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**PD-1 receptor blocker: Is it revolution in cancer therapy?**

**Muhammad Faraz Shamshad**  
Department of Internal Medicine, Karachi medical and dental college  
Corresponding author email: Dr.farazshamshad@gmail.com

**Sehrish Khan**  
Department of Internal Medicine, Karachi Medical and Dental College  
Email: khansehrish9992@gmail.com

**Disha Mitra**  
Department Of Biophysics And Molecular Biology, University Of Calcutta  
Email: mitradisha98@gmail.com

**Samiksha Gupta**  
Bachelor Of Engineering, Department Of Chemical Engineering,Birla Institute Of Technology, Mesra, Ranchi  
Email: samikashaguupta2201@gmail.com

**Shaikh Rajesh Ali**  
Assistant professor P.G. Department of Microbiology, Acharya Prafulla Chandra College, New Barrackpore  
Email: rajesh@apccollege.ac.in

**Nadeem Siddiqui**  
Department of Biotechnology, Koneru Lakshmaiah Education Foundation, Vaddeswaram, Andhra Pradesh  
Email: siddiqui@kluniversity.in

**Supriyo Mukherjee**  
Department of microbiology,university of kalyani  
Email: supriyom00@gmail.com

**Abstract**---PD-1 or the programmed cell death protein 1 plays a major role in eliciting the immune checkpoint response of T cells. They are the inhibitory receptors induced in activated T cells. The application of these receptors earns a great interest to investigate, in-depth, their mechanism of action and therapeutic success. The US FDA has successfully approved three categories of immune checkpoint inhibitors. These are PD-1 inhibitors (Nivolumab, Pembrolizumab, and
Cemiplimab), PDL-1 inhibitors (Atezolimumab, Durvalumab and, Avelumab), and CTLA-4 inhibitor (Ipilimumab). But still there lie several limitations in using this mode of treatment. Unlike, not all patients respond well to these drugs. Apart from these, anti PD-1 monoclonal antibody showed its miraculous activity in treating cancer. It showed a hundred percent cure in patients with colorectal cancer without any kind of major side effects following the treatment procedure. Anti PD-1 monoclonal antibody (Dostarlimab) has shown promising results in endometrial cancer, ovarian cancer, melanoma, head and neck cancer, and breast cancer therapy. The current review focuses on the literature regarding the mechanism of action of immune checkpoint inhibitors, their role in cancer treatment. Here we mainly emphasized on the mechanism of PD-1 and PD-L1 in cancer therapy and discussed the clinical success of the wonder drug dostarlimab.

Keywords---programmed cell death protein 1 (PD-1), immune checkpoint inhibitors, dostarlimab, anti-cancer drug, monoclonal antibody.

Introduction

Cancer is one of the deadliest diseases that humankind has ever encountered. Despite years of research on cancer etiology and therapies it has still remained a leading health problem that causes almost 10 million deaths per year. The diagnosis and treatment of cancer were negatively affected by the coronavirus disease 2019 (COVID-19) pandemic. Colorectal cancer (CRC) is one of the conditions that are the major cause of death worldwide. In 2020, about 104,610 new cases were estimated and 53,200 deaths were estimated in US. In developed countries, early detection through screening has improved the 5-year survival of patients with CRC, but the prognosis for patients with metastatic CRC remains poor. (44)

Several forms of treatment including treatment with drugs in chemotherapy, radiotherapy, surgery, and immunotherapy developed for the treatment of cancer. These therapies are generally associated with a multitude of side effects ranging from discomfort to the development of secondary tumors and severe cytotoxicity to multiple systems including the immune system. (21) Wilhelm Busch and Friedrich Fehleisen were the first to assess the interrelationship between immune system and cancer. Hence, Immunotherapy has been discovered that uses specific parts of the patient’s immune system to treat various forms of diseases. Cancer immunotherapy re-activates the immune system, which has been suppressed by tumor cells. It is developed to treat cancers and also to minimize the side effects associated with conventional methods. (30) Immunotherapies are specific in targeting cancer stem cells and their metastasis. They can able to diagnose the smallest of tumors. Immunotherapy also leads to the development of cancer vaccines, which have shown potential results in minimizing tumor growth but still fall short of eradicating it. There are also antibody-based drugs that are associated indirectly or directly to immunotherapy. (9)
There are five classes of immunotherapy, including: checkpoint inhibitors, antibody-based targeted therapies, cancer vaccines, antigenic receptor T-cells, and lastly oncolytic viruses. Immune checkpoint inhibitors (ICIs) are the immune therapy that takes advantage of immune system to fight with cancer cells. Recently, monoclonal antibody-based immunotherapy is has come into play alongside other methods. These antibodies can not only target tumor cells but can also trigger long-lasting antitumor immune responses. These versatile antibodies laid a therapeutic platform that resulted in the development of new cancer treatment strategies which will change the direction of cancer treatment in the future. (3)

This review aims to investigate in-depth the immune checkpoint inhibitors in cancer therapy, the mechanism by which the PD-1/PD-L1 pathway transmits inhibitory signals to target the cancerous cells and the therapeutic success of different inhibitory drugs. We also investigated the discovery of the newest cancer therapeutic strategy, the use of dostarlimab which has risen as a miracle drug with the hope of cancer treatment.

**Immune check point inhibitors in cancer therapy**

**History**

In the 19th century, the use of an immune system as a tool to treat neoplastic disease originated. William Coley, known as the ‘Father of Cancer Immunotherapy’, treated cancer patients with extracts of heat-inactivated *S. pyogenes* and *Serratia marcescens* to boost immunity. The extract was named after him as ‘Coley’s toxins’, which was later not considered for standard practice after the discovery of radiotherapy and chemotherapeutic agents. (45) After 120 years of research on cancer, immunotherapy is ultimately accepted as a promising approach to tackle the dynamic and complex interplay between cancer and immunity. Immunotherapy such as adoptive cell transfer (ACT), and immune checkpoint inhibitors (ICIs), has taken advantage of immune system components to fight against tumor cells. Immunotherapy alone or in combination with radiotherapy and chemotherapy has achieved considerable success in treating the number of cancers. (38)

In 2018 Dr. James Allison and Dr. Tasuku Honjo discovered programmed cell death protein-1 (PD-1) and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), for which they were awarded the Nobel Prize to honor their outstanding work in the development of immunotherapy. (32)

**Mechanism of action of immune checkpoint inhibitors**

T cell activation depends on two signals, regulated by co-stimulators or co-inhibitors known as immune checkpoints. (34)

*Signal one:* Derived from the interaction between antigenic peptide/major histocompatibility complex (MHC) on the surface of APCs and the T cell receptor (TCR).

*Signal two:* Requires an antigen-independent co-signaling molecule.
The engagement of PD-1 by programmed death ligand-1 (PDL-1) results in the recruitment of Src homology 2 (SH2) domain-containing phosphatases 1/2 (SHP1/2) and then inhibits T cell proliferation and cytokine secretion. Some cancer cells can generate inhibitory ligands that binds with a co-inhibitory receptor. This limits the normal anti-tumor immune. Therefore, immune checkpoint inhibitors are capable to invoke patient’s anti-tumor immune response. These inhibitors do not kill cancer cells directly, instead, they harness the power of the host’s immune system to re-enhance endogenous anti-tumor activity. (37) The mode of action of different immune check point inhibitors are delineate din Table 1.

Table 1: Different types of immune checkpoint inhibitors and their mode of action

<table>
<thead>
<tr>
<th>Immune checkpoint inhibitors</th>
<th>Immune checkpoint expression site</th>
<th>Drug</th>
<th>Approved in</th>
<th>Tumor treated</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTL-4</td>
<td>Activated T cell, NK cell</td>
<td>Ipilimumab</td>
<td>August 2010</td>
<td>Stage 3 or 4 malignant melanoma</td>
<td>(Mansh, 2011)</td>
</tr>
<tr>
<td>PD-1</td>
<td>T cell, B cell, NK cell, Monocytes, Dendritic cell, Tumor cell</td>
<td>Nivolumab</td>
<td>March 2015</td>
<td>Stage III-B or IV squamous NSCLC</td>
<td>(Rolfo et al., 2017)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pembrolizumab</td>
<td>October 2016</td>
<td>Stage IV non-squamous and squamous NSCLC</td>
<td>(Wu, 2021)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cemiplimab</td>
<td>September 2018</td>
<td>metastatic cutaneous squamous</td>
<td>(Migden et al., 2018)</td>
</tr>
</tbody>
</table>
Advantages and Disadvantages of immune checkpoint inhibitors

The merits and Demerits if Immune check point inhibitors are summarized in Table 2. (Tan et al., 2020)

Table 2: Advantages and Disadvantages of Immune Check Point Inhibitors

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The effect of &quot;immunoinflammatory&quot; tumor is good, and the survival rate is significantly improved</td>
<td>• In case of &quot;immune suppression type&quot; and &quot;immune exclusion type&quot; of tumors, the effect of immunotherapy is poor</td>
</tr>
<tr>
<td>• High accuracy, and specificity</td>
<td>• Immunocheckpoint inhibitors can produce negative regulation, leading to autoimmune diseases and even death</td>
</tr>
<tr>
<td>• Effective incontrolling and killing multiple types of tumors</td>
<td>• Hyperprogressive disease may occur, accelerating the death of patients.</td>
</tr>
<tr>
<td>• Persistent. Restores body's immune function and kill tumor cells for a long time</td>
<td>• The survival rate and prognosis of patients are uncertain</td>
</tr>
<tr>
<td>• Prevent tumor recurrence and metastasis</td>
<td>• Treatment costs are high</td>
</tr>
<tr>
<td>• Thoroughly remove residual tumor cells and microscopic lesions from the body</td>
<td>• Limited data regarding their safety in children</td>
</tr>
<tr>
<td>• The side effects are less</td>
<td></td>
</tr>
</tbody>
</table>
**PD-1 and PDL-1 inhibitors**

**PD-1 inhibitors**

PD-1 is an inhibitor receptor that has the role of programmed cell death signaling to regulate T cell-mediated responses. PD-1 inhibits cytokine secretion (IL-2, IFN-γ, and TNF-α) and cell proliferation through interfering CD28-costimulatory signalling pathway, which induces T cell dysfunction. (13) The expression of PD-1 is detected in different immune cells like monocytes, dendritic cells (DCs), natural killer cells (NK), T cells and, B cells. These are used in the treatment of cancers, including Merkel cell carcinoma (MCC), melanoma, head and neck squamous cell carcinoma (HNSCC), and non-small-cell lung cancer (NSCLC). The US FDA has approved 3 monoclonal antibodies as PD-1 inhibitors: Nivolumab, Pembrolizumab, and Cemiplimab. (15)

**PDL1 inhibitors**

PD-1 has 2 ligands, PD-1 ligand 1 (PD-L1) and PD-1 ligand 2 (PD-L2). PD-L1 is expressed by both tumor and immune cells. PD-L1 and PD-L2 are the biomarkers that respond to anti-PD-1/PD-L1 antibodies in some patients with different types of cancer. PD-L1, also known as B7-H1 or CD274, plays a part in inhibiting the cancer-immunity cycle through binding to negative regulators of T-cell activation such as PD-1 and B7.1 (CD80) Therefore, PD-L1 ligation is known to inhibit migration and proliferation of T cell, thereby restricting tumor cell killing. (Doroshow et al., 2021) The US FDA has approved 3 PD-L1 inhibitors: Atezolimumab, Durvalumab, and Avelumab. They are used to treat some tumors, like NSCLC, HNSCC, melanoma, and MCC. (15)

**Role of PD-1 and PD-L1 in cancer progression**

PDL1 or PDL2 is over-expressed in cancer cell lines that constrain the CD8+ T cell cytotoxic anti-tumor response. Blockade of PD1 causes suppression of the growth of transplanted cancer cells. Neutralizing the PD1 axis using monoclonal antibodies enhances T cell cytotoxicity towards tumor cells. (18) PD1 inhibition not only augments antitumoral immunity but also limits hematogenous seeding of B16 melanoma and CT26 colon carcinoma metastases. This proves that PD1:PD-L1 blockade can enhance tumour cytolysis and limit metastasis as well. Pembrolizumab and nivolumab became the first FDA-approved PD1-targeted therapeutics for the treatment of melanoma.

With the increase in PD-L1 expression on the target tumor, there is an improved response to PD1 axis blockade. PD-L1 is targeted by specific antibodies which have proved to be effective treatments in multiple forms of cancer. In 2016, the first PDL1-targeted humanized mAb, atezolizumab, was approved for the treatment of urothelial carcinoma. The other anti-PD-L1 human mAbs, avelumab and durvalumab, entered the market in 2017. Avelumab is used for the treatment of Merkel cell carcinoma, urothelial carcinoma and, advanced renal cell carcinoma. Therefore, similar to PD1, the blockade of PD-L1 has been effective in difficult-to-treat forms of cancer. (18)
**Mechanism of cancer remediation**

In cancerous cells activated T cells express programmed cell death 1 (PD1), which engages with its specific ligand (PD-L1 or PD-L2) to dampen activation. (10) The mechanism is simplified in Figure 1.

![Mechanism of cancer inhibition](image)

**Figure 1: Schematic Presentation of Mechanism of Action of Cancer Inhibition by blocking PD-1 axis**

**Literature review of different clinically approved molecules**

**Pembrolizumab (anti-PD-1)**

Herbst, R. S. et al 2015, approved pembrolizumab for the treatment of PD-L1-expressing non-small-cell lung carcinoma because it provided a 4.3-month increase in progression-free survival. It was found to be more effective than the chemotherapeutic paclitaxel. (14) Inokuchi et al 2019 concluded that pembrolizumab may be a potential first-choice second-line therapy for unresectable or metastatic urothelial carcinoma (UC) following chemotherapeutic procedure. (16) In 2021, Chen et al reported that the combination of pembrolizumab and lenvatinib has the potential therapeutic option as a first-line treatment in patients with head and neck squamous cell carcinoma (HNSCC). (5)
**Nivolumab (anti-PD-1)**

In 2014 and 2015, Nivolumab was approved by the FDA for the treatment of melanoma and renal cell carcinoma, respectively. (20) In 2015 it was approved by FDA for the treatment of squamous cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). (20)

**Atezolizumab (anti-PD-L1)**

Rosenberg et al 2016, atezolizumab was approved for the treatment of urothelial carcinoma. (36) In 2018, Mazieres et al reported that for patients with recurrent NSCLC tumours, expressing medium or high levels of PD-L1, atezolizumab demonstrated statistically significant survival advantage. (26)

**Avelumab (anti-PDL-1)**

In 2019, Angelo et al noted long-term safety with no adverse events in patients with merkel cell carcinoma (MCC) following the administration of avelumab. (6)

**Dostarlimab: Has the magic bullet for cancer therapy arrived?**

Dostarlimab is a humanized anti-programmed cell death protein (PD-1) monoclonal antibody (mAB). It is being developed by Glaxo-SmithKline (GSK) under a license from AnaptysBio Inc for the treatment of different types of cancer including endometrial cancer, colorectal cancer, ovarian cancer, SCLC, NSCLC, squamous cell carcinoma (SCC), pancreatic cancer, etc. Dostarlimab has been approved on 22 April 2021 for adults with endometrial cancer in the EU and USA. The recommended dose of dostarlimab is 500 mg every 3 weeks for the first four doses, followed by 1000 mg every 6 weeks. (41)

**Mechanism of action**

As already been discussed in the earlier section, PD-L1 and PD-L2 bind with PD-1 receptor on T-cells. This results in the inhibition of cytokine and T cell proliferation. In some cancer lesions, PD-1 ligands are upregulated, and signaling through this pathway may contribute to the suppression of active T-cell immunity. This is where the drug dostarlimab comes into play.

- It inhibits PD-1 and blocks its interaction with PD-L1 and PD-L2
- This in turn activates T-cells and enhances overall immunity.
- Dostarlimab is a functional antagonist of PD-1 resulting in increased IL-2 production.
- Thus, blocking PD-1 enables the T cells to recognize and attack the cancer cells by restoring the cytotoxic activity of the T cells.
- This finally decreases angiogenesis and tumor cell survival. (23)

**Research on the effectiveness of dostarlimab in the cancer treatment**

A pharmacokinetic study for dostarlimab was carried out on 150 endometrial cancer patients. There were no clinically significant differences observed in the
pharmacokinetic characteristics of dostarlimab based on gender, age, ethnicity, tumor type, or renal or hepatic impairment. Dostarlimab has been administered on monkeys. Doses were repeated for one and three months. There were no significant effects on male or female reproductive organs, although most animals were not sexually mature by the time of the study. (25)

GARNET trial was the first-in-human trial that evaluated the pharmacokinetics, and pharmacodynamics, of dostarlimab. The trial also evaluated the tolerability, clinical activity, and safety of dostarlimab across multiple solid cancer types. These included endometrial, NSCL, and cancer of the ovaries and fallopian tubes. In part 1, three weight-based doses (1, 3, and 10 mg/kg) were administered every 2 weeks intravenously. In part 2A, 500 mg every 3 weeks, and in part B, 1000 mg every 6 weeks intravenously. Data from Part 1 demonstrated maximum receptor occupancy at 2.4 g/mL dostarlimab serum concentrations. Furthermore, a PK model was constructed to predict dostarlimab concentrations. (19)

**Recent ongoing researches**

In June 2022 medical science faced a revolutionary discovery in the field of cancer treatment. For the first time, a new drug has been trialed and showed complete eradication of rectal cancer with no sign of reoccurrence. This is the mAB-based drug dostarlimab that was evaluated for safety under efficacy against locally advanced rectal cancer. (41) According to the previous report by Wilt in 2007, colorectal cancer is usually treated with chemoradiation, radiotherapy, and total mesorectal surgery (TME) surgery. The results from this collective therapy showed a positive results and excellent survival rates. (7)

Cercek et al 2022 in their ongoing trial mentioned that the standard method of treatment of locally advanced rectal cancer is radiation and neo-adjuvant chemotherapy followed by the surgical removal of the rectum. During the phase, it has been noted that the cause of some rectal cancers is a lack of mismatch repair. They respond to the PD-1 blockade, thus suggesting that a checkpoint blockade may be effective in mismatch repair-deficient patients. These patients were administered dostarlimab every 3 weeks for 6 months. The patients who will respond well to dostarlimab would not chemotherapy, radiotherapy, or surgery. Till now 12 patients had successfully completed treatment and are under 6 months follow-up. These 12 patients showed no form of existing tumor, progression and recurrence. No adverse events were reported. The study depicted that a single agent PD1 was highly sensitive to mismatch repair deficient, locally advanced rectal cancer and could bring about positive results; however, a longer follow-up study still needs to be performed to validate this point. (4)

Another clinical trial began on 8 May 2017, for patients with deficient mismatch mutation repair endometrial cancer. 104 women with were enrolled to receive dostarlimab 500 mg IV every 3 weeks for 4 doses followed by 1000 mg every 6 weeks. Radiographic evaluations were performed 12 weeks after the first dose, every 6 weeks until month 12, and then every 12 weeks thereafter. The results obtained from this analysis that the responses to dostarlimab were durable. The safety profile of dostarlimab was highly comparable to that of other anti-PD-1 antibodies. Treatment-related adverse events were less than 2% and no morbidity
rate. (33) Some major ongoing clinical trials on dostarlimab is summarized in Table 3.

Table 3: Some major ongoing clinical trials on dostarlimab

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cancer lesion</th>
<th>Phase of trial</th>
<th>Start date</th>
<th>End date</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dostarlimab</td>
<td>Endometrial cancer</td>
<td>I</td>
<td>15 Oct 2019</td>
<td>31 Oct 2024</td>
<td>(Washington University School of Medicine, 2022)</td>
</tr>
<tr>
<td>Dostarlimab</td>
<td>Cervical cancer</td>
<td>II</td>
<td>28 June 2019</td>
<td>Dec 2024</td>
<td>(Grupo Español de Investigación en Cáncer de Ovario, 2021)</td>
</tr>
<tr>
<td>Dostarlimab</td>
<td>Advanced clear cell sarcoma</td>
<td>II</td>
<td>19 Feb 2021</td>
<td>1 May 2024</td>
<td>(Italian Sarcoma Group, 2021)</td>
</tr>
<tr>
<td>Dostarlimab</td>
<td>Endometrial cancer</td>
<td>II</td>
<td>2 April 2021</td>
<td>February 2023</td>
<td>(Memorial Sloan Kettering Cancer Center, 2022)</td>
</tr>
<tr>
<td>Dostarlimab</td>
<td>Advanced solid tumors</td>
<td>I</td>
<td>25 June 2020</td>
<td>29 Aug 2024</td>
<td>(GlaxoSmithKline, 2022)</td>
</tr>
<tr>
<td>Dostarlimab</td>
<td>Advanced solid tumors</td>
<td>I</td>
<td>7 March 2016</td>
<td>30 July 2024</td>
<td>(Tesaro, Inc., 2022)</td>
</tr>
</tbody>
</table>

Is it a wonder drug?

Driving the patient’s immune system to act against the deadly disease of cancer could potentiate the fast remission of neoplastic cells. It is the T cell that needs to be inactivated that in turn should attack the cancer cells from proliferating. Dostarlimab is one of the immune therapies that prevent the binding of PD-1, inactivating the T cells. According to the results shown by dostarlimab in cancer treatment, it cannot be overlooked that this agent could be a star compound against colorectal cancer.

Conclusion and future perspective

Immune checkpoint inhibitor (ICI) treatment has completely transformed cancer immunotherapy. The FDA-approved anti-CTLA-4 therapy, and anti PD-1 therapy, have sparked a renewed interest among oncologists as potential antitumor agents. Initially these molecules serves the purpose of T cell activation or death, later, preclinical studies revealed that they play a crucial role in the maintenance of peripheral immunological tolerance.

Blocking CTLA-4 and PD-1 leads to the formation of anticancer immune responses that allows the body’s immune system to work against the cancer cells. Other ICIs have been revealed that can be targeted by monoclonal antibodies based on their cell surface expression, in addition to CTLA-4 and the PD-1/PD-L1
axis. Some of these molecules have a function in immunological tolerance while others appear to play a far more modest role. (37)

In addition to examining the function of existing molecules in cancers other than melanoma, NSCLC, and RCC, a novel anti PD-1 receptor is tested singly and in combinations. This was investigated in adjuvant or neoadjuvant methods, with the goal to improve the overall survival of many cancer patients. These treatments have revolutionized cancer immunotherapy by demonstrating, for the first time in many years of research, an improvement in overall survival in metastatic cancers. Dostarlimab is one such drug that showed its magical response.

However, the systemic effects of various immunotherapies should be known to gain a better knowledge of how the immune system begins and maintains an effective antitumor response. It is expected that the combination of ICIs, chemotherapy, and radiotherapy could be performed in particular patients who have not experienced a favorable response to ICI-based therapies. There is limited data regarding their safety in children even though they showed positive results in adults. It was demonstrated that dose-dependent adverse events of CTLA-4 blockade ranging from mild to moderate occurred in more than 70% of patients. (1) The toxicities are lesser in PD-1/PD-L1 blockades as compared to CTLA-4 inhibitors. Fatigue is found to be the most common adverse event in patients receiving PD-1 and PD-L1 inhibitors. (29) As of now, the concept of immunotherapy could mark a revolution in oncotherapy.

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