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ADVANCEMENTS IN CANCER IMMUNOTHERAPY: A COMPREHENSIVE REVIEW OF IMMUNE CHECKPOINT INHIBITORS

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ABSTRACT

This comprehensive review delves into the transformative landscape of cancer immunotherapy, focusing on the pivotal role of Immune Checkpoint Inhibitors (ICIs) in revolutionizing treatment strategies. Addressing the limitations of conventional cancer therapies, the paper navigates through the mechanisms and applications of ICIs across various cancer types. The exploration begins with an in-depth analysis of Nivolumab, an engineered monoclonal antibody targeting PD-1. Emphasizing its fully human design and IgG4 subtype selection, the paper details Nivolumab's potent binding affinity to PD-1 and its strategic avoidance of antibody-dependent cellular cytotoxicity (ADCC). Insights into its effectiveness in blocking PD-1 interactions with B7-H1 and B7-DC underscore the preservation of crucial immune cell activity. Pembrolizumab, another key player in cancer immunotherapy, takes the spotlight, with a focus on its role in advanced melanoma and Non-small cell lung cancer (NSCLC) treatment. The review navigates through its mechanism of action, inhibiting PD-1 receptors on lymphocytes, and explores the delicate balance between enhanced immune responses and potential immune-related side effects. Atezolizumab, a modified monoclonal antibody designed for human-like interactions, is discussed in the context of preventing PD-L1 interactions with PD-1 and B7, thereby boosting T-cell activity. Approval for metastatic urothelial cancer and NSCLC, along with promising results from the IMmotion 151 trial in advanced ccRCC patients, highlights its significance. The paper extends its purview to colorectal cancer (CRC), emphasizing the promising prospects of ICIs in addressing immune evasion in mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic CRC. The potential of anti-CTLA-4, anti-PD-1, and anti-PD-L1 in CRC therapy, particularly in combination, is explored. While recognizing the transformative potential of ICIs, the review candidly addresses the challenge of immune-related adverse effects (irAEs). The differential severity between anti-CTLA-4 and anti-PD-1/PD-L1 antibodies is discussed, underscoring the critical need for effective management, especially in combination therapies. In conclusion, the review reflects on the evolving landscape of cancer treatment with ICIs, acknowledging the delicate balance required to harness their therapeutic benefits while effectively managing associated risks. The paper underscores the profound impact of ICIs in offering renewed hope to cancer patients and the ongoing research shaping the future of cancer immunotherapy.

KEYWORDS: Immunotherapy, microRNA, Immune Checkpoint Inhibitors.

1. INTRODUCTION

In the past few years, significant advancements, especially in the realm of personalized medicine and cancer treatment, have been made (Smith et al., 2021). Immunotherapy, including approaches like adoptive cell transfer (ACT) and immune checkpoint inhibitors (ICIs), represents a category of cancer therapies that harness the components of the immune system to combat tumor cells (Sadeghi et al. 2021). Immunotherapy, whether used independently or in conjunction with traditional treatments like radiotherapy and chemotherapy, has achieved noteworthy success as a standard treatment for various types of cancer (Barbari et al. 2020).

An immune checkpoint inhibitor is a type of medication or therapy used in cancer treatment. It works by blocking certain proteins on the surface of immune cells or cancer cells, which are called checkpoint proteins. These proteins play a crucial role in regulating the immune system's response to threats like cancer cells. Normally, checkpoint proteins help prevent the immune system from attacking healthy cells in the body by putting the brakes on immune responses. Ipilimumab, the pioneer among immune checkpoint inhibitors for advanced melanoma treatment, focuses on cytotoxic T-lymphocyte antigen-4 (CTLA-4). This antibody hinders the suppression of T-cells, fostering the activation and

expansion of effector T cells. Subsequent to ipilimumab's approval, there was a scrutiny of other antibodies designed to target immune checkpoints (Hodi et al. 2010; Robert et al. 2011; Gibney et al. 2016). However, cancer cells can sometimes exploit these checkpoint proteins to evade detection and destruction by the immune system. Immune checkpoint inhibitors work by interfering with these checkpoint proteins, essentially releasing the brakes on the immune system. This allows the immune system to recognize and attack cancer cells more effectively. Common checkpoint proteins targeted by inhibitors include programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Programmed cell death 1 (PD-1) and cytotoxic T lymphocyte antigen 4 (CTLA-4) are co-inhibitory receptors found on the surface of T cells, serving to dampen T cell-driven immune reactions. However, cancer cells manipulate these inhibitory molecules to promote tumor tolerance and T cell exhaustion (Sadeghi et al. 2021). Consequently, immune checkpoint inhibitors (ICIs) like anti-CTLA-4, anti-PD-1, and anti-PD-L1 can bind to these co-inhibitory receptors, reawakening the immune response against cancer cells (Seidel et al. 2018). The US Food and Drug Administration (FDA) have granted approval for treating multiple cancer types using three distinct categories of immune checkpoint inhibitors. These categories comprise PD-1 inhibitors (such as Nivolumab, Pembrolizumab, and Cemiplimab), PDL-1 inhibitors (including Atezolimumab, Durvalumab, and Avelumab), and CTLA-4 inhibitor (Ipilimumab) (Liebl and Hofman, 2019). Nivolumab (BMS-936558) is an IgG4 antibody that specifically targets PD-1 and is of fully human origin. In an initial phase I trial (Checkmate-003 study), nivolumab exhibited encouraging clinical effectiveness, especially among individuals displaying elevated levels of PD-L1 expression (Topalian et al. 2012; Gettinger et al. 2015; Kazandjian et al. 2016). Pembrolizumab (MK-3475) is a fully humanized monoclonal antibody of the IgG4 class that specifically targets PD-1. In a phase Ib clinical trial (Keynote-001 study), pembrolizumab exhibited encouraging clinical effectiveness, especially in individuals with elevated PD-L1 expression levels (Garon et al. 2015). Atezolizumab (MPDL-3280A) is a humanized monoclonal antibody of the IgG1 class with antagonistic properties, designed to specifically target PD-L1. Its engineering prevents the activation of T cells expressing PD-L1 through antibody-dependent cell-mediated cytotoxicity (ADCC). In a phase I trial that included expansion cohorts involving patients with NSCLC, atezolizumab exhibited encouraging clinical effectiveness (Herbst et al.2014).

Immunotherapy represents a recent cornerstone in the field of cancer treatment, offering innovative avenues for addressing solid tumors. Within this context, the exploration of novel medications that focus on immune checkpoints has emerged as a hopeful strategy in the management of colorectal and lung cancer. This approach holds promise for triggering precise and long-lasting anticancer responses. While there have been significant strides in the application of immunotherapy for colorectal and lung cancer, challenges and impediments to achieving effective treatment persist. One of the contributing factors to suboptimal treatment outcomes in colorectal and lung cancer patients is the immunosuppressive role played by the tumor microenvironment (TME). Tumors consist of cancer cells as well as stromal components including blood vessels, fibroblasts, and immune cells that together create what is known as the tumor microenvironment (TME). This TME can vary significantly from one tumor to another and plays a crucial role in supporting tumor development, dissemination, and it has the ability to evade immune-mediated eradication (Whiteside T.L 2008; Zou, 2005). Efficacy of T-cells may be suppressed by TME. Aberrant cancer cell proliferation can result in intrinsic immunosuppressive characteristics within tumors, including hypoxia and increased lactate levels, which can impede the functioning of effector T cells (Fischer et al. 2007). Regulatory T-cells (Treg) are also found in solid tumors and induces immune suppression by secreting immunosuppressive cytokines, vying for activating cytokines with different effector cells and exhibiting direct cellular contact with effector cells which tend to infiltrate into TME (Budhu et al. 2017; Nishikawa and Sakaguchi, 2010).

While anti-CTLA-4 and anti-PD-1/PD-L1 therapies have shown success, their benefits are limited to a fraction of patients. The effectiveness of immune checkpoint inhibitors (ICIs) can vary due to the complex regulatory factors within the tumor microenvironment (TME) that govern antitumor immunity. The TME can be categorized into three primary types based on the infiltration of immune cells: immune desert, immune excluded, and immune inflamed (Chen and Mellman, 2017). Each of these phenotypes has its own mechanisms that hinder the immune system's ability to eliminate tumor cells (Chen and Mellman, 2017). Immune deserts are characterized by the absence of T cells in the TME and a deficiency in suitable T cell priming or activation. The immune excluded phenotype exhibits the presence of multiple chemokines, vascular factors, or mediators, along with stromal-based inhibition, yet it still prevents the infiltration of T cells into the TME. In contrast, immune inflamed tumors show infiltration of various subtypes of immune cells (Chen and Mellman, 2017).

Colorectal and lung cancer stands as a widespread form of malignancy characterized by a significant global mortality rate. Despite significant advancements in cancer therapeutics, these cancers continue to exact a heavy toll on individuals worldwide, marked by high mortality rates and substantial challenges in treatment. The emergence of immunotherapy, particularly the use of immune checkpoint inhibitors, has heralded a promising paradigm shift in the management of these two malignancies. These agents have showcased remarkable potential in unleashing the body's immune

defenses against cancer cells, offering renewed hope for patients facing these aggressive diseases. This research paper delves into the multifaceted role of immune checkpoint inhibitors in the context of colorectal and lung cancer, exploring their mechanisms of action, clinical applications, evolving treatment strategies, and the crucial implications they hold for the future of oncology. Through an in-depth analysis of current research and clinical experiences, this paper seeks to shed light on the transformative impact of immune checkpoint inhibitors and their potential to reshape the landscape of cancer care for lung and colorectal cancer patients.

2. Explanation of how immune checkpoint inhibitors work

While cancer cells arise daily, the majority of them are effectively eliminated by the body's immune response. These immune responses against cancer cells are referred to as cancer-immunity cycles, which consist of seven stages: (1) the release of cancer antigens when cancer cells die, (2) the presentation of these cancer antigens to T cells by antigen-presenting cells like dendritic cells, (3) the activation of T cells (priming phase), (4) the migration of T cells, (5) the infiltration of T cells into the cancer site, (6) the recognition of cancer cells by T cells, and (7) the attack and elimination of cancer cells (effector phase) (Chen and Mellman, 2013). Nevertheless, cancer cells with limited immunogenicity, unable to present cancer antigens, can evade this immune response and persist for an extended period (equilibrium phase) (Chen and Mellman, 2013; Schreiber et al. 2011). Additionally, the accumulation of mutations in cancer cells triggers immunosuppressive mechanisms, leading to the emergence of regulatory T cells (Tregs) and immunosuppressive cells like myeloid-derived suppressor cells (MDSCs). Furthermore, the expression of immune checkpoint molecules like PD-L1 contributes to uncontrolled tumor growth (escape phase) (Chen and Mellman, 2013; Schreiber et al. 2011).

Unlike cytotoxic anticancer drugs that hinder cell division or targeted drugs that bind to specific gene mutation sites to inhibit cancer cell growth, ICIs (Immune Checkpoint Inhibitors) operate by harnessing the body's autoimmune functions to combat tumors. Presently, anti-PD-1/PD-L1 antibodies are being used in clinical settings for treating lung cancer and a variety of other cancer types. In the case of lung cancer, PD-L1 expression serves as a biomarker for determining treatment eligibility. Microsatellite instability has also been explored as a potential biomarker for anti-PD-1/PD-L1 antibody treatment in gastric cancer, particularly as a second-line option following standard therapy, as well as in triple-negative breast cancer and as a candidate biomarker in colorectal cancer.

In 2011, the Food and Drug Administration (FDA) approved the use of ipilimumab, a monoclonal antibody targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4), as a standalone therapy for advanced-stage malignant melanoma. In 2015, the FDA gave its approval for the combination of nivolumab and ipilimumab for clinical use. Studies comparing the combination of ipilimumab and nivolumab with sunitinib alone in renal cell carcinoma and the use of ipilimumab and nivolumab in non-small cell lung cancer have yielded promising outcomes (Motzer et al. 2018; Carbone et al. 2017).

The significance of ipilimumab in combination therapy is still under evaluation, with future results expected to shed light on whether two-drug combinations of immune checkpoint inhibitors, such as the ipilimumab and nivolumab combination therapy, can enhance survival rates compared to either using immune checkpoint inhibitors alone or combining them with chemotherapy. Given the numerous uncertainties surrounding the in vivo mechanisms of action of ICIs, this review delves into the mechanisms that are generally considered.

Anti-PD-1/PD-L1 antibodies play a crucial role in the effector stage of the cancer-immunity cycle. During this phase, effector T cells are responsible for targeting and attacking cancer cells. However, the interaction between PD-L1, found on the surface of cancer cells, and PD-1, present on the surface of effector T cells, serves to dampen the T cells' assault on cancer cells. Anti-PD-1/PD-L1 antibodies are designed to disrupt this interaction through pharmacological means, thereby enhancing the ability of T cells to attack cancer cells. Moreover, it is believed that these antibodies also have the potential to dampen the immune response during the initial priming phase of the cancer-immunity cycle (Hui et al. 2017).

Despite its clear significance in treating human cancer, the mechanism through which PD-1 inhibits T cell function remains poorly comprehended. Early research indicated that when PD-1 binds to PD-L1, it leads to the phosphorylation of two tyrosines within the PD-1 cytoplasmic section. Experiments involving co-immunoprecipitation (co-IP) and colocalization in transfected cells demonstrated that once PD-1 becomes phosphorylated, it subsequently incorporates cytosolic tyrosine phosphatases Shp2 and Shp1, the TCR-phosphorylating kinase Lck, and the inhibitory tyrosine kinase Csk, either directly or indirectly (Sheppard et al. 2004; Yokosuka et al. 2012). It is crucial to determine the specific targets of these inhibitory agents to gain insight into the mechanism of anti-PD-L1/PD-1 immunotherapy. However, our understanding of the downstream targets influenced by PD-1-bound effectors remains limited. Recent studies have proposed that PD-1 activation hinders TCR signaling (Sheppard et al. 2004; Yokosuka et al. 2012; Zinselmeyer et al. 2013), CD28 costimulatory signaling (Parry RV et al. 2005). ICOS costimulatory signaling (Bennett F et al. 2003), or combination of these pathways. Reports have also noted reduced phosphorylation of various signaling molecules like ERK, Vav, PLCγ, and PI3 kinase (PI3K) (Yokosuka

et al. 2012; Parry RV et al. 2005). Nevertheless, it's important to note that these molecules are shared effectors between the TCR and co stimulatory pathways and may not be direct targets of PD-1.

Anti-CTLA-4 antibodies work during the initial phase of antigen presentation, known as the priming phase. In this phase, dendritic cells present antigens and activate T cells. T-cell activation relies on two key factors: T-cell receptors (TCRs) and the complex formed between MHC molecules and cancer antigens on the surface of dendritic cells (the main activation signal). Additionally, T-cell activation involves the interaction between B7 (CD80/86) on dendritic cells and CD28 on T cells (co stimulation) (Sansom, 2000). CTLA-4, similar to CD28, is found on the surface of T cells and binds to B7 with a higher affinity than CD28 does. Therefore, when CTLA-4 is upregulated, it remains bound to B7, preventing the transmission of the costimulatory signal, ultimately leading to the suppression of T cell activation (Rowshanravan et al. 2017).

Anti-CTLA-4 antibodies disrupt the binding between CTLA-4 and B7. This disruption results in increased binding between CD28 and B7, which in turn promotes T-cell activation and exerts antitumor effects (Malas et al. 2014). Additionally, CTLA-4 is present on the surfaces of regulatory T cells (Tregs), which can be induced by cancer cells. CTLA-4 on Tregs inhibits T-cell activation by binding to B7 on dendritic cells (Walunus et al. 1994). Therefore, it is believed that anti-CTLA-4 antibodies may also contribute to antitumor effects by facilitating the binding of Tregs to CTLA-4 and potentially directly removing Tregs.

3. Brief description of immune checkpoint inhibitors

Immune checkpoints are categorized as receptors found on the surface of immune cells, which play a role in regulating the activation or suppression of the immune system (Esfahani et al.2020). Immune checkpoint inhibitors (CPIs) constitute a form of immunotherapy aimed at enhancing the body's immune response against tumors by preventing the interaction of T lymphocyte surface receptors (Shiravand et al. 2022).This category of immunotherapy has been extensively researched and is currently among the well-studied approaches, playing a significant role in the management of various types of cancer (Riley et al. 2019). Over the past decade, two particularly promising strategies for checkpoint inhibition that have gained widespread use involve targeting the PD-1/PD-L1 and CTLA-4 molecules for blockade (Seidel et al. 2018).Ongoing research is exploring additional targets, including inhibitory receptors like T-cell immunoglobulin and mucin 3 (Tim-3), V-domain Ig suppressor of T-cell activation (VISTA), lymphocyte activation gene 3 (Lag-3), as well as activating molecules such as OX40 (CD134) and glucocorticoid-induced TNFR-related protein (GITR) (Pardoll et al.2012; Webb et al. 2018; Granier et al. 2017; Saleh et al. 2019; Qin et al. 2019; Mohsenzadegan et al. 2021).

3.1 *PD-1 Inhibitors*

PD-1 functions as a receptor that inhibits certain cellular processes crucial for programmed cell death signaling and the regulation of T-cell mediated responses (Riella et al. 2012). When PD-1 is engaged, it can lead to a decrease in the secretion of cytokines like IL-2, IFN-γ, and TNF-α, as well as hinder cell proliferation by disrupting the CD28-costimulatory signaling pathway (Han and Liu, 2020). PD-1 expression has been observed on various types of immune cells present in the tumor microenvironment (TME), including activated monocytes, dendritic cells (DCs), natural killer (NK) cells, T cells, and B cells (Han and Liu, 2020) (Refer to fig 1). Importantly, therapies targeting the PD-1 pathway have brought about significant advancements in the treatment of various cancers such as Merkel cell carcinoma (MCC), melanoma, head and neck squamous cell carcinoma (HNSCC), and non-small-cell lung cancer (NSCLC) (Huang et al.2021). The US FDA has approved three monoclonal antibodies, namely Nivolumab, Pembrolizumab, and Cemiplimab, as PD-1 inhibitors (Huang et al.2021).

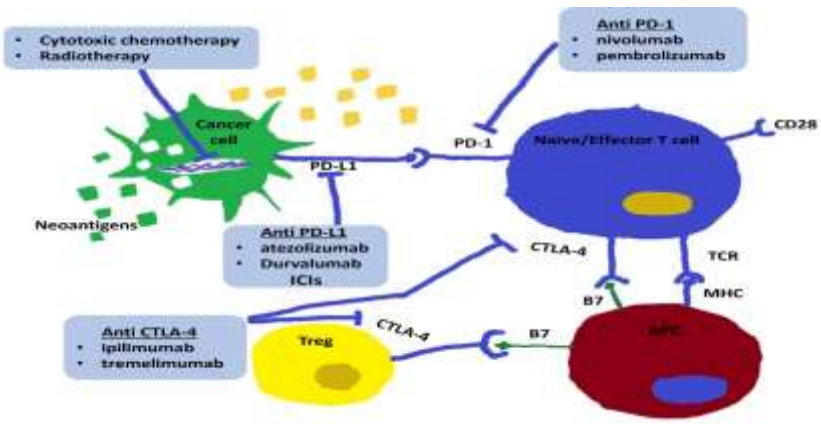

Fig. 1: FDA has approved immune checkpoint inhibitors such as Pembrolizumab, Nivolumab, and Cemiplimab functioning as anti-PD-1 antibodies, Ipilimumab serving as an anti-CTLA-4 antibody and Atezolizumab, Avelumab, and Durvalumab acting as anti-PD-L1 antibodies.

Nivolumab (known by various names like BMS-936558, ONO-4538, or MDX1106, marketed as Opdivo by Bristol-Myers Squibb in Princeton, NJ, USA) represents a groundbreaking monoclonal antibody (mAb) of the IgG4 type that serves as a novel inhibitor. It effectively curbs the activity of PD-1 by specifically targeting and blocking the interaction between its ligands (PD-L1 and PD-L2) and the PD-1 receptor (Rizvi et al. 2015). Tumor cells have demonstrated their capacity to evade immune surveillance by exploiting the PD-1/PD-L1 pathway, resulting in a weakened cellular immune response (Rizvi et al. 2015). The FDA granted approval for Nivolumab in 2014 for treating renal cell carcinoma and melanoma (Refer to fig 1). Furthermore, Nivolumab gained FDA approval in 2015 for the management of squamous cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) (Kazandjian et al. 2016). In a 2010 study, Brahmer and colleagues illustrated the clinical efficacy of MDX-1106 (an earlier name for Nivolumab) in patients with various tumor types, including colorectal cancer, renal cell cancer, melanoma, NSCLC, and castration-refractory prostate cancer (Brahmer et al. 2010).

Pembrolizumab, marketed as Keytruda by Merck, is another humanized IgG4 monoclonal antibody that disrupts the PD-1/PD-L1 pathway (Liebl and Hofmann, 2019). Its FDA approval for the treatment of various tumor types is based on the strong objective responses observed and its commendable pharmacokinetic and safety record (Liebl and Hofmann, 2019). On October 13, 2021, the FDA officially endorsed the use of pembrolizumab in combination with chemotherapy drugs, with or without bevacizumab, as a beneficial therapeutic approach for patients with recurrent metastatic cervical cancer whose tumor cells exhibit high PD-L1 expression levels (De Felice et al. 2021). Several studies have indicated that pembrolizumab elicits comprehensive and robust responses in a manner that targets the immune system rather than the tumor cells themselves (Le D.T et al. 2017). Notably, the FDA recently granted approval for pembrolizumab as the first tissue-agnostic/site-agnostic drug for the treatment of patients with mismatch repair deficient/metastatic microsatellite instability-high (dMMR/MSI-H) conditions (Le D.T et al. 2017). This FDA approval positions pembrolizumab as a potential therapeutic option for patients with advanced rare cancers. However, further research is required to thoroughly investigate the drug's efficacy and safety profile in these patient populations (Refer to fig 1). (Groisberg et al. 2017).

Cemiplimab, marketed as Libtayo® and developed by Regeneron Pharmaceuticals/Sanofi, is categorized as a fully humanized IgG4 monoclonal antibody that hinders the interaction between the PD-1 receptor and its ligands. It is employed for the treatment of patients with metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC) who are not suitable candidates for curative resection or radiotherapy. The FDA granted approval for this treatment in September 2018, and it received approval from the European Medicines Agency (EMA) in June 2019 (Argenziano et al. 2022). Cemiplimab holds the distinction of being the first drug sanctioned by the FDA for the treatment of CSCC. Furthermore, it is prominently featured and recommended in the 2020 European interdisciplinary guidelines, jointly issued by the EDF, EADO, and EORTC, as the primary therapeutic option for cancer patients who are not eligible for radiotherapy or surgical intervention (Refer to fig 1). (Stratigos et al. 2020).

3.2 *CTLA-4 Inhibitors*

CTLA-4 is a member of the immunoglobulin superfamily with coinhibitory properties, and it plays a role in downregulating T cell activation by interacting with its ligands, namely B7-1 (CD80) and B7-2 (CD86) (Littman, 2015). CTLA-4 and CD28 share highly similar protein sequences and are located near each other on chromosome 2q33 (Naluai et al.2000). Both molecules can form homodimers and bind the same ligands, albeit with varying affinities (Rudd et al. 2009). CTLA-4 has a higher binding affinity and can outcompete CD28 for ligand binding, resulting in the dampening of T cell signaling (Alegre et al.2001). In the context of regulating immune responses against tumors, CTLA-4 operates during the early stages of T cell activation in lymph nodes, as its ligands are predominantly expressed on antigen-presenting cells (APCs) (Fife and Bluestone, 2008). This implies that the absence of CTLA-4 may lead to uncontrolled T cell proliferation, prompting exploration into the potential enhancement of antitumor immune responses through CTLA-4 blockade (Refer to fig 1).

Numerous research studies have demonstrated that blocking CTLA-4 can elicit an immune response against tumors in animal models of various cancers, including breast, prostate, lymphoma, colon, and melanoma (Van et al. 1999; Kwon et al. 1997; Van et al.2000; Saha and Chatterjee 2010; Sutmuller et al. 2001). The growing body of evidence showcasing substantial antitumor effects in preclinical investigations has paved the way for further exploration of CTLA-4 blockade in clinical trials. Ipilimumab, a monoclonal antibody of the human IgG1 class designed to target CTLA-4, marked a significant milestone in this regard by becoming the first approved treatment for melanoma in 2010 (Refer to fig 1) (Boasberg et al. 2010). This treatment was associated with notable improvements in patient survival, the establishment of enduring responses lasting over 2.5 years, and the potential for long-term disease control (Robert et al.2011; Hodi et al. 2010).

4. Important immune checkpoint pathways

4.1 *CTLA-4 Pathways*

T-cell activation is an intricate process that necessitates more than one activating signal. While the T-cell receptor (TCR) binding to major histocompatibility complex (MHC) molecules imparts specificity to T-cell

activation, additional signals are imperative. The interaction between B7-1 (CD80) or B7-2 (CD86) molecules on antigen-presenting cells (APC) with CD28 molecules on T cells triggers signaling pathways within the T cell. Sufficient levels of CD28 binding to B7-1/2 result in T cell proliferation, enhanced T-cell survival, and differentiation, accomplished through the production of growth cytokines like interleukin-2 (IL-2), increased energy metabolism, and the upregulation of genes associated with cell survival.

CTLA-4, a molecule similar to CD28, exhibits significantly higher affinity for B7 molecules (specifically B7-1 and B7-2) (Chambers et al. 2001; Collins et al. 2002). However, unlike CD28, when CTLA-4 binds to B7, it does not trigger a stimulatory response. Consequently, this competitive binding can block the typical costimulatory signal initiated by CD28:B7 interaction (Chambers et al. 2001; Egen et al. 2002; Parry et al. 2005). The balance between the levels of CD28:B7 binding and CTLA-4:B7 binding determines whether a T cell becomes activated or enters a state of anergy (Krummel and Allison, 1995). Additionally, some evidence suggests that CTLA-4 binding to B7 might actually generate inhibitory signals that counteract the stimulatory signals resulting from CD28:B7 and TCR: MHC interactions (Fallarino et al. 1998; Masteller et al. 2000). Proposed mechanisms for these inhibitory signals include direct inhibition at the TCR immune synapse, suppression of CD28 or its signaling pathway, or increased T cell mobility, which reduces their ability to engage with antigen-presenting cells (APCs) (Egen et al. 2002; Masteller et al. 2000; Schneider et al.2006).

CTLA-4 undergoes regulation, especially through its cellular localization. In resting, inexperienced T cells, CTLA-4 is primarily situated inside the cell (Linsley et al. 1998). Activation signals triggered by both TCR and CD28:B7 binding stimulate an increase in the presence of CTLA-4 on the cell's surface through the release of vesicles containing CTLA-4 (Linsley et al. 1998). This process operates as a continuous feedback loop, with stronger TCR signaling leading to greater translocation of CTLA-4 to the cell surface. When there is an overall negative signal due to CTLA-4:B7 binding, it prevents the full activation of T cells by inhibiting the production of IL-2 and the progression of the cell cycle (Krummel and Allison, 1996).

CTLA-4 plays a role in various aspects of immune regulation. Regulatory T cells (Tregs) are responsible for modulating the activities of effector T cells, making them essential in maintaining peripheral tolerance (Piccirillo and Shevach, 2004; Takahashi et al. 2000). Unlike effector T cells, Tregs constantly express CTLA-4, and this is believed to be crucial for their ability to suppress immune responses (Takahashi et al. 2000). In animal studies, the absence of CTLA-4 in Tregs due to genetic deficiency was found to impair their suppressive functions (Takahashi et al. 2000; Wing et al. 2008). One mechanism through which Tregs are believed to control effector T cells is by reducing the expression of B7 ligands on antigen-presenting cells (APCs), which leads to decreased CD28 costimulation (Wing et al. 2008; Qureshi et al. 2011).

4.2 *PD-1 Pathway*

PD-1 belongs to the costimulatory receptor family known as B7/CD28. Its function involves the regulation of T-cell activation by interacting with its ligands, programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2) (Keir et al. 2008). Similar to the signaling of CTLA-4, when PD-1 binds to these ligands, it hinders T-cell proliferation and reduces the production of interferon-γ (IFN-γ), tumor necrosis factor-α, and IL-2 while diminishing T-cell survival, (Keir et al. 2008). When both the T-cell receptor (TCR) and PD-1 bind simultaneously, the signals generated by PD-1 prevent the phosphorylation of critical TCR signaling components, leading to the early termination of TCR signaling and a decrease in T-cell activation (Parry et al. 2005; Bennette et al. 2003). Notably, the expression of PD-1 is a characteristic feature of "exhausted" T cells that have encountered extensive stimulation or insufficient CD4+ T-cell support (Wherry, 2011). This state of exhaustion typically arises in chronic infections and cancer, resulting in T-cell dysfunction and suboptimal control of infections and tumors.

Both CTLA-4 and PD-1 binding result in comparable negative impacts on T-cell function. However, there are distinctions in when this downregulation occurs, the signaling pathways involved, and where in the body these immune checkpoints exert their inhibitory effects. In contrast to CTLA-4, which is restricted to T cells, PD-1 is found on a wider range of immune cells, including activated T cells, B cells, and myeloid cells(Fife and Bluestone, 2008; Keir et al. 2008). CTLA-4 primarily functions during the early activation stage of T cells, while PD-1 predominantly operates during the later effector phase, mainly within peripheral tissues (Keir et al.2008).

The distribution of PD-1 ligands sets them apart from those of CTLA-4. CTLA-4's B7 ligands are typically found on professional antigen-presenting cells (APCs), which are mainly located in lymph nodes or the spleen (Fife and Bluestone, 2008). However, PD-L1 and PD-L2 have a broader expression pattern (Fife and Bluestone, 2008; Parry et al. 2005; Chen et al. 2012; Latchman et al. 2004). PD-L1 can be found on various leukocytes, nonhematopoietic cells, and in tissues outside the lymphatic system. It can also be induced on parenchymal cells by inflammatory cytokines like IFN-γ or signaling pathways related to tumorigenesis (Chen, 2004). PD-L1 expression is observed in various tumor types and is associated with increased tumor-infiltrating lymphocytes (TILs) and a worse prognosis (Hino et al. 2010; Taube et al. 2014; Zou and Chen, 2008). On the other hand, PD-L2 is primarily seen on dendritic cells and monocytes but

can be induced on different immune and non-immune cells depending on the local environment (Rozali et al. 2014). PD-1 binds more strongly to PD-L2 than to PD-L1, and this difference might account for their distinct roles in immune responses (Youngnak et al. 2003). Since PD-1 ligands are present in peripheral tissues, it's believed that interactions between PD-1 and PD-L1/PD-L2 help maintain immune tolerance within these locally infiltrated tissues (Fife and Bluestone, 2008).

As might be anticipated, the presence of multiple ligands for PD-1 results in varying biological outcomes depending on which ligand is engaged. One model has illustrated contrasting effects of PD-L1 and PD-L2 signaling in the activation of natural killer T cells (Akbari et al.2010). Inhibiting the binding of PD-L2 leads to heightened TH2 activity,(Huber et al. 2010) while PD-L1 binding to CD80 has been demonstrated to hinder T-cell responses (Butte et al. 2007). These distinct biological effects likely contribute to differences in the efficacy and side effects of antibodies targeting PD-1 (preventing binding to both ligands) compared to those targeting PD-L1, and consequently, these findings have potential implications for therapeutic applications.

While regulatory T cells (Tregs) do express both PD-1 and CTLA-4, the role of PD-1 expression on these cells remains uncertain. PD-L1 has been demonstrated to play a part in converting naive CD4+ T cells into Treg cells (Wang et al.2008) and in suppressing T-cell responses by facilitating the generation and sustenance of Tregs (Francisco el al. 2009). In line with these discoveries, blocking PD-1 can reverse the suppression of effector T cells mediated by Tregs in laboratory settings (Wang et al. 2014).

The interaction between PD-1 and its ligands reduces the strength of the immune response in T cells that are actively involved in an effector T-cell response (Wherry et al. 2011). This leads to a narrower range of T-cell activation compared to when CTLA-4 is blocked. This difference may clarify why PD-1 blockade appears to be linked to a lower occurrence of immune-related adverse events (AEs) compared to CTLA-4 blockade (Ott PA et al. 2013).

5. The involvement of PDL1 in evading the immune system by tumors

The role of PDL1 in immune evasion by tumors is notable as it is expressed on neoplastic cells in various cancer types. This expression leads to the inhibition of T-cells by binding to PD1, effectively allowing tumor cells to avoid immune attacks. PDL1 overexpression can be attributed to two underlying mechanisms: intrinsic and adaptive (Topalian et al.2015). Intrinsic PDL1 expression in cancer cells is associated with genetic abnormalities in these neoplastic cells, with cellular signaling pathways like AKT and STAT contributing to increased PDL1 expression (Parsa et al. 2007). For instance, gene fusion events, such as MHC class II transactivator (CIITA) fusion with PDL1 or PDL2, result in the overexpression of these proteins in primary mediastinal B-cell lymphomas. Amplification of chromosome 9p23–24, the location of PDL1 and PDL2, leads to heightened expression of both proteins in classical Hodgkin lymphoma (Roemer et al. 2016). Epstein Barr virus (EBV) infection in tumor cells also triggers an increase in PDL1 expression (Chen et al. 2016). Adaptive mechanisms involve the induction of PDL1 expression within the tumor microenvironment. Neoplastic cells can have PDL1 induced in response to interferon γ, and myeloid cells like dendritic cells and monocytes also express PDL1, contributing to the immunosuppressive environment(Curiel et al. 2003). In microsatellite instability colon cancer, PDL1 is primarily expressed on myeloid cells within the tumors (Llosa et al. 2015). Antigen-presenting cells (APCs) express PDL1, and the interaction of PDL1 with PD1 on T-cells leads to the induction of regulatory T-cells (Tregs), which subsequently suppress the function of cytotoxic T-cells (Francisco et al. 2009).

6. Role of immune checkpoint inhibitors in lung cancer

In 2014, a groundbreaking development occurred with the introduction of nivolumab, the world's inaugural immune checkpoint inhibitor (ICI) designed to target PD-1. This marked a significant milestone in the realm of therapeutic options for malignant melanoma. The year following, in 2015, a pivotal phase-III comparative investigation took place, evaluating the effectiveness of nivolumab and docetaxel (DTX) as secondary treatments for both squamous and non-squamous lung cancers. The research encompassed two studies, CheckMate017 (NCT01642004) and CheckMate057 (NCT01673867), which focused on these respective types of lung cancer. Both studies yielded compelling results, demonstrating that nivolumab substantially extended overall survival (OS) when compared to DTX. In specific terms, CheckMate017 reported a 6.0-month OS with nivolumab versus 9.2 months with DTX, with a Hazard Ratio (HR) of 0.59. Similarly, CheckMate057 showed an OS of 9.4 months for nivolumab versus 12.2 months for DTX, with an HR of 0.73(Brahmer et al. 2015; Borghaei et al. 2015). Consequently, based on these significant findings, the scope of nivolumab's application was expanded to include second-line treatment for non-small cell lung cancer (NSCLC). This marked the inaugural approval of immune checkpoint inhibitors (ICIs) for the treatment of lung cancer, signifying a pivotal moment in the field.

In 2016, there was another significant development involving an anti-PD-1 antibody known as pembrolizumab. A phase-III comparative study was conducted to assess pembrolizumab and docetaxel (DTX) as second-line therapy for non-small cell lung cancer (NSCLC) patients with PD-L1 levels of 1% or higher. This study revealed that pembrolizumab substantially increased patient survival when compared to DTX. Specifically, the survival outcomes were 8.5

months with pembrolizumab versus 10.4 months with DTX (for the 2 mg/kg dose of pembrolizumab) or 12.7 months (for the 10 mg/kg dose of pembrolizumab) (Herbst et al.2016).

Additionally, the OAK trial (NCT02008227) examined the efficacy of the anti-PD-L1 antibody atezolizumab as a second-line treatment for NSCLC, comparing it to DTX. This trial demonstrated that atezolizumab significantly extended patient survival, with results showing 9.6 months for atezolizumab versus 13.8 months for DTX, with a Hazard Ratio (HR) of 0.73 (Rittmeyer et al. 2017).

As a result of these compelling findings, pembrolizumab and atezolizumab, in addition to nivolumab, were introduced as second-line treatment options for NSCLC patients. This marked a significant advancement in the management of this type of lung cancer.

In 2019, the IMpower133 clinical trial (NCT02763579) revealed that when atezolizumab was combined with platinum-based chemotherapy as the initial treatment for small-cell lung cancer (SCLC), it led to significant extensions in both progression-free survival (PFS) and overall survival (OS). The study found that PFS increased from 4.3 months to 5.2 months with the combination therapy, with a Hazard Ratio (HR) of 0.77. Moreover, OS improved from 10.3 months to 12.3 months with the combination therapy, having an HR of 0.70 [19]. These findings indicate a promising role for immune checkpoint inhibitors (ICIs) in the treatment of SCLC.

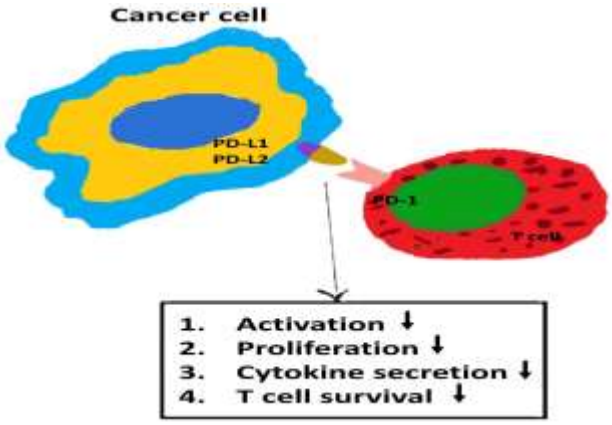

Fig. 2: The PD-1/PD-L1 axis hinders the activation, growth, and survival of T cells, as well as the release of cytotoxic substances against cancer cells.

6.1 Nivolumab in lung cancer

Nivolumab, also known as MDX-1106, BMS-936558, or ONO-4538, is a genetically engineered monoclonal antibody that is fully human and designed to specifically target human PD-1 (Refer to table 1) (Refer to fig 2). This antibody belongs to the IgG4 subtype of immunoglobulinG4 (IgG4), which was deliberately chosen for its lack of antibody-dependent cellular cytotoxicity (ADCC) capability. Unlike many monoclonal antibodies used in cancer therapies that are of the IgG1 subtype, which possess strong ADCC activity, IgG4 has minimal ADCC potential. This design choice is crucial because a fully functional ADCC has the potential to deplete activated T cells and tumor-infiltrating lymphocytes, which could diminish the effectiveness of PD-1 inhibition. Since PD-1 is expressed on T effector cells and other immune cells, preserving their activity is important.

Nivolumab exhibits a strong binding affinity to PD-1, with a dissociation constant (KD) of 2.6 nmol/l when tested on polyclonally activated human T cells. Additionally, it effectively blocks PD-1's interactions with both B7-H1 and B7-DC, as demonstrated by previous research (refer to fig 2) (Chen et al. 2012, Brahmer et al. 2012).

6.2 Pembrolizumab in lung cancer

Pembrolizumab (commercially known as Keytruda™) is a monoclonal antibody that specifically targets PD-1. It gained accelerated approval from the US FDA on September 4th, 2014, for the treatment of advanced or unresectable melanoma in patients who do not show positive responses to other available treatments (refer to fig 2) (Galluzi et al. 2014). Pembrolizumab is a therapeutic antibody mostly used in case of Non-small cell lung cancer (NSCLC) that targets and inhibits PD-1 found on lymphocytes, a receptor typically responsible for regulating the immune system to avoid self-tissue damage, known as an immune checkpoint (Refer to table 1) (Francisco et al., 2010; Buque et al. 2015). Ordinarily, when activated T-cells have the PD-1 receptor, they interact with the PD-L1 or PD-L2 ligands found on healthy cells in the body. This interaction essentially stops any potential cell-mediated immune response against those normal cells (Riley, 2009). In the case of many cancers like NSCLC they produce proteins like PD-L1 that can also bind to the PD-1 receptor, effectively suppressing the body's ability to eliminate the cancer. Pembrolizumab functions by blocking the PD-1 receptors on lymphocytes, thereby preventing the ligands from deactivating them and hindering an immune response. As a result, this enables the immune system to

identify and eradicate cancer cells (Syn et al. 2017; Francisco et al. 2010). However, it also disrupts a critical mechanism that otherwise prevents the immune system from mistakenly targeting the body itself. Consequently, the checkpoint inhibitory action of pembrolizumab leads to immune-related side effects (Buque et al. 2015).

6.3 Atezolizumab in lung cancer

Atezolizumab is a monoclonal antibody that has been modified to be more human-like, and it works by preventing the interaction between PD-L1 and its receptors PD-1 and B7(Refer to table 1) (Crist and Balar, 2017). This action boosts the immune system's ability to fight cancer by enhancing T-cell activity. Atezolizumab, when used on its own, has been given approval for the treatment of metastatic UC and NSCLC (refer to fig 2). Recently, in the phase 3 IMmotion 151 trial, atezolizumab was combined with bevacizumab (an anti-VEGF drug) and compared to sunitinib as a first-line treatment for ccRCC. Research shows that atezolizumab/bevacizumab achieved one of its main objectives, demonstrating improved progression-free survival (PFS) compared to sunitinib in advanced ccRCC patients with PD-L1 expression on at least 1% of immune cells that have infiltrated the tumor as assessed by immunohistochemistry (Atkins and Tannir, 2017).

Table 1: Experiments involving ICIs in the context of advanced stage NSCLC.

ICIs: Immune checkpoint inhibitors; NSCLC: non-small cell lung cancer; PD-L1: programmed cell-death ligand 1; OS: overall survival; PFS: progression-free survival; NR: not reached.

Treatment Regimen	Trial	Patient Population	Primary Outcome Results
Nivolumab	CheckMate 017	Stage IIIB/IV squamous NSCLC; disease recurrence after platinum-based chemotherapy	Median OS: 9.2 months (95% CI: 7.3–13.3); 12 months OS: 42% (95% CI: 34–50%)
Nivolumab	CheckMate 057	Stage IIIB/IV non-squamous NSCLC; disease recurrence after platinum-based chemotherapy	Median OS: 12.2 months (95% CI: 9.7–15.1); 18 months OS: 39% (95% CI: 34–45%)
Atezolizumab	OAK	Stage IIIB/IV; disease progression after platinum-based chemotherapy	Median OS: 13.8 months (95% CI: 11.8–15.7); PP-ITT; improved OS/PFS in patients with PD-L1 expression > 1%
Chemotherapy + Bevacizumab ± Atezolizumab	IMpower 150	Stage IIIB/IV; untreated metastatic non-squamous NSCLC	Median PFS: 8.3 months (95% CI: 7.7–9.8); Median OS: 19.8 months (95% CI: 17.4–24.2)
Pembrolizumab	KEYNOTE 024	Stage IV; untreated disease; PD-L1 expression > 50%	Median PFS: 10.3 months (95% CI: 6.7–NR); 6 months PFS: 62.1% (95% CI: 53.8–69.4%)
Chemotherapy ± Pembrolizumab	KEYNOTE 189	Stage IIIB/IV; untreated metastatic non-squamous NSCLC	Median OS: 22.0 months (95% CI: 19.5–25.2); 12 months OS: 69.2% (95% CI: 64.1–73.8%)
Chemotherapy ± Pembrolizumab	KEYNOTE 407	Stage IIIB/IV; untreated metastatic squamous NSCLC	Median OS: 15.9 months (95% CI: 13.2–NR); 12 months OS: 65.2% (95% CI: 57.7–71.6%

7. Role of immune check point inhibitors in colorectal cancer

Traditional cancer treatments, like surgical procedures, radiation therapy, and chemotherapy, are widely utilized in the management of various cancer types. While these methods can be quite effective during the early stages of cancer, they may lead to resistance and severe adverse reactions (Holohan et al. 2013; Van der Bij et al. 2009). Furthermore, in numerous patients, the ability of tumor cells to evade the body's immune system is a crucial factor in the development and progression of cancer. As a result, there is a need for innovative strategies to address these challenges and ensure effective cancer therapy. One promising and recently approved approach is the use of immune checkpoint inhibitors (ICIs) in immunotherapy, which has shown promise in treating malignancies such as melanoma, non-small cell lung cancer (NSCLC), and colorectal cancer (CRC) (Emambux et al. 2018; Gotwals et al. 2017).

Table 2: Clinical Trial in Colorectal Cancer (CRC).

Patients	Target	mAbs	Phase	Trial	Ref
mCRC	**CTLA-4**	Tremelimumab	II	A study that showed no significant activity of Tremelimumabasmonotherapy in refractory metastatic colorectal cancer patients.	(Chung et al.2010)
dMMR/MSI-H	**PD-1**	Nivolumab	II	A study evaluating Nivolumab in	(Overman et

mCRC				colon cancer was associated with durable responses in patients with previous treatments.	al.2017)
MSI-H/MSS mCRC	**PD-1**	Pembrolizumab	I/II	An assessment of Pembrolizumab with napabucasin that showed antitumor effects with acceptable toxicities in mCRC patients.	(Kawazoe et al. 2017)
MMRp CRC	**PD-1**	Pembrolizumab	II	A study to investigate efficacy of Pembrolizumab plus with GVAX/Cy showed no efficacy in mismatch repair proficient CRC.	(Yarchoan et al. 2020).
MSI-H CRC	**Anti-PD-L1**	Durvalumab	II	An evaluation of the efficacy and safety of Durvalumab demonstrated a well-tolerable response in MSI-H CRC patients.	(Segal et al. 2019)

7.1 Anti-CTL-4

Blocking CTLA-4 using monoclonal antibodies (mAbs) presents a promising strategy for combating cancer by enhancing the activation of T cells, which play a crucial role in the body's antitumor response (Saltz, 2009). These anti-CTLA-4 antibodies can bind to their respective receptors, namely CTLA-4 and B7, found on the surface of T cells. By doing so, they extend the activity of T cells, thereby improving their ability to counter tumors (Lynch and Murphy, 2016). Regulatory T cells (Treg cells), known for their suppressive role in the immune system, consistently express CTLA-4. Consequently, employing anti-CTLA-4 mAbs can heighten antitumor responses by reducing the inhibitory function of Treg cells (Gotwalls et al. 2017).

In the case of patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC), immune checkpoint blockade emerges as a promising therapeutic approach (Kamatham et al. 2019). One such antibody, Ipilimumab, is a fully human IgG1 that received FDA approval for melanoma treatment in 2011(refer to table 2) (Zhao et al. 2018). By specifically blocking CTLA-4, Ipilimumab enhances T cell responses against tumors. It achieves this by preventing CTLA-4 from binding to B7, thereby allowing CD28 to engage with B7, leading to sustained T cell activation (Sanghavi et al. 2020). When combined with Nivolumab, an anti-PD-L1 monoclonal antibody, this immune checkpoint blockade yields a robust antitumor response in patients with dMMR/MSI-H mCRC (Overman et al. 2018).

Tremelimumab, another fully human IgG2 immunoglobulin anti-CTLA-4 mAb, is currently undergoing investigation for the treatment of solid tumors (refer to table 2) (Camacho, 2008). While it did not exhibit effectiveness as a standalone treatment in patients with refractory metastatic CRC in a phase II clinical study, Tremelimumab has demonstrated its therapeutic potential in advanced hepatocellular carcinoma (refer to table 2) (Sangro et al. 2013; Duffy et al. 2017). Furthermore, the results of a phase II study have indicated that combining Tremelimumab (anti-CTLA-4) with Durvalumab (anti-PD-L1) can significantly extend the overall survival (OS) of patients with advanced refractory CRC (Chen et al. 2020). As a result, the combination of anti-CTLA-4 with other immune checkpoint inhibitors, such as anti-PD-L1, appears to be a more effective approach in CRC treatment compared to targeting anti-CTLA-4 in isolation.

7.2 Anti- PD-1

The PD-1/PD-L1 pathway, serving as an inhibitory mechanism, plays a vital role in regulating T-cell activation and maintaining peripheral tolerance (Makuku et al. 2021).

Using monoclonal antibodies (mAbs) to block this pathway can enhance the antitumor activity of T cells (Arasanz et al. 2017). Notably, PD-1 expression increases on the surface of T CD8+ cells within the colorectal cancer (CRC) tumor microenvironment (TME). Hence, inhibiting PD-1 presents a practical approach for CRC treatment (Wu et al. 2014). Two FDA-approved anti-PD-1 mAbs are Nivolumab and Pembrolizumab. Nivolumab initially received FDA approval in 2014 for advanced melanoma patients and is a fully humanized IgG4 monoclonal antibody (refer to table 2) (Hahn et al. 2017). It has since gained approval for various cancers, including melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and Hodgkin's lymphoma (Berger et al. 2018). In a study involving dMMR/MSI-H metastatic CRC patients, Nivolumab demonstrated lasting responses. In this trial, patients received 3 mg/kg of Nivolumab intravenously every two weeks until disease progression, death, unacceptable side effects, consent withdrawal, or study completion. Notably, 31% of the 74 patients achieved an objective response, and 69% maintained manageable disease for 12 months or longer during a median follow-up of 12 months (Overman et al.2017). Phase I and II clinical trials have also shown positive results for Nivolumab and other immune checkpoint inhibitors (ICIs) in MSI-H mCRC therapy(Jacome et al. 2019).

Another anti-PD-1 mAb, Pembrolizumab, is an FDA-approved fully humanized IgG4 antibody (Marcus et al. 2019; Scapin et al. 2015). It was evaluated alongside napabucasin in MSI-H/MSS mCRC patients, with the results from a phase I/II trial confirming the effectiveness of this combination (Kawazoe et al. 2020).A separate study assessed the impact of Pembrolizumab in CRC patients expressing PD-L1, reaffirming its suitability for PD-L1-positive CRC patients(O'Neil et al. 2017). Moreover, targeting PD-1 immune checkpoints with a combination of anti-PD-1 mAbs, such as Nivolumab with low-dose Ipilimumab, holds promise as a therapeutic strategy for previously treated MSI-H/dMMR mCRC patients (Morse et al. 2019).

7.3 Anti-PD-L1

PD-L1 is recognized as a part of the PD-1/PD-L1 pathway, which hinders the antitumor function of T cells by binding to its ligand, PD-1. Alongside PD-1, PD-L1 can be targeted using monoclonal antibodies (mAbs) to prevent the weakening of T cell signaling (Taube et al. 2014; Balar et al. 2017). Anti-PD-L1 mAbs, such as Atezolizumab, Durvalumab, and Avelumab, are employed in the treatment of melanoma, non-small cell lung cancer (refer to table 2) (NSCLC), and renal cell carcinoma (RCC), respectively (Hahn et al. 2017; Carretero-González et al. 2018). Atezolizumab, a humanized IgG1 mAb against PD-L1, demonstrates therapeutic effectiveness in various cancers, including metastatic urothelial cancer and lung cancer (Balar et al. 2017; Horn et al. 2018). A phase Ib study investigating Atezolizumab in combination with Bevacizumab (an anti-VEGF-A antibody) for 10 patients with microsatellite instability-high metastatic colorectal cancer (MSI mCRC) revealed an overall response rate (ORR) of 30% and a disease control rate of 90% without unexpected side effects(Hochster et al. 2017). Durvalumab, another human IgG1 mAb targeting PD-L1, impedes the interaction between PD-1 and PD-L1 (refer to table 2) (Tan et al. 2018). The efficacy and safety of Durvalumab as monotherapy were examined in MSI-H tumors with 10 mg/kg intravenous administration every two weeks for 12 months, showing an ORR of 23% for MSI-H tumors and 22% for colorectal cancer (CRC) patients. These results indicate Durvalumab as a promising treatment option for MSI-H tumors. Avelumab, a fully human IgG1 mAb that binds PD-L1 and disrupts the interaction between PD-L1 and its receptors, restores immune responses, including T cell antitumor responses. An investigation to determine the effective dose of Avelumab in 53 patients with metastatic or locally advanced solid tumors, such as CRC, indicated that the drug can be administered in 20 mg/kg doses every two weeks, with further studies ongoing (Heery et al. 2017). PD-L2, another ligand for PD-1, is expressed in around 40% of CRC patients and its increased expression in CRC is associated with IFNγ expression and glycosylation (refer to table 2) (Wang et al. 2017). Furthermore, PD-L2 can impact tumor cell invasion, making it a potential candidate for CRC treatment (Guo et al. 2018).

8. Adverse effects resulting from immune checkpoint inhibitors

In spite of the significant progress achieved in cancer treatment through Immune Checkpoint Inhibitors (ICIs), the presence of side effects remains a prominent challenge and limitation in ICI therapies. These adverse effects stemming from ICIs are referred to as immune-related adverse effects (irAEs), and they tend to be more prevalent in organs like the skin, gastrointestinal system, lungs, kidneys, liver, and nervous system. Research indicates that the toxicities associated with monoclonal antibodies (mAbs) targeting CTLA-4 is more severe compared to anti-PD-1/PD-L1 antibodies. This heightened severity is attributed to the critical and comprehensive role of CTLA-4 in various T cell subgroups (including naive and memory cells) within lymph nodes (Myers, 2018).

Some of the adverse effects that can result from ICI usage encompass symptoms like itching, skin rashes, diarrhea, colitis, hepatic issues, hyperthyroidism, hypothyroidism, and pneumonitis (Zhang et al.2018). Notably, colitis stands out as the most common irAE linked to anti-CTLA-4 antibodies, while irAEs such as pneumonitis, hepatitis, and neurotoxic effects are more commonly associated with anti-PD-1/PD-L1 therapies (Wang et al. 2018). It's worth noting that the combination of ICIs tends to produce more potent irAEs than monotherapy (Friedman et al. 2016). For instance, a case report study revealed that the concurrent use of Ipilimumab and Nivolumab was correlated with more severe cases of toxic epidermal necrolysis (TEN) compared to monotherapy in patients with metastatic melanoma (Logan et al.2020). Furthermore, the combination of Nivolumab and Ipilimumab was found to induce autoimmune myositis and myasthenia gravis in metastatic melanoma patients (Sutaria et al. 2019). In summary, managing and mitigating these irAEs is an essential aspect of ICI treatment, and treatments such as corticosteroids may be considered based on the grading of irAE severity (grades 1-4) (Myers, 2018).

9. CONCLUSION

In conclusion, this systematic review has provided a comprehensive overview of ICIs and their significance in cancer treatment. The field of immunotherapy has witnessed remarkable advancements in recent years, and ICIs have emerged as a pivotal component of this progress. We have explored the mechanism of action, the types of ICIs, and their applications across various cancer types.

While ICIs have shown tremendous promise in enhancing the body's immune response against cancer cells, they are not without their challenges. Immune-related adverse effects (irAEs) and the differences in toxicities between various ICIs have been discussed.

Understanding and managing these side effects are essential for optimizing ICI therapy and ensuring the safety and well-being of patients.

The combination of ICIs, which has become a subject of intense research, has demonstrated both increased efficacy and an amplified potential for irAEs. This raises important considerations regarding the balance between therapeutic benefits and risks when choosing treatment approaches.

As our knowledge of ICIs continues to expand, ongoing research is vital to uncover new applications and combinations that can further improve cancer outcomes. The promise of precision medicine, personalized treatment plans, and innovative approaches to mitigate irAEs holds great potential for the future of cancer immunotherapy.

In summary, the potential of Immune Checkpoint Inhibitors in revolutionizing cancer treatment is undeniable. They have opened new doors in the fight against cancer, offering hope to patients and healthcare professionals alike. Continued research, clinical trials, and close monitoring of patient responses are key to harnessing the full potential of ICIs and translating their benefits into improved outcomes for cancer patients worldwide.

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Conflict of interest

The authors declare no conflicts of interest associated with the publication of this paper. This work was conducted with impartiality, and the authors have no financial, personal, or professional affiliations that could potentially bias the content or interpretation of the paper.

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