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New Developments in Cancer Management and A Focus on Cancer Biomarkers: Pd-1 and Pd-L1

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ABSTRACT
In the early years, the principal treatment for cancer were chemotherapy, radiation, and surgery. However, medical research shows that these methods have some limitations and frequently fall short of improving patients' long-term survival who have advanced solid tumors. Researchers have discovered that the tumor microenvironment is immunosuppressive as they continue to explore malignancies in the domains of immunology, cellular biology, and genetic breakthroughs in technology. According to studies, immunosuppression and the development and spread of cancer are strongly correlated. The immune checkpoint inhibitors PD-1 (programmed cell death protein -1) and PD-L1 (programmed death ligand-1) have, however, revolutionized the way that cancer is treated by acting as promising biomarkers for cancer therapy. Therapies aimed at targeting PD-1 and PD-L1 are frequently utilized as the first-line therapy for diverse cancer types. Non-small cell lung carcinoma, progressive melanoma, metastatic renal cell cancer, and urothelial carcinoma are the most common cancers that are currently treated with these immune checkpoint inhibitors. In this article, we analyze the therapeutic possibilities associated with PD-1 blocking, and current developments in cancer therapy given the increasing prevalence of cancer patients globally and how PD-1 and PD-L1 may be used to combat the spread of cancer with the recent discoveries of checkpoint inhibitors.
Keywords: *Immunotherapy, chemotherapy, radiotherapy, biomarker, checkpoint inhibitors.*

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INTRODUCTION

Cancer is a disease characterized by unregulated cell development, dedifferentiation, loss of function, invasion of the surrounding tissues, and spread or metastasis to other parts of the body. There are various types of cancer. More than 200 distinct illnesses are included in this category. Each year, nearly 15 lakh additional cases are found in India. At present, one in four Americans dies from cancer. Lung cancer accounts for 1 in 17 fatalities. Breast cancer is more common in women, whereas lung cancer is more common in men. The division, rest, and production of the body's regular processes depend significantly on proteins. However, proteins can occasionally change and mutate. For example, Smoking causes mutations that cause our lung cells to produce abnormal proteins. Cells may turn malignant when proteins cease to function normally. To eliminate cancer cells, T lymphocytes are activated. But why do people get cancer when T-cells are able to identify and eradicate it? The immune system sometimes fails to do this, and when this occurs, the body's defenses against exposure to cancer could be inadequately potent enough to stop it from spreading.

RECENT ADVANCES IN THE TREATMENT OF CANCER

Patients with cancer have access to cutting-edge therapies that are constantly being discovered and enhanced. Immunotherapy is a sort of cancer treatment that strengthens the body's innate ability to combat the disease by using the immune system to fight cancer. It stimulates the immune system via therapies or other treatments so that it can identify and get rid of cancer cells. Immune therapy for cancer has greatly improved patients' prognoses and quality of life when contrasted with prior cancer treatment. The immunotherapy approach has been proven to be an effective cornerstone of treatment for a variety of cancer types, beginning in the advanced phase and continuing through postoperative and preoperative settings (1). Advanced cancer therapy biomaterials, such as inhibitors of immune checkpoints, cancer vaccinations, T-cell treatments, and sophisticated drug delivery technologies, such as nanoparticles, could effectively benefit from immunotherapies and boost their potency while lowering harmful side effects.

Cancer vaccines

Vaccines used in cancer therapy are different from those used to prevent viruses. A cancer vaccine activates the body's immunity to target cancer cells. They are meant to strengthen the body's defenses to combat, an already-present infection. Cancer vaccines can occasionally be created using cells from cancer, cancer cell fragments, or pure antigens (2). Sometimes, to create the vaccine, the patient's own immune system cells are taken out and treated with these substances in a lab. The body prepares for cancer defense, and the vaccine is administered intravenously. Cancer vaccines that focus on neoantigens are a potential cancer treatment strategy. These vaccinations aim to stimulate or improve the immune system's reaction to neoantigens expressed by a patient's cancer cells (3). Neoantigens are novel antibodies that are not found in normal cells and are exclusively found in cancer cells. They are a favored target for cancer immunotherapy in comparison to other tumor-associated antigens, as neoantigens are highly immunogenic, have a low risk of self-tolerance and a low frequency of tumor antigen deletions, and can elicit a larger immune response.(4)

Adoptive t-cell transfer

T cell adaptation is a procedure used in adoptive cell therapy or immune cell therapy. From the patient, T cells are removed and grown in vitro. When they are transferred to the patient's body, the t-cells have either been strengthened or trained to recognize cancer (5). Chimeric antigen receptor T-cell treatment and tumor-infiltrating lymphocyte therapy are the two primary forms of T-cell transfer therapy. TIL therapy entails the removal of antibody-producing cells from tumor tissue, their detection by laboratory testing, and their subsequent growth to a large number before being reintroduced to the patient. Contrarily, CART-cell therapy modifies human T cells that are grown in a lab so they can connect to specific proteins on cancer cells, increasing their ability to fight cancer (6). T-cell treatments are continually developing, getting better, and giving cancer patients more options. For a number of cancer types, chemotherapy using cells is now being evaluated in clinical studies, both alone and in combination with already available medications (7,8).

Nanoparticle therapy

Nanoparticle therapy is a potential cancer treatment strategy. This therapy uses nanoparticles, which are incredibly small particles, to target specific cancer cells. Nanoparticles are used to transport medications precisely to the location of the tumor, improving the efficacy of cancer therapy. One of the main advantages of nanoparticle therapy is that it can deliver drugs that are not very soluble in water. As a result, the likelihood of side effects may be reduced and the drug's effectiveness may be increased. When cancer cells have developed resistance to a single treatment, nanoparticle therapy can also be used to provide many medicines at once. Theragnostic carriers, liposomes, tiny quantum dots, polymeric micelles, nanotubes made of carbon, dendrimers, carbon nanoparticles, metallic nanoparticles, nanodiamonds (ND), fullerenes, carbon nanotubes (CNTs), graphene oxide, and graphene oxide nanocomposites are a few examples of nano systems utilized in the detection, diagnosis, and management of cancer (9, 10). The use of nanoparticles along with other anticancer drugs inhibits a variety of processes that contribute to the growth, metastasis, and treatment resistance of cancer cells at various stages. This is accomplished by maintaining drug stability, ensuring bioavailability, long-term uptake, and preferential medicine buildup in tumor locations. However, only a small number of nanoproducts are presently accessible for use in clinical trials because of the exorbitant cost of nanodrugs in contrast to already available cancer drugs (10).

Checkpoint inhibitors / blockers

Checkpoint blockers are medications that target particular molecules on the surfaces of immune cells, thereby allowing them to detect and fight cancer cells more efficiently. They inhibit a type of checkpoint protein, which is produced by some cancer cells and some immune system cell types like T-cells (11). These immunological checkpoints function to inhibit excessive immune responses and, in some cases, to prevent T lymphocytes from attacking cancerous cells. Once these detection mechanisms are disabled, T lymphocytes can target tumor cells more efficiently. Checkpoint proteins like CTLA-4, B7-1, B7-2, PD-1, PD-L1 and PD-L2 are examples that can be present on T lymphocytes or cancerous cells. Several immunological checkpoint inhibitors are used to treat cancer. According to some research methodologies, the use of immune checkpoint blockers such as programmed cell death protein-1(PD-1) and programmed death ligand-1(PD-L1) can be used as a possible biomarker to treat cancer (12). Cancer treatment has benefited from PD-1 as well as PD-L1, as they play a major role in immune modulation. The CD28 receptor family includes the immune-suppressive co-stimulatory signal receptor PD-1/Programmed Cell Death. PD-1 a protein, is produced by a wide range of immune cells, notably monocytes, B lymphocytes, dendritic cell types (DC), and T lymphocytes that target malignancies specifically (13). Its function is to control T-cell activity and avoid excessive immunological responses that might harm healthy tissues. It prevents the activation of antigen receptors by PD-ligand 1 and PD-L2, members of the B7 family of co-stimulatory signals (14). Programmed death ligand 1 is a protein that can be found on cancer cells as well as hematopoietic and non-hematopoietic cells (such as arterial and stromal tissue cells, cells from the islet

cells of the pancreas, placental syncytiotrophoblasts, and keratinocytes) (15). Its purpose is to bind to PD-1 on T cell receptors and inhibit their activity, allowing cancer cells to avoid detection by the immune system. When PD-L1 binds to the PD-1 protein, it decreases the production of cytokines and promotes apoptosis in PD-1-positive cells. Furthermore, PD-L1 is important in a broad spectrum of malignancies because it reduces the host defense system's response to tumor cells (16).

ROLE OF PD-1 AND PD-L1 IN CANCER TREATMENT

PD-1 and PD-L1 play an essential role in cancer immunotherapy, enabling cancer immune escape by overexpressing PD-L1. PD-1 adheres to PD-L1 and prevents the immune system's T-cells from attacking cells that carry PD-L1, including cancer cells. This checkpoint causes the death of PD-L1-deficient cells. However, tumor cells circumvent the body's immune system by expressing the PD-1 receptor, which allows them to bypass the checkpoint. The defense system's ability to fight off cancer cells is strengthened by PD-1 and PD-L1 drugs, which specifically inhibit whether PD-1 or PD-L1.

Immune checkpoint blockade eliminates the barriers that prevent the activation of T cells , allowing tumor-reactive T cells to get through impediments and successfully mount an anticancer response. A significant selective pressure from the body's immunity on the development of cancer results in immune tumor editing. Malignant tumors then use immunological tolerance and suppressive tactics to prevent the breakdown of the immune system. Immune checkpoint suppression stops T-cell-negative costimulation, permitting the escape of anticancer T-cell reactions and potentially identifying tumour markers (17). The vital biological roles of PD-1 include preserving tolerance to peripheral stimuli and preserving responses from T-cells within a specified physiological range. As a result of immune responses' activation of PD-1/PD-L1 regulatory mechanisms, tissue damage is reduced locally and T-cell responses are attenuated. In collaboration with PD-L1 and PD-L2, PD-1 controls T-cell activation. T cells as well as B cells that have been activated express PD-1, respectively(18).

MECHANISM OF ACTION

The PD-1 protein is made up of three parts: an immunotyrosine-based inhibitory motif (ITIM), an immunoreceptor inhibitory tyrosine-based switch motif (ITSM), and an extracellular IgV domain. These domains have potential phosphorylation sites, creating hydrophobic permeability in the cytomembrane. Its inhibitory impact on active T cells requires an activated switch motif (ITSM), and its inhibitory phosphatase SHP-2 can be bound by its ITIM and ITSM (19). Fig 1 demonstrates the mechanism of action of PD-1. Immune checkpoints PD-1 binds with its two ligands, PD-L1and PD-L2, that are essential for suppressing the body's immunity by increasing regulatory T immune cells and decreasing T-cell activity, which reduces autoimmunity and promotes tolerance to one's own immune system. Tyrosine phosphatases are recruited after PD-L1 or PD-L2 ligation, and this activity creates an inhibitory signal that blocks the PI3K/Akt pathway's downstream effects, which leads to a pause in the cell phase and diminishes the stimulation of T cells (20). Cancer cells begin to excessively express PD-L1/PD-L2, that reduce T-cell effectiveness and promote immunological escape when the immune system of the body targets them (21). CTLA-4, which is present on reactive CD8+ cells and CD4+ T cells, interacts with the costimulatory molecules B7-1 and B7-2 for binding to the ligands generated by antigen- presenting cells. This eventually hinders an adequate immune response to tumors by suppressing T cell proliferation and IL-2 production (7).

PD-1 AND PD-L1 MONOCLONAL ANTIBODIES

Immune checkpoints, which are immuno-cell surface molecules that either govern the induction or inhibition of immunological reactions, precisely regulate the development of cancer. Additionally, triggering the body's defense ability is necessary to stop the spread of cancer but also results in autoimmune disease. By boosting immune activation at different phases of the immunological period, the identification and subsequent clinical testing of monoclonal antibody therapies that focus on immune system proteins such as PD-1 and CTLA-4 have evoked strong anticancer responses (18). Tables 1 and 2 provides a comprehension of the PD-1 and PD-2 targeted medications that have received FDA approval for cancer treatment, respectively.

Retifanlimab (Zynyz)

Retifanlimab inhibits the PD-1 protein for programmed cell death. It is suggested for therapy in individuals with recurrent advanced Merkel cell carcinoma that has metastasized or returned (22). Incyte Biosciences withdrew their request for a marketing authorization for the administration of Retifanlimab for the management of anal canal squamous cancer on October 20, 2021 (23). The FDA authorized Retifanlimab in March 2023 for the management of recurrent Merkel cell carcinoma (MCC) that has spread or recurred. Metastatic gastroesophageal adenocarcinoma has been examined in combination with other cancer treatments using Retifanlimab .(24)

Dostarlimab (Jemperli)

Dostarlimab received accelerated clearance from the FDA in April 2021 for the use in treating patients who have advanced or recurrent mismatched repair deficient (dMMR), endometrial carcinoma who continue to progress despite receiving platinum-containing treatment regimens (25). Dostarlimab is being considered as a potential treatment for rectal tumors that lack mismatch repair. In an ongoing phase II investigation, all twelve patients with mismatched repair failure and progressing local rectal cancer experienced a complete clinical response .(26)

Cemiplimab (Libtayo)

Cemiplimab, a PD-1-inhibiting mab, is used to treat cancers such as non-small cell lung cancer, cutaneous squamous cell cancer (27), and basal cell carcinoma. It inhibits PD-1, also referred to as the "negative modulator" of T cell activity, and stops the proliferation of T cells. The PD-1 inhibitor cemiplimab boosts T-cell-mediated antitumor responses. On September 28, 2018, the FDA granted the first drug approval for Cemiplimab, which is used to treat advanced squamous cell carcinoma of the cutaneous skin, especially for those who are not appropriate candidates for definitive chemotherapy and surgical treatment (3). The FDA has now authorized a drug specifically for advanced CSCC for the first time. According to the Healio trial from May 8 2023, cemiplimab enhanced the standard of living among individuals who had advanced non-small cell lung cancer. (28).

Pembrolizumab (Keytruda)

Humanized antibody pembrolizumab, marketed as Keytruda, is used in cancer immunotherapy for the curative purpose of melanoma (29), non-small-cell cancer of the lung, cervical carcinoma, head and neck carcinoma, lymphoma Hodgkin's, malignancies of the stomach, triple-negative breast cancer (30), and advanced bladder carcinoma in people who are incapable of benefiting from cisplatin-based radiotherapy due to increased levels of PD-l1. The FDA has given Keytruda the go-ahead to be used in tandem with other medications to treat certain cancers. According to the Randomized Phase III Study 309/KEYNOTE-775, which has been updated on the safety and effectiveness of pembrolizumab, using pembrolizumab concurrently with Lenvatinib significantly increased the rate of progression-free survival and life expectancy compared to chemotherapy in patients who have progressed endometrial cancer. Nevertheless, Keytruda is authorized for specific cancer types. However, Keytruda is permitted for use alone in specific cancer types. For example, Keytruda can be treated alone in stage III lung cancer if it has not progressed beyond the chest region.

Avelumab (Bavencio)

Metastatic Merkel cell carcinoma, advanced urothelial cancer, and metastatic carcinoma of the kidney are all treated with the monoclonal antibody avelumab. In adults and children older than 12 years, avelumab is recommended for the treatment of metastatic Merkel cell cancer. For individuals with urothelial cancer (UC) who have had first-line platinum-containing chemotherapy but have not improved, the FDA consented Avelumab on June 30, 2020. Drugs that target PD-1 and PD-L1 are frequently utilized as first therapies for different cancer types. Today, progressive skin cancer, lung tumor, kidney cell carcinoma, and urothelial cancer are the most prevalent cancers that are treated with these immune-mediated checkpoint inhibitors (30). Therapies that focus on PD-1 and PD-L1 assist the body's defenses in detecting and eradicating cancer cells and, therefore, can improve the effectiveness of cancer therapy.

Durvalumab (Imfinzi)

Durvalumab is used to alleviate both urothelial carcinoma and clinically advanced, inoperable non-small cell lung cancer. Patients with locally progressed or advanced urothelial cancer who have progressed before or after receiving platinum-containing treatment with chemotherapy or have advanced within the first year of receiving either neo-adjuvant or postoperative platinum-containing chemotherapy are treated with durvalumab. Patients with third stage non-small cell lung carcinoma (NSCLC), which is incurable and has persisted after concurrent platinum-based radiation therapy and chemotherapy treatment, are administered durvalumab (31). The FDA initially authorized durvalumab in May 2017 for those who had advanced bladder cancer and had already received therapy. Based on the findings of TOPAZ-1, a Phase 3 international research study, the Central Drug Standards and Control Organization (CDSCO) has authorized durvalumab for use as the first therapy for metastatic biliary tract cancer (32). According to preclinical research, a promising treatment for patients with advanced cancer is the combined use of PD-1/PD-L1 inhibitors with cytotoxic radiation therapy, opening up a new therapeutic alternative for cancers that were previously difficult to treat (2). Immune checkpoint inhibitors may be more effective when used in combination with chemotherapy or radiation therapy than other cancer treatments (19). For instance, PD-1 and PD-L1 immune checkpoint blockers and cytotoxic drug therapy are currently utilized in combination to treat advanced forms of small cell and non-small cell lung cancer. However, some combination therapies may have more severe side effects, so careful consideration and monitoring should be given when using them. The possible drawback of these medications is that they cause auto-immune reactions and have an impact on healthy body cells that interact with PD-1/PD-L1. Because of this, it's important to carefully

monitor and manage any potential adverse effects when taking these medications. Besides, not every form of cancer responds the same way to immune checkpoint inhibitors, and further investigation is required to determine why some tumors are resistant to these medications (33). Immune checkpoint inhibitors have revolutionized the way that cancer is treated. Their efficacy and breadth of uses in the control of cancer will keep evolving with ongoing research to better understand their underlying mechanisms of action and resistance.

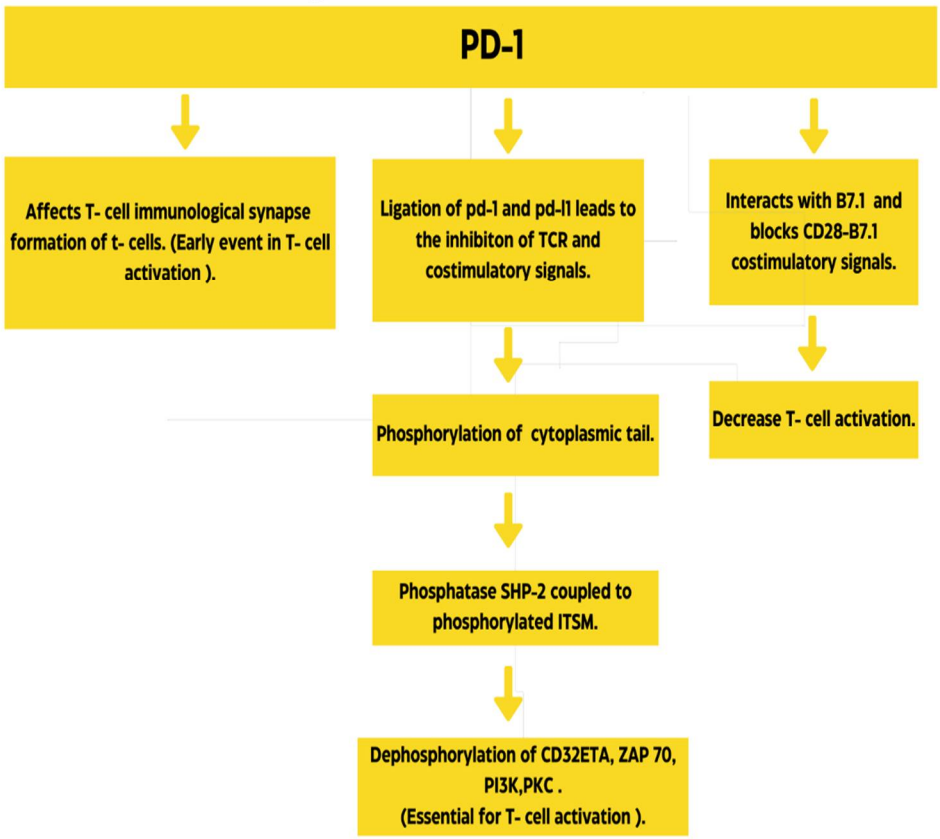
Table 1: PD-1-targeted medications that have received FDA approval for the cancer treatment

PD-1 targeted drugs	Approved year	Treatment
Retifanlimab	2023	Metastatic Locally Advanced Merkel Cell Carcinoma, continually localized advanced Merkel Cell Cancer.
Dostarlimab	2021	Mismatch repair deficient recurrent or advanced solid tumors, endometrium cancer.
Cemiplimab	2018	Metastatic epidermal squamous cell carcinoma.
Pembrolizumab	2014	Melanoma, gastric, cervical, uterine, breast, and typical Hodgkin lymphoma cancers.
Nivolumab	2014	Melanoma, malignant renal cell carcinoma, Hodgkin's lymphoma, neck and head cancer, urothelial cancer, bowel carcinoma, esophageal squamous cell cancer, liver cancer, stomach cancer, and throat cancer.

Table 2: PD-L1-targeted medications that have received FDA approval for the cancer treatment

PD-L1 targeted drugs	Approved year	Treatment
Avelumab	2017	Urothelial, renal, and Merkel cell carcinomas.
Durvalumab	2017	Bladder cancer, cancer of lung, and biliary tract cancer.
Atezolizumab	2016	Hepatic carcinoma, urothelial cancer, triple-negative breast cancer, non-small cell lung carcinoma, and small cell lung carcinoma.

Fig 1: Mechanism of action of PD-1.



CONCLUSION

Cancer immunotherapy that focuses on immune checkpoints has developed into a powerful tool against the disease. It took many years of basic research discoveries and consequent clinical trials to conclusively demonstrate the effectiveness of immune system regulation in the prevention and therapy of cancer. The research on PD-1 and PD-L1 checkpoint inhibition which possess the possibility to significantly improve therapeutic results and improve prognosis, has now offered cancer patients hope for innovative treatment protocols. The nascent field of immunotherapy for cancer keeps growing as the conditions for currently approved treatments increase and researchers explore new therapeutic targets. The immune checkpoint inhibitors PD-1 and PD-L1 may further strengthen their impact and offer hope for a better treatment of cancer, considering the spread of cancer and the development of innovative cancer therapies.

REFERENCES

1. Akinleye A, Rasool Z. (2019). Immune checkpoint inhibitors of PD-L1 as cancer therapeutics. J. Hematol. Oncol.,12(1):92
2. Xie N, Shen G, Gao W, Huang Z, Huang C, Fu L. (2023). Neoantigens: promising targets for cancer therapy. Signal Transduct Target Ther.,8(1):9.
3. Biswas N, Chakrabarti S, Padul V, Jones LD, Ashili S. (2023). Designing neoantigen cancer vaccines, trials, and outcomes. Front. immunol.,14: 1105420.
4. Yang L, Ning Q, Tang SS. (2022). Recent advances and next breakthrough in immunotherapy for cancer treatment. J. Immunol. Res.
5. Xue G, Zheng N, Fang J, Jin G, Li X, Dotti G, Yi Q, Lu Y. (2021). Adoptive cell therapy with tumor-specific Th9 cells induces viral mimicry to eliminate antigen-loss-variant tumor cells. Cancer cell.,39(12):1610-22.
6. Liu S, Sun Q, Ren X. (2023). Novel strategies for cancer immunotherapy: counter-immunoediting therapy. J. Hematol. Oncol.,16(1):38.
7. Alsaab HO, Sau S, Alzhrani R, Tatiparti K, Bhise K, Kashaw SK, Iyer AK. (2017). PD-1 and PD-L1 checkpoint signaling inhibition for cancer immunotherapy: mechanism, combinations, and clinical outcome. Front. Pharmacol.,8:561.
8. Waldman AD, Fritz JM, Lenardo MJ. (2020). A guide to cancer immunotherapy: from T cell basic science to clinical practice. Nat. Rev. Immunol.,20(11):651-68.
9. Verma J, Warsame C, Seenivasagam RK, Katiyar NK, Aleem E, Goel S. (2023). Nanoparticle-mediated cancer cell therapy: Basic science to clinical applications. Cancer Metastasis Rev.,1-27.
10. Gurunathan S, Kang MH, Qasim M, Kim JH. (2018). Nanoparticle-mediated combination therapy: Two-in-one approach for cancer. Int. J. Mol. Sci.,19(10):3264.
11. Wang X, Yang X, Zhang C, Wang Y, Cheng T, Duan L, Tong Z, Tan S, Zhang H, Saw PE, Gu Y. (2020). Tumor cell-intrinsic PD-1 receptor is a tumor suppressor and mediates resistance to PD-1 blockade therapy. Proc. Natl. Acad. Sci.,117(12):6640-50.
12. Wu X, Gu Z, Chen Y, Chen B, Chen W, Weng L, Liu X. (2019). Application of PD-1 blockade in cancer immunotherapy. Comput Struct Biotechnol J.,17:661-74.
13. Hudson K, Cross N, Jordan-Mahy N, Leyland R. (2020). The extrinsic and intrinsic roles of PD-L1 and its receptor PD-1: implications for immunotherapy treatment. Front. immunol.,2362.
14. Chamoto K, Hatae R, Honjo T. (2020). Current issues and perspectives in PD-1 blockade cancer immunotherapy. Int. J. Clin. Oncol.,25:790-800.
15. Chamoto K, Hatae R, Honjo T. (2020). Current issues and perspectives in PD-1 blockade cancer immunotherapy. Int. J. Clin. Oncol.,25:790-800.
16. Han Y, Liu D, Li L. (2020). PD-1/PD-L1 pathway: current researches in cancer. Am. J. Cancer Res.,10(3):727.
17. Wei SC, Duffy CR, Allison JP. (2018). Fundamental mechanisms of immune checkpoint blockade therapy. Cancer Discov.,8(9):1069-86.
18. Esfahani K, Roudaia L, Buhlaiga NA, Del Rincon SV, Papneja N, Miller WH. (2020). A review of cancer immunotherapy: from the past, to the present, to the future. Curr. Oncol. Rep.,27(s2):87-97.
19. Ai L, Chen J, Yan H, He Q, Luo P, Xu Z, Yang X. (2020). Research status and outlook of PD-1/PD-L1 inhibitors for cancer therapy. Drug Des Devel Ther.,8:3625-49.
20. Zheng P, Zhou Z. (2015). Human cancer immunotherapy with PD-1/PD-L1 blockade. Cancer Biomark.,7:BIC-S29325.
21. Li Y, Li F, Jiang F, Lv X, Zhang R, Lu A, Zhang G. (2020). A mini-review for cancer immunotherapy: molecular understanding of PD-1/PD-L1 pathway & translational blockade of immune checkpoints. Int. J. Mol. Sci.,17(7):1151.
22. Park SY, Doolittle-Amieva C, Moshiri Y, Akaike T, Parvathaneni U, Bhatia S, Zaba LC, Nghiem P. (2021). How we treat Merkel cell carcinoma: within and beyond current guidelines. Future Oncol.,17(11):1363-77.
23. Kaplon H, Crescioli S, Chenoweth A, Visweswaraiah J, Reichert JM. (2023). Antibodies to watch in 2023. InMAbs (Vol. 15, No. 1, p. 2153410).Taylor & Francis.
24. Catenacci DV, Kang YK, Yoon HH, Shim BY, Kim ST, Oh DY, Spira AI, Ulahannan SV, Avery EJ, Boland PM, Chao J. (2022). Margetuximab with retifanlimab as first-line therapy in HER2+/PD-L1+ unresectable or metastatic gastroesophageal adenocarcinoma: MAHOGANY cohort A. ESMO open.,7(5):100563.

25. Cercek A, Lumish M, Sinopoli J, Weiss J, Shia J, Lamendola-Essel M, El Dika IH, Segal N, Shcherba M, Sugarman R, Stadler Z. (2022). PD-1 blockade in mismatch repair–deficient, locally advanced rectal cancer. N Engl J Med.,386(25):2363-76.
26. Migden MR, Rischin D, Schmults CD, Guminski A, Hauschild A, Lewis KD, Chung CH, Hernandez-Aya L, Lim AM, Chang AL, Rabinowits G. (2018). PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. N Engl J Med.,379(4):341-51.
27. Markham A, Duggan S. (2018). Cemiplimab: First global approval. Drugs.,78(17):1841–6.
28. Makharadze T, Quek RGW, Melkadze T, Gogishvili M, Ivanescu C, Giorgadze D, et al. (2023). Quality of life with cemiplimab plus chemotherapy for first-line treatment of advanced non–small cell lung cancer: Patient-reported outcomes from phase 3 EMPOWER-Lung 3. Cancer. 2023.
29. Bagegni NA, Davis AA, Clifton KK, Ademuyiwa FO. (2022). Targeted Treatment for High-Risk Early-Stage Triple-Negative Breast Cancer: Spotlight on Pembrolizumab. Vol. 14, Breast Cancer: Targets and Therapy. Dove Med Press.,113–23.
30. Zhou Y, Chen C, Zhang X, Fu S, Xue C, Ma Y, Fang W, Yang Y, Hou X, Huang Y, Zhao H. (2018). Immune-checkpoint inhibitor plus chemotherapy versus conventional chemotherapy for first-line treatment in advanced non-small cell lung carcinoma: a systematic review and meta-analysis. J. Immunother. Cancer.,6(1):1-1.
31. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. (2017). Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. N Engl J Med.,377(20):1919–29.
32. Syed YY. (2017). Durvalumab: First Global Approval. Drugs.,77(12):1369–76.
33. Zhang JY, Yan YY, Li JJ, Adhikari R, Fu LW. (2022). PD-1/PD-L1 based combinational cancer therapy: icing on the cake. Front. pharmacol.,11:722.

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