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PD 1: A Trending Target in Anti-cancer Research

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Abstract: Cancer has been identified as a major cause of mortality around the world fora long. To improve the recovery rates of cancer patients, the development of more effective chemopreventive techniques and treatment methods has become important day by day. Recently, various immune inhibitors, mainly including anti-PD-1 and anti-PDL-1, derived from single cells of monoclonal antibodies, have emerged for a group of cancer patients. Functions of T-cells and tumor-infiltrating lymphocytes (TIL) are suppressed by PD-1 and PDLs, while the function of immunosuppressive regulatory T-cells (Tregs) is increased by the latter. To summarize the role of PD-1 and PDLs immune inhibitors in immuno-oncology (I-O), a huge literature survey has been carried out in Science Direct, Scopus, Pubmed, and various other literature hubs for collection of data. This article is focused on cancer immunotherapy, the mechanism of action of PD-1 and PDLs as immune inhibitors, combinatorial immunotherapy, and various FDA-approved target anticancer drugs working against PD-1 and PDLs, a very novel and important target in the field of personalized anticancer drug delivery. Further, there is a wide scope for cancer researchers in this area to explore in the near future.

Keywords: cancer; immune checkpoints; immunotherapy; PD-1.

1. Introduction

Over the past decade, an important area of personalized medicine, namely immuno-oncology (I-O), has emerged due to its significant role in potentiating the body's immune system to fight against cancer. Immuno-oncology works on the body's immune system to make it recognize and eliminate malignancies using the action of the target drugs on the various immune checkpoints of the body. The uncontrolled growth of abnormal cells in any part of the body is known as cancer. Cancer cells, malignant cells, or tumor cells are used to describe these abnormal cells. Normal body tissues can be infiltrated by these cells. The name of the tissue from which the abnormal cells originated is used to identify many tumors and the abnormal cells that produce from cancer tissue (for example, breast cancer, lung cancer, colorectal cancer, and so on) [1]. Under normal conditions, the immune system uses several co-inhibitory and costimulatory receptors and their ligands, known as immunological checkpoints, to protect the host from autoimmunity, allergies, and infectious diseases [2, 3]. In current scenarios, inhibitory checkpoints, such as PD-1 (programmed cell death protein 1), CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4), and PD-L1 (programmed cell death-ligand 1), have been identified to block antitumor immune responses in solid tumors [4].

Recent studies have recognized a few new immune checkpoint targets likeVISTA(V-domain Ig suppresser of T-cell activation), LAG-3 (lymphocyte activation gene-3), TIGIT (Tcell immunoglobulin andITIM domain), TIM-3 (T-cell immunoglobulin and mucin-domain containing-3). Preclinical research and possible clinical trials have shown good outcomes in researching these molecules [5]. With several treatments in clinical and preclinical development, the number of approval of the immunotherapeutic drugs is being increased. However, the immunotherapies of concern for cancer treatment have severe adverse effects, such as generation of autoimmunity, nonspecific inflammation, etc. Hence, the targeted control of the immune system has become a major challenge in the general use of immunotherapies for malignancies [6, 7].

The FDA has approved several drugs that target immune checkpoints to date, and others are presently undergoing clinical and preclinical testings (Tables 1 and 2). Malignant growth cells can evade the immune system with the help of anti-immune regulatory molecules, including PD-1 and PDL-1. The interaction between PD-1 and PD-L1 inhibits T-cells and tumor-infiltrating lymphocytes, while immunosuppressive regulatory T-cells are thereby increased [8]. The growth and development of current biomedical researchers can be traced back to a study on the human PD-1 gene. However, research on PD-1 has not been completed yet [9]. Presently, a combination of immunotherapy with chemotherapy or radiation therapy is recommended for cancer treatment, and it is synergistic via different mechanisms[10].

Immunotherapy has arisen as a component in malignant growth therapy, besides other medical procedures, including chemotherapy and targeted drug delivery. The future of malignant growth immune therapy depends on the treatment with a targeted drug that inhibits the human PD-1 immune checkpoint [11]. Thus, presently, cancer immune therapy has changed how people think about cancer treatment; these treatments aim to enhance antitumor immune responses with fewer side effects than those in chemotherapies and cytotoxic agents killing cancer cells directly. In cancer chemo immune therapy, target drugs are used to work on or improve the immune system's activity to encounter the cancer-causing cells [12,13]. As a consequence, immunotherapy is being considered by modern researchers as a promising strategy for the treatment and cure of certain cancers. Cell treatments, vaccinations, cytokines, and transfection agents are examples of various immune agents used in cancer immune therapy [14].

In recent research, it has been observed that the problem of adverse effects associated with synthetic anticancer drugs can be partly overcome by introducing combination drug therapy in the field of cancer treatment by combining plant-derived bioactive with the synthetic anticancer medications, resulting in the reduction of doses of the synthetic APIs and imparting synergistic effect due to addition of the natural anticancer components [15].

2. Anti PD-1 and Anti PDL-1 Immunotherapy

T-cells contain the immunological checkpoint receptor PD-1, which negatively controls the human immune response. However, results suggest that individual patients suffering from the same type of cancer may react to PD-1 inhibition immunotherapy differently. The concept of PD-1 inhibition therapy with a targeted drug has initiated the pathway of a new cancer immune therapy targeting the PD-1 immune checkpoint [16].

When PD1 binds to PDL-1 on tumor cells, it prevents T-lymphocytes from proliferating, migrating, and secreting cytotoxic agents and killing the cancer cells. In addition, PD-1 and PD-L1 connect with the cell-surface protein ligands of the B7 family, CD80 (B7-1)

and CD86 (B7-2), to produce negative signals on T cells and inhibit cancer immunity [17, 18]. The immune checkpoint inhibitors against PD-1 and PD-L1 have demonstrated clinical efficacy against various cancers [17]. Access to the PD-1 checkpoint is blocked and inhibited by PD-1 inhibitors that prevent T-cell inhibition and increase anticancer immunity in cancer patients, resulting in prolonged anticancer and anti malignant tumorigenic effects [18]. The development of anticancer target drugs against PD-1 and PD-L1 has enhanced the clinical applications of cancer immunotherapy. Similarly, several reduced ICH (immunohistochemistry)-based tests for indicating the presence of the PD-L1 protein in tumors are also currently available [19]. These tests are classified into two categories: partner diagnostic tests, which include data required for the safe and effective use of similar drugs, and co-symptomatic (reciprocal) tests, which are important in the selection of therapy but not for the safe and effective use of similar drugs [20].

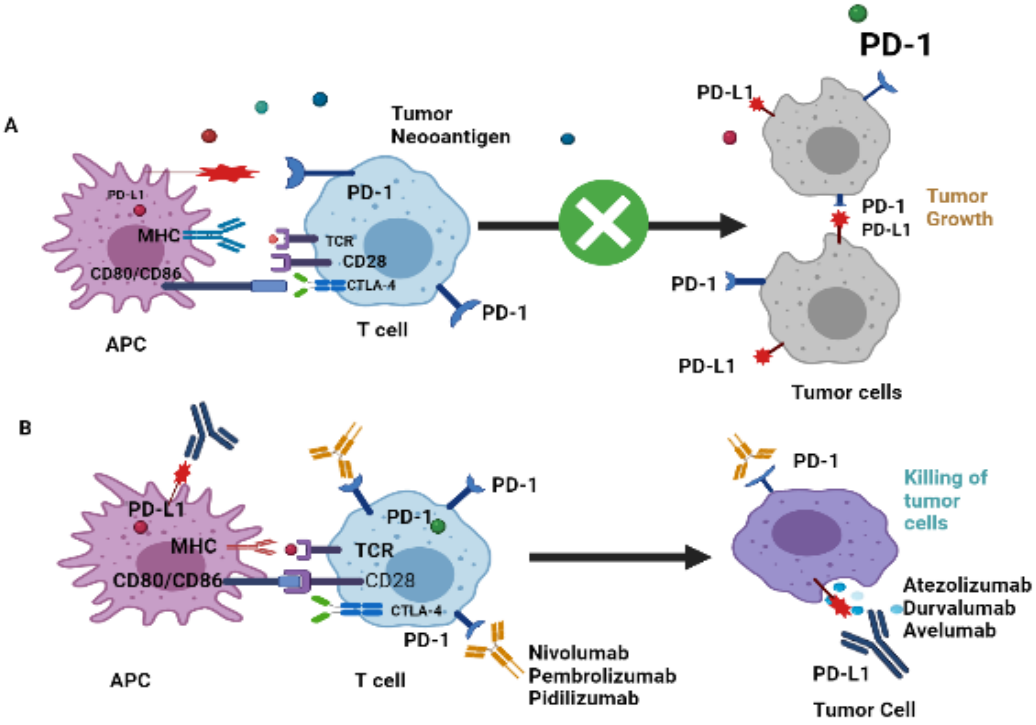

Figure 1. Immunosuppression triggered by the PD-1/PD-L1 pathway in the tumor microenvironment.

As described in (A), PD1 and CTLA-4 are present in T-cells, and PD-L1,CD80/CD86 are present in antigen-presenting cells (APC). Usually, the various immune checkpoints keep the T-cells inactive, thereby preserving the normal cells from the harmful effect of the latter. Cancer cells take advantage of this phenomenon to keep themselves from being destroyed by the T-cells. In the presence of the activated T-cells, PD-L1becomes over-expressed on tumor cells, and the over-expressed PD-L1 thus interferes with the body's anticancer immune response by binding to its receptor, PD-1. Thus, the cytotoxic activity of the T-cells is deactivated, thereby aggravating the tumor development. To overcome this problem, monoclonal antibodies like nivolumab, pembrolizumab, and pidilizumab have been introduced to bind with PD-1 and thereby inhibiting PD1-PD-L1 interaction from restoring the antitumor activity of the immune system, as described in (B). (B) describes that the monoclonal antibodies developed against PD-1 immune checkpoints, such as nivolumab, pembrolizumab, and pidilizumab, block the interaction of PD-1 with the PD-Ls. They enhance T cell cytotoxicity, TAM (tumor-associated macrophage) function, cytokine yield, and eventually

destroy the tumor cells. The PD-L1+ tumor cells can cause T-cell apoptosis, energy, practical exhaustion, and the production of interleukin-10. Antibodies against PD-L1 (durvalumab, atezolizumab, and avelumab) have similar effects to those against PD1, and they also inhibit the interaction between PD-L1 and PD-1[21].

3. Use of Natural Bioactives with Anticancer Potential

Recently, plant-derived compounds in cancer treatment have been proved to be highly successful and effective with minimized adverse effects. Several naturally occurring dietary and non-dietary photochemical have shown to be effective in preventing and treating a wide range of cancers, as reported in Figure 2. In various anticancer researches, the effects of natural bioactives have been studied on different types of malignancies, including breast cancer, lung cancer, gynecological malignancies, melanoma/skin cancer, colorectal cancer, and others[22]. Phyto-compounds hold an important potential in the chemoprevention and treatment of melanoma, even during metastasis.

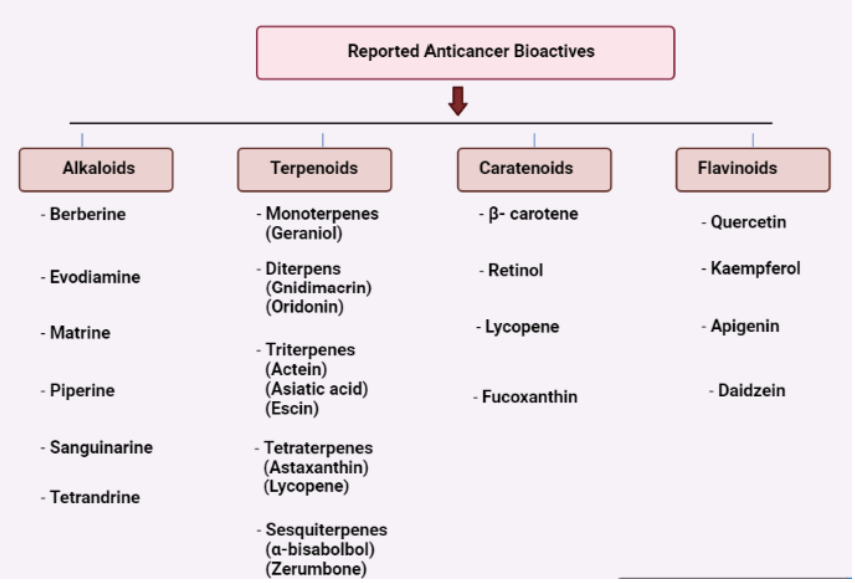

Figure 2. Reported naturally obtained anticancer bioactives [24-26].

The main advantage of natural products relies on their multi-target activity, with one compound being able to interact with multiple proteins and receptors. Further, there are a number of crude extracts or enriched fractions derived from plants, for which the active compound(s) could not be singled out yet to explain a specific anticancer activity. Therefore, the use of multi-component crude plant extracts or enriched fractions from the same have more prominent use in anticancer therapy to date [23].

Table 1. FDA-approved immune checkpoint inhibitors against various types of cancer.

S.No.	Drug Name	Cancer Type	Target Protein	Year of FDA Approval	Ref. No.
1.	Pembrolizumab	Metastatic melanoma	PD-1	2014	[27]
2.	Nivolumab	Metastatic SQ NSCLC	PD-1	2015	[28]
3.	Nivolumab	NSCLC(non-small-cell lung cancer)	PD-1	2015	[29]
4.	Nivolumab	RCC (renal cell carcinoma)	PD-1	2015	[30]
5.	Pembrolizumab	NSCLC (non-small-cell lung cancer)	PD-1	2016	[31]
6.	Nivolumab and Pembrolizumab	Head and neck squamous cell carcinoma (advanced and metastatic)	PD-1	2016	[32]

S.No.	Drug Name	Cancer Type	Target Protein	Year of FDA Approval	Ref. No.
7.	Atezolizumab	Locally advanced or metastatic urothelial carcinoma	PD-L1	2016	[33]
8.	Atezolizumab	NSCLC (non-small-cell lung cancer)	PD-L1	2016	[34]
9.	Durvulumab	Advanced urothelial cancer	PD-L1	2016	[35]
10.	Pembrolizumab	Head and neck cancer	PD-1	2016	[36]
11.	Pembrolizumab and Nivolumab	Head and neck squamous cell carcinoma	PD-1	2016	[37]
12.	Nivolumab	Hodgin's lymphoma	PD-1	2016	[38]
13.	Durvalumab	Advanced urothelial carcinoma	PD-L1	2017	[39]
14.	Atezolizumab	Locally advanced or metastatic urothelial carcinoma	PD-L1	2017	[40]
15.	Durvalumab	NSCLC (non-small-cell lung cancer)	PD-L1	2017	[41]
16.	Avelumab	MCC (Merkel cell carcinoma) with metastatic	PD-L1	2017	[42]
17..	Avelumab	Urothelial cancer	PD-L1	2017	[43]
18.	Avelumab	Locally advanced or metastatic urothelial carcinoma	PD-L1	2017	[44]
19.	Nivolumab	Metastatic colorectal cancer	PD-1	2017	[45]
20.	Nivolumab	Hepatocellular carcinoma	PD-1	2017	[46]
21.	Pembrolizumab	Hodgin's lymphoma	PD-1	2017	[47]
22.	Pembrolizumab	Urothelial carcinoma	PD-1	2017	[48]
23.	Pembrolizumab	Gastric and gastroesophageal carcinoma	PD-1	2017	[49]
24.	Pembrolizumab	Advanced gastric cancer	PD-1	2017	[50]
25.	Atezolizumab	Advanced urothelial cancer/ metastatic urothelial cancer	PD-1	2017	[51]
26.	Cemiplimab	Cutaneous squamous cell carcinoma	PD-1	2018	[52]
27.	Combination of nivolumab and ipilimumab	Renal cell carcinoma	PD-1	2018	[53]
28.	Combination of avelumab and axitinib	Advanced renal cell carcinoma	PD-L1	2019	[54]
29.	Durvalumab	Small cell lung cancer (extensive stage)	PD-L1	2020	[55]
30.	Combination of axitinib with pembrolizumab or avelumab	Advanced renal cell carcinoma	PD-1	2020	[56]
31.	Pembrolizumab	Advanced Esophageal or Gastroesophageal Junction Carcinoma	PD-1	2021	[57]
32.	Atezolizumab	Advanced Unresectable or Metastatic Hepatocellular Carcinoma	PD-L1	2021	[58]
33.	Cemipilumab	Locally Advanced and Metastatic Basal Cell Carcinoma	PD-1	2021	[59]
34.	Toripalimab	Nasopharyngeal Carcinoma and Urothelial Carcinoma	PD-1	2021	[60]

Table 2. Anti PD-1 / PD-L1 therapy for different cancer types.

S. No.	Target	Cancer Types	Drugs Used	Outcomes	Ref. No.
1.	PD-L1	Breast cancer	Pembrolizumab	The results suggest that pembrolizumab has shown antitumor activity in metastatic TNBC (triple-negative breast cancer) with PD-L1-positive patients.	[61]
2.	PD-L1	Triple-negative breast cancer	Atezolizumab	The results have shown clinical benefits in patients with mTNBC (metastatic triple-negative breast cancer), which has been stable in earlier lines of treatments.	[62]
3.	PD-L1	Metastatic breast cancer	Avelumab	In patients with metastatic breast cancer, avelumab has been found to be well-tolerated with good clinical activity.	[63]
4.	PD-1	Triple-negative breast cancer	Nivolumab	The results suggest that nivolumab has been found to have long-lasting and good responses but no difference in survival as compared to the investigator's choice chemotherapy (ICC).	[64]

S. No.	Target	Cancer Types	Drugs Used	Outcomes	Ref. No.
5.	PD-1	Triple-negative breast cancer	Pembrolizumab	It has been demonstrated that various types of tumors that are least affected by DNA variant repair are susceptible to PD-1 blockade.	[65]
6.	PD-L1	Metastatic urothelial cancer	Atezolizumab	The study's findings show that atezolizumab is well tolerated by cancer patients compared to other treatments and has a long-term therapeutic benefit in metastatic urothelial carcinoma.	[66]
7.	PD-1	Melanoma	Pembrolizumab	The results have shown that the drug is generally well-tolerated and safe in patients treated with pembrolizumab.	[67]
8.	PD-L1	Advanced TNBC	Atezolizumab and Nab-Paclitaxel	Atezolizumab and nab-paclitaxel continuous survival with no progression among patients with metastatic TNBC in both treatment-minded individuals and a small PD-L1-positive group have been studied.	[68]
9.	PD-L1	Locally advanced or metastatic urothelial carcinoma	Durvalumab	The results have shown that durvalumab has an outstanding clinical feature of an encouraging and portable safety profile for patients with advanced/local UC (urothelial carcinoma).	[69]
10.	PD-L1	Metastatic urothelial carcinoma	Avelumab	It has demonstrated that avelumab exhibits promising endurance results, and metastatic melanoma has been arrested.	[70]
11.	PD-L1	Bladder cancer	Atezolizumab	The results suggest that the treatment with platinum-based compounds has not been possible unless the patients are PD-1 positive.	[71]
12.	PD-L1	Bladder cancer	Avelumab	The results show that avelumab creates an antitumor antagonistic response in patients with advanced urothelial cancer with advanced tumors during or after a study of platinum-based chemotherapy.	[72]
13.	PD-L1	Bladder and lung cancers	Durvalumab	The results suggest that major ctDNA(circulating tumor DNA) mutations are associated with PD-L1 antagonists from treatment and may be a worthy indicator of effective immunotherapy.	[73]
14.	PD-1/ PD-L1	Bladder cancer	Pembrolizumab	Pembrolizumab shows a more extended means of treatment for the endurance of roughly three months, contrasted with paclitaxel, docetaxel, and vinflunine.	[70]
15.	PD-L1	Squamous-cell non-small cell lung cancer	Nivolumab	The study has demonstrated that in the case of PD-L1 expression, the results show nivolumab to be substantially better than docetaxel.	[74]
16.	PD-L1	Metastatic urothelial carcinoma	Nivolumab	In patients with locally advanced urothelial carcinoma treated with platinum chemicals, nivolumab monotherapy has been associated with good and adequate protection.	[75]
17.	PD-1/ PD-L1	Metastatic urothelial carcinoma	Pembrolizumab	Current analysis shows continuous overall survival benefit and higher anticarcinogenic activity of pembrolizumab over chemotherapy in second-line UC (urothelial carcinoma).	[76]
18.	PD-L1	Advanced urothelial bladder cancer	Durvalumab	Durvalumab shows the safety profile of clinical efficacy in UBC-L1 (urothelial bladder carcinoma ligand-1)-positive patients.	[77]
19.	PD-1	Melanoma	Nivolumab	Researchers have reported that nivolumab improves the long-term survival rate for melanoma.	[78]
20.	PD-L1	Advanced Melanoma	Pembrolizumab	Though tumor biopsy expression of PD-L1 is linked to the response rate, PFS (progression-free survival), and OS, patients with PD-L1 negative tumors can also have better outcomes.	[79]
21.	PD-1/ PD-L1	Lung cancer	Nivolumab	Nivolumab is essential for patients with advanced SSC (squamous cell carcinoma), according to these findings.	[80]

S. No.	Target	Cancer Types	Drugs Used	Outcomes	Ref. No.
22.	PD-L1	Lung cancer	S-allylcysteine (SAC)	The study has reported an organosulphur compound, S-allylcysteine (SAC), to serve as a novel chemotherapeutic agent with antitumor activity to combat lung cancer by inhibiting the PD-L1 immune checkpoint.	[81]
23.	PD-1/ PD-L1	Non-small-cell lung cancer	Atezolizumab	Use of atezolizumab in the treatment of chemotherapy-naive stage-IV NSCLC and the stage-1 NSCLC.	[82]
24.	PD-1/ PD-L1	Non-small-cell lung cancer	Durvalumab	The functions of other screening inhibitors have been clarified in this review, as well as the protection of radiation-related immunotherapies.	[83]
25.	PD-1	Non-squamous NSCLC	Nivolumab and docetaxel	Patients with advanced non-small-cell lung cancer (NSCLC), during or after platinum-based chemotherapy, have shown better effects bynivolumab than docetaxel, according to the study.	[84]
26.	PD-1	Advanced cutaneous squamous cell carcinoma	Cemiplimab	The results have demonstrated that cemipilimabis associated with common adverse effects like other immune checkpoint inhibitors.	[85]
27.	PD-1/PD-L1	Non-small cell lung carcinoma	Durvalumab	As per the study, treatment with durvalumab has led to much longer survival than that with the placebo.	[86]
28.	PD-L1	Metastatic NSCLC (non-small-cell lung cancer)	Atezolizumab	Individuals with platinum-based chemical reactions and patient-based therapies have been studied.	[87]
29.	PD-1	Advanced hematologic malignancies	Pidilizumab	In this trial, the pidilizumab has shown safe and well-tolerated responses in treated patients.	[88]
30.	PD-1/ PD-L1	Metastatic renal cell carcinoma (mRCC)	Nivolumab	Nivolumab has been found to demonstrate the antitumor activity with a safety profile in all mRCC studies.	[89]
31.	PD-1/ PD-L1	Advanced melanoma	Pembrolizumab	The information upholds that the utilization of pembrolizumab is more gainful for advanced melanoma.	[90]
32.	PD-1	Advanced solid tumor	Spartalizumab	Spartalizumab is well tolerated in all doses tested in patients with severe pre-existing tumors. Immune-mediated efficacy of the treatment has been observed in tumor biopsies.	[91]
33.	PD-1	Advanced melanoma	MEDI0680	This investigation has demonstrated that MEDI0680 treatment upgraded CD4+ and CD8+ T-cell multiplication in tumors and advanced plasma IFN-Y.	[92]
34.	PD-L1	Locally advanced and metastatic urothelial carcinoma	Atezolizumab	Atezolizumab has an effective and tolerable safety profile for a particular cancer stage, including local or advanced metastatic cancers.	[93]
35.	PD-1/ PD-L1	NSCLC (Non-small cell lung cancer)	Pembrolizumab	The results have indicated that chemotherapy may be more successful by utilization of immunotherapy.	[94]
36.	PD-L1	Advanced Cervical Cancer	Pembrolizumab	These results suggest that the treatment with pembrolizumab provides a sensible treatment option in a subset of the clinic for patients previously treated for cervical cancer.	[95]
37.	PD-L1	(NSCLC) Non-small-cell lung cancer	Nivolumab	The activity of nivolumab intracerebral has been found to be similar to its reported external activity, with an acceptable safety profile.	[96]
38.	PD-L1	Esophagogastric Cancer	Nivolumab and nivolumab plus ipilimumab	In developed chemotherapy-refectory esophagogastric cancer, nivolumab and a combination of nivolumab and ipilimumab have clinically demonstrated antitumor activity and safety profile.	[97]

S. No.	Target	Cancer Types	Drugs Used	Outcomes	Ref. No.
39.	PD-L1	(NSCLC) Non-small-cell lung cancer	Atezolizumab	It demonstrates the therapeutic effectiveness and safety of atezolizumab in detecting PD-L1 in human patients.	[98]
40.	PD-1	Melanoma	Pembrolizumab + nivolumab	Anti-PD1 pembrolizumab + nivolumab has been shown to have clinical benefits for certain subgroups of melanoma, such as desmoplastic melanoma and untreated brain metastases.	[99]
41.	PD-1/ PD-L1	Melanoma	Nivolumab	This approach to the immune system can produce responses that preserve after the combination of treatments and can lead to gastrointestinal upset.	[100]
42.	PD-1/ PD-L1	Melanoma	Atezolizumab,Nivolumab,	The presence of PD-L1 in the tumor or TIL (tumor-infiltrating lymphocyte) has been found to be associated with better outcomes.	[101]
43.	PD-L1	Melanoma	Nivolumab, Ipilmumab, Ipilimumab plus Nivolumab	The results suggest that patients with PD-L1 malignant tumors have longer PFS and OS as compared to that with nivolumab monotherapy.	[102]
44.	PD-1	Melanoma	Pembrolizumab	The study results have shown that the removal of anti-PD1 can be an independent marker of the severity of the disease.	[103]
45.	PD-1/ PD-L1	Melanoma	Combination of Ipilimumab and Nivilumab	These results suggest that nivolumab and ipilumab may be administered simultaneously with a portable safety profile. Tumor responses have been observed to be much faster, lasting longer, and deeper than those observed with single-agent treatment.	[104]
46.	PD-1	Melanoma	Pembrolizumab	These studies suggest that immunotherapy is the most effective way to treat melanoma.	[105]
47.	PD-1/ PD-L1	CNS (Central Nervous System Metastatic Disease	Combination of Nivolumab and Ipilimumab	The results of the study depicts that the combination of nivolumab and ipilimumab has been more toxic as compared to that of nivolumab.	[106]
48.	PD-1/PD-L1	Metastatic Cervical Cancer	Pembrolizumab	The result of the study shows that at the current price in the United States, adding pembrolizumab to chemotherapy is expensive and may not be cost-effective for persistent, recurring, or metastatic cervical cancer.	[107]
49.	PD-L1	Bilary Tract Cancer	Atezolizumab	In BTC, atezolizumab monotherapy has shown minimal antitumor effectiveness, highlighting the necessity for combination therapies to unlock efficient anticancer immunity, as well as the development of prognostic biomarkers to enrich the population.	[108]
50.	PD-L1	Bilary Tract Cancer	Durvalumab	The anti-PD-L1 inhibitor durvalumab is currently under investigation in several clinical trials as monotherapy or combination with other pharmacological agents.	[109]
51.	PD-L1	Esophageal cancer	Nivolumab	For resectable EC patients with residual pathologic disease who had received neoadjuvant chemoradiotherapy followed by surgery, adjuvant nivolumab monotherapy revealed a substantial disease-free survival benefit against placebo.	[110]
52.	PD-1	Cutaneous Squamous Cell Carcinoma	Cemiplimab	After exhibiting quick and sustained responses in more than 40% of patients in a clinical trial with an acceptable safety profile, cemiplimab became the first PD-1 inhibitor to receive an indication in CSCC.	[111]
53.	PD-1/PD-L1	Non squamous NSCLC	pembrolizumab + chemotherapy versus atezolizumab + chemotherapy+/-bevacizumab	Pembrolizumab + chemotherapy had a considerably higher OS and PFS than atezolizumab + chemotherapy, as well as a significantly better PFS than atezolizumab + chemotherapy + bevacizumab, according to MAIC findings.	[112]
54.	PD-L1	NSCLC	Durvalumab	Patients with EGFR-mutated NSCLC did not benefit from consolidation durvalumab in this	[113]

S. No.	Target	Cancer Types	Drugs Used	Outcomes	Ref. No.
				study, and they had a significant rate of irAEs. Patients who start osimertinib after receiving durvalumab may experience irAEs.	
55.	PD-1/PD-L1	Squamous Cell Carcinoma	Cetuximab	Cetuximab is an EGFR inhibitor that has been licensed for a variety of uses in squamous cell carcinoma of the head and neck, including simultaneous treatment with platinum-based drugs and radiotherapy, as well as monotherapy in cases where platinum-based therapy has failed.	[114]
56.	PD-1	Renal Cell Carcinoma	Nivolumab and Ipilumab	These findings imply that a combination of nivolumab and ipilimumab therapy for individuals with mRCC may provide a potentially long-lasting response, while further long-term evidence is needed to confirm this.	[115]
57.	PD-1/PD-L1	Renal Cell Carcinoma	Lenvatinib + pembrolizumab	Lenvatinib + pembrolizumab exhibited promising antitumor activity and a reasonable safety profile, suggesting that it could be used to treat metastatic RCC after ICI.	[116]
58.	PD-L1	Locally Advanced ESCC	Atezolizumab	The synergistic efficacies of sequentially combining CRT and atezolizumab should improve the CR rate, resulting in improved survival for patients with locally advanced ESCC that is unresectable.	[117]
59.	PD-1/PD-L1	Triple Negative Breast Cancer	Pembrolizumab	Pembrolizumab, in combination with neoadjuvant chemotherapy, has been proven to improve event-free survival in stage II–III TNBC, leading to its adoption as the new standard of care in this condition.	[118]
60.	PD-1/PD-L1	Triple Negative Breast Cancer	Immuno-Oncology Agent either as Single or in Combination.	The efficacy of IO with chemotherapy in TNBC demonstrates the possibility for novel medicines to work in early phase clinical trials in well-chosen patients.	[119]

4. Conclusions

The advancement in immuno-oncology has introduced a novel approach to combating cancer. Unfortunately, the response to cancer immunotherapy has been found to be limited to date due to a lack of knowledge, awareness, and research facilities. Inhibition of immune checkpoints allows us to customize immunotherapy and develop complementary approaches to improve cancer treatment outcomes. The aim of this review is to explain the mechanism of immunotherapy and present an overview of the developments and latest advances in cancer immunotherapy.

Presently, researchers in the field of immuno-oncology come across multiple challenges to better understand the relationship between tumor biology, immune system, and tumor microenvironment. In the near future, the application of advanced technologies in cancer immunotherapy will gradually help researchers overcome the challenges in cancer immunotherapy by showing promising results against various types of cancers. Future research is likely to use the combined therapeutic potential of epigenetics and immune checkpoint therapy.

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Conflict of interest

The authors declare no conflict of interest.

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