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

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***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

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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. Unlikely, 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

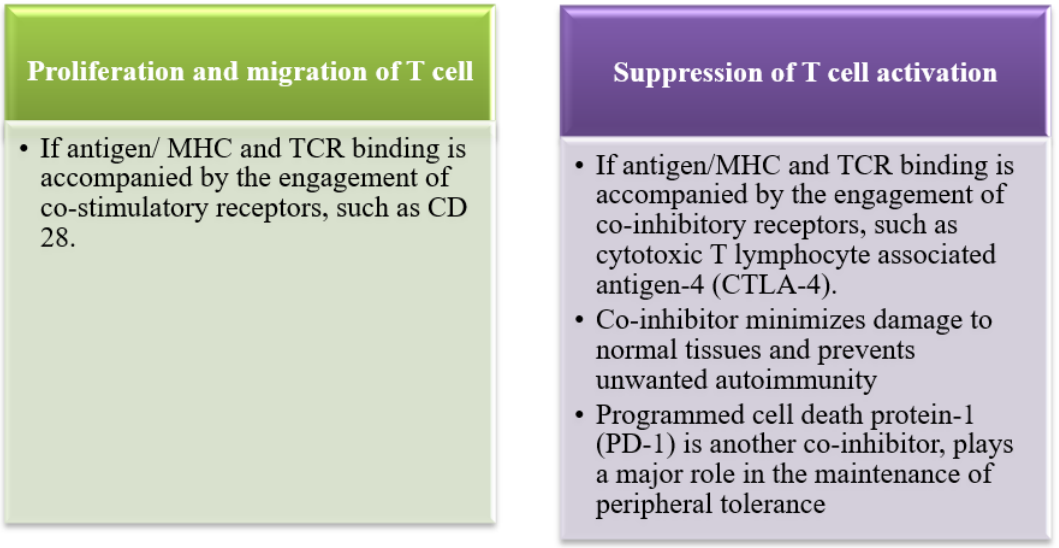
In the 19th century, the use of an immune system as a tool to treat neoplastic disease originated. William Coley, known as the 'Father of Cancer Immunotherapy', treated cancer patients with extracts of heat-inactivated *S. pyogenes* and *Serratia marcescens* to boost immunity. The extract was named after 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

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

				cell carcinoma	
PDL-1	Dendritic cell, macrophages, Tumor cell	Atezolizumab	October 2016	Stage III-B or IV nonsquamous and squamous NSCLC	(Li et al., 2019)
		Avelumab	March 2017	Histologically confirmed metastatic Merkel cell carcinoma	(Shirley, 2018)
		Durvalumab	February 2016	Stage III non-small-cell lung cancer (NSCLC)	(Paz-Ares et al., 2020)

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

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

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)

PD-L1 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.

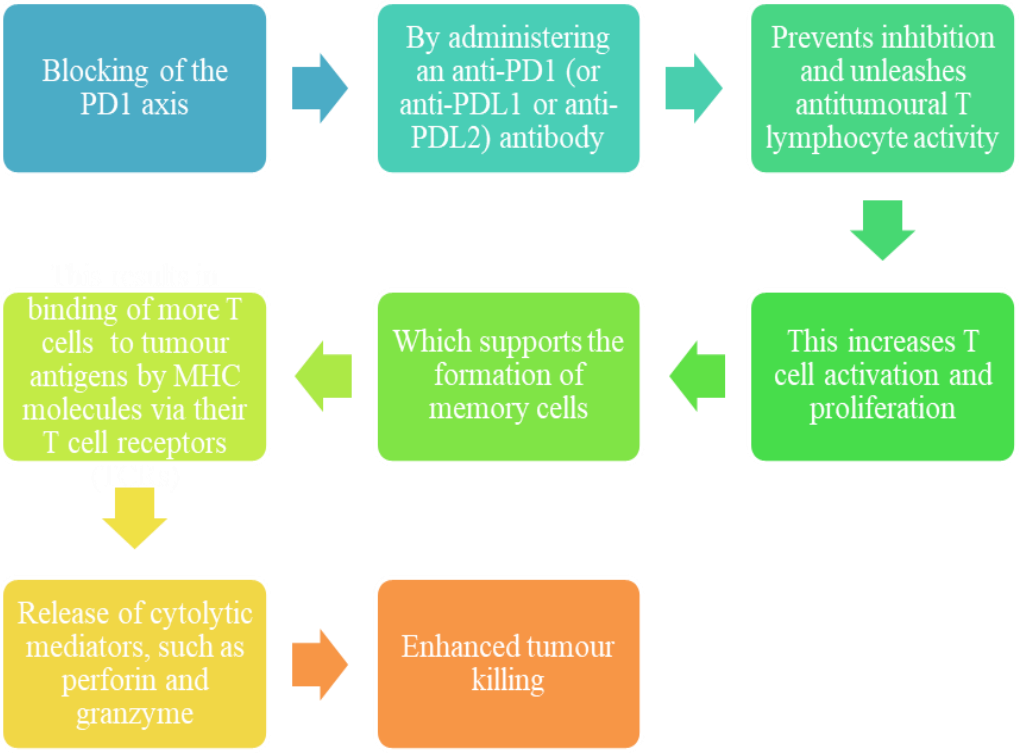


Figure 1: Schematic Presentation of Mechanism of Action of Cancer Inhibition by blocking PD-1 axis

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 effectivity of dostarliamb 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 dostalimab 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 ummarize din Table 3.

Table 3: Some major ongoing clinical trials on dostarlimab

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

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.

References

1. Abdel-Rahman, O., Helbling, D., Schmidt, J., Petrausch, U., Giryes, A., Mehrabi, A., Schöb, O., Mannhart, M., Oweira, H., 2017. Treatment-related Death in Cancer Patients Treated with Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. Clinical Oncology 29, 218–230. https://doi.org/10.1016/j.clon.2016.11.007
2. Aggen, D.H., Drake, C.G., 2017. Biomarkers for immunotherapy in bladder cancer: a moving target. j. immunotherapy cancer 5, 94. https://doi.org/10.1186/s40425-017-0299-1
3. Bandaru, R., Rout, S.R., Kamble, O.S., Samal, S.K., Gorain, B., Sahebkar, A., Ahmed, F.J., Kesharwani, P., Dandela, R., 2022. Clinical progress of therapeutics and vaccines: Rising hope against COVID-19 treatment. Process Biochem 118, 154–170. https://doi.org/10.1016/j.procbio.2022.04.011
4. Cercek, A., Lumish, M., Sinopoli, J., Weiss, J., Shia, J., Lamendola-Essel, M., El Dika, I.H., Segal, N., Shcherba, M., Sugarman, R., Stadler, Z., Yaeger, R., Smith, J.J., Rousseau, B., Argiles, G., Patel, M., Desai, A., Saltz, L.B., Widmar, M., Iyer, K., Zhang, J., Gianino, N., Crane, C., Romesser, P.B., Pappou, E.P., Paty, P., Garcia-Aguilar, J., Gonen, M., Gollub, M., Weiser, M.R., Schalper, K.A., Diaz, L.A., 2022. PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer. N Engl J Med 386, 2363–2376. https://doi.org/10.1056/NEJMoa2201445
5. Chen, T.-H., Chang, P.M.-H., Yang, M.-H., 2021. Combination of pembrolizumab and lenvatinib is a potential treatment option for heavily pretreated recurrent and metastatic head and neck cancer. J Chin Med Assoc 84, 361–367. https://doi.org/10.1097/JCMA.0000000000000497

6. D'Angelo, S.P., Bhatia, S., Brohl, A.S., Hamid, O., Mehnert, J.M., Terheyden, P., Shih, K.C., Brownell, I., Lebbé, C., Lewis, K.D., Linette, G.P., Milella, M., Georges, S., Shah, P., Ellers-Lenz, B., Bajars, M., Güzel, G., Nghiem, P.T., 2020. Avelumab in patients with previously treated metastatic Merkel cell carcinoma: long-term data and biomarker analyses from the single-arm phase 2 JAVELIN Merkel 200 trial. J Immunother Cancer 8, e000674. https://doi.org/10.1136/jitc-2020-000674
7. de Wilt, J.H.W., Vermaas, M., Ferenschild, F.T.J., Verhoef, C., 2007. Management of locally advanced primary and recurrent rectal cancer. Clin Colon Rectal Surg 20, 255–263. https://doi.org/10.1055/s-2007-984870
8. Doroshow, D.B., Bhalla, S., Beasley, M.B., Sholl, L.M., Kerr, K.M., Gnjatic, S., Wistuba, I.I., Rimm, D.L., Tsao, M.S., Hirsch, F.R., 2021. PD-L1 as a biomarker of response to immune-checkpoint inhibitors. Nat Rev Clin Oncol 18, 345–362. https://doi.org/10.1038/s41571-021-00473-5
9. Esfahani, K., Roudaia, L., Buhlaiga, N., Del Rincon, S.V., Papneja, N., Miller, W.H., 2020. A Review of Cancer Immunotherapy: From the Past, to the Present, to the Future. Current Oncology 27, 87–97. https://doi.org/10.3747/co.27.5223
10. Fritz, J.M., Lenardo, M.J., 2019. Development of immune checkpoint therapy for cancer. Journal of Experimental Medicine 216, 1244–1254. https://doi.org/10.1084/jem.20182395
11. GlaxoSmithKline, 2022. A Phase 1 First-Time-in-Human, Open-Label Study of GSK6097608 Administered as Monotherapy and in Combination With Anticancer Agents in Participants With Advanced Solid Tumors (Clinical trial registration No. NCT04446351). clinicaltrials.gov.
12. Grupo Español de Investigación en Cáncer de Ovario, 2021. A Randomized, Open Label, Phase II Trial of Anti-PD1, TSR-042, as Maintenance Therapy for Patients With High-risk Locally Advanced Cervical Cancer After Chemo-radiation (Clinical trial registration No. NCT03833479). clinicaltrials.gov.
13. Han, Y., Liu, D., Li, L., 2020. PD-1/PD-L1 pathway: current researches in cancer. Am J Cancer Res 10, 727–742.
14. Herbst, R.S., Baas, P., Kim, D.-W., Felip, E., Pérez-Gracia, J.L., Han, J.-Y., Molina, J., Kim, J.-H., Arvis, C.D., Ahn, M.-J., Majem, M., Fidler, M.J., de Castro, G., Garrido, M., Lubiniecki, G.M., Shentu, Y., Im, E., Dolled-Filhart, M., Garon, E.B., 2016. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. The Lancet 387, 1540–1550. https://doi.org/10.1016/S0140-6736(15)01281-7
15. Huang, Q., Zheng, Y., Gao, Z., Yuan, L., Sun, Y., Chen, H., 2021. Comparative Efficacy and Safety of PD-1/PD-L1 Inhibitors for Patients with Solid Tumors: A Systematic Review and Bayesian Network Meta-analysis. J Cancer 12, 1133–1143. https://doi.org/10.7150/jca.49325
16. Inokuchi, J., Eto, M., 2019. Profile of pembrolizumab in the treatment of patients with unresectable or metastatic urothelial carcinoma. CMAR Volume 11, 4519–4528. https://doi.org/10.2147/CMAR.S167708
17. Italian Sarcoma Group, 2021. Phase II Study on TSR-042 in Advanced Clear Cell Sarcoma (Clinical trial registration No. NCT04274023). clinicaltrials.gov.
18. Iwai, Y., Ishida, M., Tanaka, Y., Okazaki, T., Honjo, T., Minato, N., 2002. Involvement of PD-L1 on tumor cells in the escape from host immune system

and tumor immunotherapy by PD-L1 blockade. Proc. Natl. Acad. Sci. U.S.A. 99, 12293–12297. https://doi.org/10.1073/pnas.192461099
19. Kasherman, L., Ahrari, S., Lheureux, S., 2021. Dostarlimab in the treatment of recurrent or primary advanced endometrial cancer. Future Oncol 17, 877–892. https://doi.org/10.2217/fon-2020-0655
20. Kazandjian, D., Suzman, D.L., Blumenthal, G., Mushti, S., He, K., Libeg, M., Keegan, P., Pazdur, R., 2016. FDA Approval Summary: Nivolumab for the Treatment of Metastatic Non-Small Cell Lung Cancer With Progression On or After Platinum-Based Chemotherapy. The Oncologist 21, 634–642. https://doi.org/10.1634/theoncologist.2015-0507
21. Lettieri-Barbato, D., Aquilano, K., 2018. Pushing the Limits of Cancer Therapy: The Nutrient Game. Front. Oncol. 8, 148. https://doi.org/10.3389/fonc.2018.00148
22. Li, J.-X., Huang, J.-M., Jiang, Z.-B., Li, R.-Z., Sun, A., Lai-Han Leung, E., Yan, P.-Y., 2019. Current Clinical Progress of PD-1/PD-L1 Immunotherapy and Potential Combination Treatment in Non–Small Cell Lung Cancer. Integr Cancer Ther 18, 153473541989002. https://doi.org/10.1177/1534735419890020
23. Lu, S., Bowsher, R.R., Clancy, A., Rosen, A., Zhang, M., Yang, Y., Koeck, K., Gao, M., Potocka, E., Guo, W., Jen, K.Y., Im, E., Milton, A., 2021. An Integrated Analysis of Dostarlimab Immunogenicity. AAPS J 23, 96. https://doi.org/10.1208/s12248-021-00624-7
24. Mansh, M., 2011. Ipilimumab and cancer immunotherapy: a new hope for advanced stage melanoma. Yale J Biol Med 84, 381–389.
25. Markham, A., 2021. Dostarlimab: First Approval. Drugs 81, 1213–1219. https://doi.org/10.1007/s40265-021-01539-5
26. Mazières, J., Park, K., Lewanski, C., Gadgeel, S., Fehrenbacher, L., Rittmeyer, A., Han, J.-Y., Artal-Cortes, A., Braiteh, F., Vansteenkiste, J., 2018. 136PD_PR 3-year survival and duration of response in randomized phase II study of atezolizumab (atezo) vs docetaxel (doc) in 2L+ NSCLC (POPLAR). Journal of Thoracic Oncology 13, S79. https://doi.org/10.1016/S1556-0864(18)30410-6
27. Memorial Sloan Kettering Cancer Center, 2022. Adjuvant Checkpoint Blockade Plus Radiation In Locally Advanced, Mismatch Repair Deficient/Microsatellite Instability-High (MMR-D/MSI-H) Endometrial Cancer (Clinical trial registration No. NCT04774419). clinicaltrials.gov.
28. Migden, M.R., Rischin, D., Schmults, C.D., Guminski, A., Hauschild, A., Lewis, K.D., Chung, C.H., Hernandez-Aya, L., Lim, A.M., Chang, A.L.S., Rabinowits, G., Thai, A.A., Dunn, L.A., Hughes, B.G.M., Khushalani, N.I., Modi, B., Schadendorf, D., Gao, B., Seebach, F., Li, S., Li, J., Mathias, M., Booth, J., Mohan, K., Stankevich, E., Babiker, H.M., Brana, I., Gil-Martin, M., Homsi, J., Johnson, M.L., Moreno, V., Niu, J., Owonikoko, T.K., Papadopoulos, K.P., Yancopoulos, G.D., Lowy, I., Fury, M.G., 2018. PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma. N Engl J Med 379, 341–351. https://doi.org/10.1056/NEJMoa1805131
29. Naidoo, J., Page, D.B., Li, B.T., Connell, L.C., Schindler, K., Lacouture, M.E., Postow, M.A., Wolchok, J.D., 2015. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol 26, 2375–2391. https://doi.org/10.1093/annonc/mdv383

30. Oiseth, S.J., Aziz, M.S., 2017. Cancer immunotherapy: a brief review of the history, possibilities, and challenges ahead. JCMT 3, 250. https://doi.org/10.20517/2394-4722.2017.41
31. Paz-Ares, L., Spira, A., Raben, D., Planchard, D., Cho, B.C., Özgüroğlu, M., Daniel, D., Villegas, A., Vicente, D., Hui, R., Murakami, S., Spigel, D., Senan, S., Langer, C.J., Perez, B.A., Boothman, A.-M., Broadhurst, H., Wadsworth, C., Dennis, P.A., Antonia, S.J., Faivre-Finn, C., 2020. Outcomes with durvalumab by tumour PD-L1 expression in unresectable, stage III non-small-cell lung cancer in the PACIFIC trial. Annals of Oncology 31, 798–806. https://doi.org/10.1016/j.annonc.2020.03.287
32. Qin, S., Xu, L., Yi, M., Yu, S., Wu, K., Luo, S., 2019. Novel immune checkpoint targets: moving beyond PD-1 and CTLA-4. Mol Cancer 18, 155. https://doi.org/10.1186/s12943-019-1091-2
33. Redondo, A., Gallego, A., Mendiola, M., 2022. Dostarlimab for the treatment of advanced endometrial cancer. Expert Rev Clin Pharmacol 15, 1–9. https://doi.org/10.1080/17512433.2022.2044791
34. Robert, C., 2020. A decade of immune-checkpoint inhibitors in cancer therapy. Nat Commun 11, 3801. https://doi.org/10.1038/s41467-020-17670-y
35. Rolfo, C., Caglevic, C., Santarpia, M., Araujo, A., Giovannetti, E., Gallardo, C.D., Pauwels, P., Mahave, M., 2017. Immunotherapy in NSCLC: A Promising and Revolutionary Weapon, in: Naing, A., Hajjar, J. (Eds.), Immunotherapy, Advances in Experimental Medicine and Biology. Springer International Publishing, Cham, pp. 97–125. https://doi.org/10.1007/978-3-319-53156-4_5
36. Rosenberg, J.E., Hoffman-Censits, J., Powles, T., van der Heijden, M.S., Balar, A.V., Necchi, A., Dawson, N., O'Donnell, P.H., Balmanoukian, A., Loriot, Y., Srinivas, S., Retz, M.M., Grivas, P., Joseph, R.W., Galsky, M.D., Fleming, M.T., Petrylak, D.P., Perez-Gracia, J.L., Burris, H.A., Castellano, D., Canil, C., Bellmunt, J., Bajorin, D., Nickles, D., Bourgon, R., Frampton, G.M., Cui, N., Mariathasan, S., Abidoye, O., Fine, G.D., Dreicer, R., 2016. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. The Lancet 387, 1909–1920. https://doi.org/10.1016/S0140-6736(16)00561-4
37. Seidel, J.A., Otsuka, A., Kabashima, K., 2018. Anti-PD-1 and Anti-CTLA-4 Therapies in Cancer: Mechanisms of Action, Efficacy, and Limitations. Front Oncol 8, 86. https://doi.org/10.3389/fonc.2018.00086
38. Shiravand, Y., Khodadadi, F., Kashani, S.M.A., Hosseini-Fard, S.R., Hosseini, S., Sadeghirad, H., Ladwa, R., O'Byrne, K., Kulasinghe, A., 2022. Immune Checkpoint Inhibitors in Cancer Therapy. Current Oncology 29, 3044–3060. https://doi.org/10.3390/curroncol29050247
39. Shirley, M., 2018. Avelumab: A Review in Metastatic Merkel Cell Carcinoma. Targ Oncol 13, 409–416. https://doi.org/10.1007/s11523-018-0571-4
40. Siegel, R.L., Miller, K.D., Fuchs, H.E., Jemal, A., 2022. Cancer statistics, 2022. CA A Cancer J Clinicians 72, 7–33. https://doi.org/10.3322/caac.21708
41. Singh, V., Sheikh, A., Abourehab, M.A.S., Kesharwani, P., 2022. Dostarlimab as a Miracle Drug: Rising Hope against Cancer Treatment. Biosensors 12, 617. https://doi.org/10.3390/bios12080617

42. Tan, S., Li, D., Zhu, X., 2020. Cancer immunotherapy: Pros, cons and beyond. Biomedicine & Pharmacotherapy 124, 109821. https://doi.org/10.1016/j.biopha.2020.109821
43. Tesaro, Inc., 2022. A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-042, an Anti-PD-1 Monoclonal Antibody, in Patients With Advanced Solid Tumors (Clinical trial registration No. NCT02715284). clinicaltrials.gov.
44. Van Cutsem, E., Cervantes, A., Adam, R., Sobrero, A., Van Krieken, J.H., Aderka, D., Aranda Aguilar, E., Bardelli, A., Benson, A., Bodoky, G., Ciardiello, F., D'Hoore, A., Diaz-Rubio, E., Douillard, J.-Y., Ducreux, M., Falcone, A., Grothey, A., Gruenberger, T., Haustermans, K., Heinemann, V., Hoff, P., Köhne, C.-H., Labianca, R., Laurent-Puig, P., Ma, B., Maughan, T., Muro, K., Normanno, N., Österlund, P., Oyen, W.J.G., Papamichael, D., Pentheroudakis, G., Pfeiffer, P., Price, T.J., Punt, C., Ricke, J., Roth, A., Salazar, R., Scheithauer, W., Schmoll, H.J., Tabernero, J., Taïeb, J., Tejpar, S., Wasan, H., Yoshino, T., Zaanan, A., Arnold, D., 2016. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Annals of Oncology 27, 1386–1422. https://doi.org/10.1093/annonc/mdw235
45. Waldman, A.D., Fritz, J.M., Lenardo, M.J., 2020. A guide to cancer immunotherapy: from T cell basic science to clinical practice. Nat Rev Immunol 20, 651–668. https://doi.org/10.1038/s41577-020-0306-5
46. Washington University School of Medicine, 2022. A Phase I Study of PD-1 Inhibition With TSR-042 in Addition to Standard of Care Definitive Radiation for Inoperable Endometrial Cancer (Clinical trial registration No. NCT03955978). clinicaltrials.gov.
47. Wu, G., 2021. Therapeutic Effects of Pembrolizumab Combined with Paclitaxel and Cisplatin Chemotherapy on Advanced Non-Squamous Non-Small Cell Lung Cancer and Influencing Factors. ijps 83. https://doi.org/10.36468/pharmaceutical-sciences.757