify the efficacy and guarantee of using this method. It is important to note that immunotherapy takes time to establish itself as a key component of cancer treatment. In the past decade, it has been rapidly developed and authorized for various malignancies Although there have been notable advancements, the complications of cancer treatment have not been totally resolved by the use of immune checkpoint inhibitors (ICI). Although immunotherapy has presented promising opportunities, further research and development are still required. Our goals for the next decade include identifying biomarkers for predicting the efficacy and toxicity of ICIs, optimizing ICI regimens and exploring new combinations. Although cancer treatment has significantly improved patients' chances of survival and quality of life, response and toxicity predictions vary widely among different cancer types. Therefore, further investigation is needed in the area of cancer immunology in order to overcome these obstacles and drive the field forward.

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