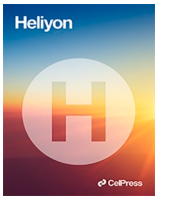
Heliyon 9 (2023) e23169

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

An extension of cancer immunotherapy with dostarlimab, the PD1-PD L1 pathway blocker

Sitangshu Sekhar Biswas [a], Sarath BabuV [b], Abhipsa Chakraborty [c], Amarnath Chakraborty [d], Hasheetha Jayashankar [e], Kudiyarasan Swamynathan [f,*]

[a] *Independent Researcher,SRMIST, Chennai, India*
[b] *Associate Professor of Physiology, Vels Medical College & Hospital, India*
[c] *.Freelancer, Amity University, Kolkata, India*
[d] *Peerless Hospital and BK Roy Research Center, Kolkata, India*
[e] *Junior Research Fellow, Central Council for Research in Homoeopathy, Goa, India*
[f] *Electrical Group, Bharatiya Nabhikya Vidyut Nigam Limited (BHAVINI), Department of Atomic Energy, Kalpakkam, Tamilnadu, 603 102, India*

ARTICLE INFO

Keywords:
Cancer immunotherapy
Monoclonal antibody
PD1
PD L1
Dostarlimab
B7.1

ABSTRACT

Cancer immunotherapy is a treatment that uses the body's own immune system to fight against cancer. Malignant cells in the human body have the ability to mutate themselves in such a way that they can escape from immune system surveillance and proliferate. So, if the human immune system could be boosted or its surveillance and defensive mechanisms improved so that our bodies can detect cancer cells and kill them by combining all of the human body's defensive mechanisms, it would be much easier to deal with cancer. A recent trial at Memorial Sloan Kettering Cancer Center in New York found that by using a drug called Dostarlimab, rectal adenocarcinoma could be cured by boosting the human immune system to detect and kill cancer cells. This could be considered a validated extension of cancer immunotherapy. This paper will explain how dostarlimab works on the body's immune system and destroys cancer cells in a simple way that anyone who is not in the medical field also can understand.

1. Introduction

When a pathogen (in the form of a complex protein, it contains amino acids, but some non-amino acid group also may present as a prosthetic group or co-factor) crosses the human body barrier and enters, our innate immune system is activated, and phagocytes (monocytes and macrophages, granulocytes and dendritic cells) kill and ingulf the pathogens via phagocytosis. The immune system, on the other hand, recruits antibodies, which are immunoglobulins that bind to pathogens and form a complex protein. Our complement immunity system degrades the pathogen's activity by destroying the complex protein. However, cancer cells in our bodies have the ability to mask themselves so that the body's immune system does not recognize them as an unwanted cell, allowing them to easily overcome the immunity barrier and proliferate. If the masking mechanism of cancer cells is understood and can be broken or stopped, the cancer cell's growth will be under the body's immune surveillance, or the cancer cells can be destroyed by introducing some

* **Corresponding author**.
E-mail addresses: sitangshu_sekharbiswas@srmuniv.edu.in (S.S. Biswas), drsarathkmc@gmail.com (S. BabuV), abhitorsa99@gmail.com (A. Chakraborty), chakrabortydramarnath@gmail.com (A. Chakraborty), ashitha99j@gmail.com (H. Jayashankar), kudiyarasan@rediffmail.com (K. Swamynathan).

https://doi.org/10.1016/j.heliyon.2023.e23169
Received 24 March 2023; Received in revised form 21 November 2023; Accepted 28 November 2023
Available online 1 December 2023

monoclonal antibodies (which are clones of human inherent antibodies made externally in laboratories that stimulate the body's immune system), this is known as cancer immunotherapy. Other therapies, such as surgery, chemotherapy, radiation therapy, targeted therapy, hormone therapy, and so on, can then be avoided, and our body's immune system will be strong enough to fight against cancer.

2. Masking mechanism of cancer cells

When our immune system is triggered, body's T cells become activated. T cells have two important receptors called PD1 (programmed cell death protein 1, found on the surface of B and T cells) and B7.1 (Type I membrane protein under immunoglobulin family which also found in activated antigen-presenting cells). When B7.1 binds to CD28 and CD152 (which are also surface proteins of T cells), it can send co-stimulatory signals to the body's immune system, indicating that some unwanted protein is present in the body in the form of antigen or as neoplastic cells. So, in the human body, B7.1 acts as an immune system alarm, and PD1 acts as a security scanner to detect pathogens or malignant cells. If any pathogens or neoplastic cells are detected by PD1, B7.1, it begins signaling and our body's defensive mechanisms detect and kill them. In case of cancer cells, it deactivates the action of PD1 and B7.1, making it easier for them to evade the body's immune surveillance and alarming system, allowing them to proliferate uncontrollably. Cancer cells in the human body have another receptor called PD L1 (programmed cell death ligand 1), which is a transmembrane protein that works as an immune system inhibitory factor when combined with PD1 (PD1-PD L1 pathway) and reduces the proliferation of PD1 cells, which inturn reduces the PD1-induced apoptosis. As a result, cancer cells hide from the body's immune system and can spread uncontrollably. In Fig. 1 the PD1-PD L1 was elaborated pictorially.

Other programmed cell death ligands such as PD-L2 bind to PD1 and RGMb, a member of the repulsive guidance molecule (RGM) family that aids in nervous system development, acts as a bone morphogenetic protein (BMP) co-receptor that regulates BMP signalling and promotes neuronal adhesion. Through BMP signalling, RGMb can sometimes operate as a negative regulator in breast and prostate cancer. However, the expression of PD L1 and PD L2 differs. PD-L1, also known as CD274 and B7–H1, is a transmembrane protein discovered on the surface of antigen-presenting cells and colorectal carcinoma tumour cells. PD-L2 is more typically found in HNSCC, SGC, prostate cancer, gastric cancer, oesophageal adenocarcinoma, and bladder cancer. Dostarlimab, a monoclonal antibody that binds to the PD-1 receptor, prevents PD-1 from interacting with PD-L1 and PD-L2, allowing the anti-tumor immune response to proceed unhindered. However, because our focus was on rectal adenocarcinoma and PD-L1 expression is more significant in APCs in this situation, we primarily developed the PD-1 PD-L1 pathway inhibitor.

3. Monoclonal antibody (mAB or moAb)

As the name implies, mono specific antibodies are made externally in laboratories and are identical immune cells of the human body. This monoclonal antibody can only bind to a single antigen or epitope. When we need it, we inject the specific antigen or epitope (the cancer cells in the case of cancer immunotherapy) into the targeted mammals and collect various spleen cells from the mammals [1].

The spleen cells are then fused with myeloma cells (a type of white blood cell called a plasma cell that helps to fight against infections by producing antibodies that recognize antigens or harmful cells to the body) to form hybridomas. The targeted hybridomas are separated and cultured in HAT medium (hypoxanthine-aminopterin-thymidine medium), which supports hybridoma growth. The antibodies are then separated from the hybridoma and are known as monoclonal antibodies. The formation of hybridoma and its extraction is shown in Fig. 2. Dostarlimab is a monoclonal antibody that inhibits the PD1-PD L1 pathway [2].

4. Dostarlimab and cancer immunotherapy

Dostarlimab therapy, which is a monoclonal antibody used to treat adults with mismatch repair deficient (dMMR) and advanced rectal adenocarcinoma, is a type of cancer immunotherapy. Dostarlimab's molecular formula is $C_{6420}H_{9832}N_{1690}O_{2014}S_{44}$. The European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) approved the commercialization of dostarlimab in February 2021 for the treatment of specific kinds of recurrent or advanced endometrial cancer. In April 2021, the

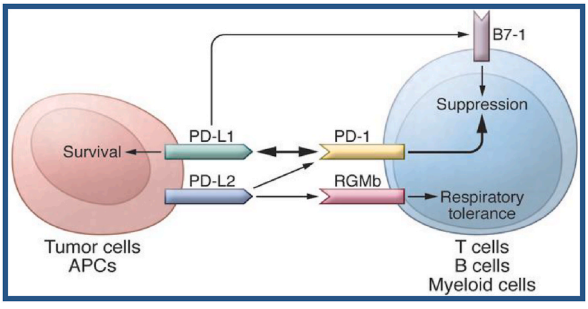


Fig. 1. PD1-PD L1 pathway to mask the cancer cell and proliferate.

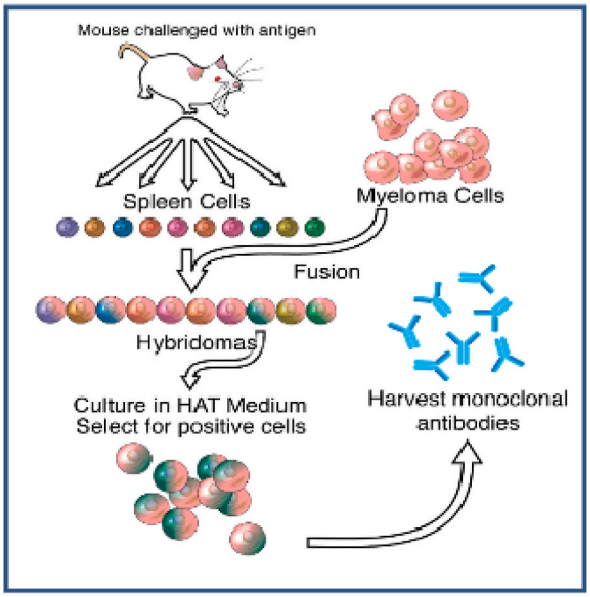


Fig. 2. A typical mechanism of Monoclonal antibody preparation with mouse by injecting specific antigen.

European Union approved dostarlimab for medical usage. This monoclonal antibody is now accessible in India to treat some forms of cancer.

Fig. 3 describes in the absence of Dostarlimab (top), PD L1 binds to PD1 and B7.1 receptors, inactivating T cells and promoting cancer cell proliferation. However, when dostarlimab is administered (bottom), it binds to the PD1 receptor and prevents PD L1 from binding with PD1, activating the T cell, causing it to multiply and kill cancer cells through self-immunity.

As discussed in section 2, cancer cells have a ligand protein (PD L1) that binds to PD1 and B7.1 and suppresses T cell activity in order to fight against malignancy. Dostarlimab is a monoclonal antibody that acts as a PD L1 blocker, allowing the PD1 and B7.1 activities to remain unchanged while the body's immune system detects and destroys neoplastic cells through self-defence [3]. There is an evidence and a clinical trial by "Memorial Sloan Kettering Cancer Centre, New York" that patients with rectal adenocarcinoma can be completely cured without surgery or other therapies by using dostarlimab. Dostarlimab is marketed under the brand name Jemperli [4].

5. Trial result analysis

Dostarlimab therapy (without chemotherapy or surgery) for mismatch repair-deficient was administered to 12 patients with rectal cancer at Memorial Sloan Kettering Cancer Center in New York, and all 12 patients responded positively and were cured [5–8].

Endoscopy, fluorodeoxyglucose (FDG)-positron emission tomography (PET), MRI, and biopsy results show that dostarlimab began to improve and shrink the tumours which were shown in Fig. 4 [9,10]. There were no significant side effects observed in the patients. The presence of mucin pools ensures the absence of neoplastic epithelium ("acellular" mucin). The presence of mucin pools in neo-adjuvant dostarlimab therapy for rectal cancer is associated with a positive response to treatment and downstaging [11,12], as well as improved survival. A biopsy image after the start of dostarlimab therapy is shown in Fig. 5 with acellular residual mucin pools

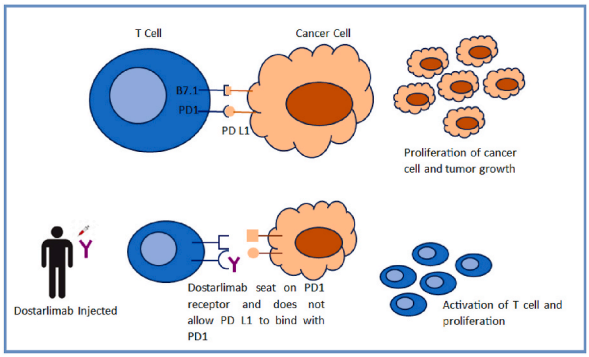


Fig. 3. Interaction of PD1 and PDL1 in the absence and presence of Dostarlimab.

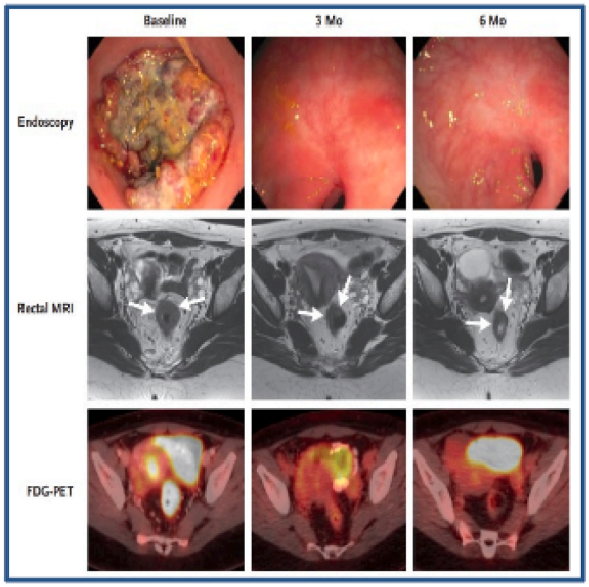


Fig. 4. Various medical imaging demonstrates how tumours begin to shrink and are cured after 6 months of dostarlimab therapy [13].

indicated by an arrow.

Among the 12 patient, 10 random patients were considered and their tumour growth was monitored with a specified time interval after the Dostarlimab therapy started, the shrinkage rate was observed different for different patients but once the tumour shrinked completely, it was not developed further. Fig. 6 A graphical representation of the shrinkage of ten random patients' tumours from the baseline to regular time intervals after starting dostarlimab therapy shows that starting dostarlimab therapy at an early stage increases the shrinkage rate in a faster way.

According to section 4, PD L1 proliferates significantly during the rapid growth of cancer cells in order to mask the cancer cells. However, once down staging begins, the concentration of PD L1 begins to fall. As shown in Fig. 7(a–d), the concentration of PD L1 (represented in yellow) gradually decreased once dostarlimab therapy was initiated [14].

Table 1 shows that the acellular mucin percentage reduces gradually once the dostarlimab therapy started. Four patients were chosen randomly and it was tabulated below.

In Fig. 8 0th Day is the day from when Dostarlimab therapy started and PD L1 concentration, where the highest PD L1 concentration among the five patients are considered as 100 %. To observe the gradual degradation of PD L1 concentration, the Fluorescent image of 5 patients were considered randomly, and it was converted to a scaled colour contour by further image processing, the same was

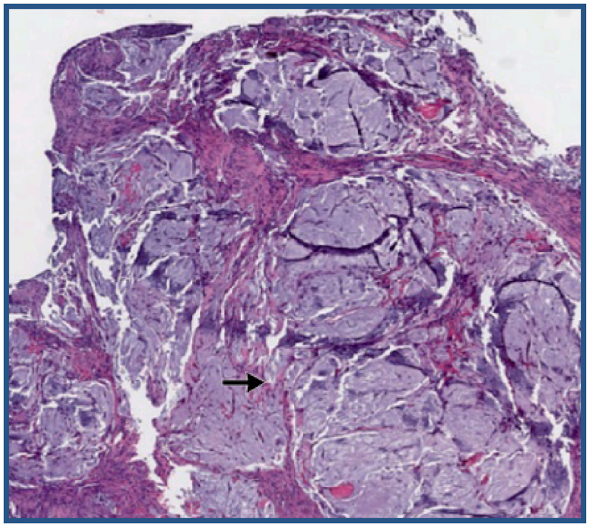


Fig. 5. A biopsy image shown after the initiation of dostarlimab therapy where acellular residual mucin pools were observed which is marked by arrow [13].

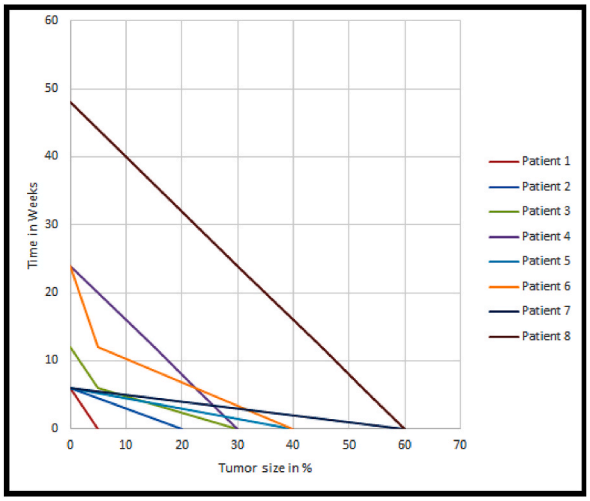


Fig. 6. At the start of Dostarlimab therapy, the cure period with tumour shrinkage percentage.

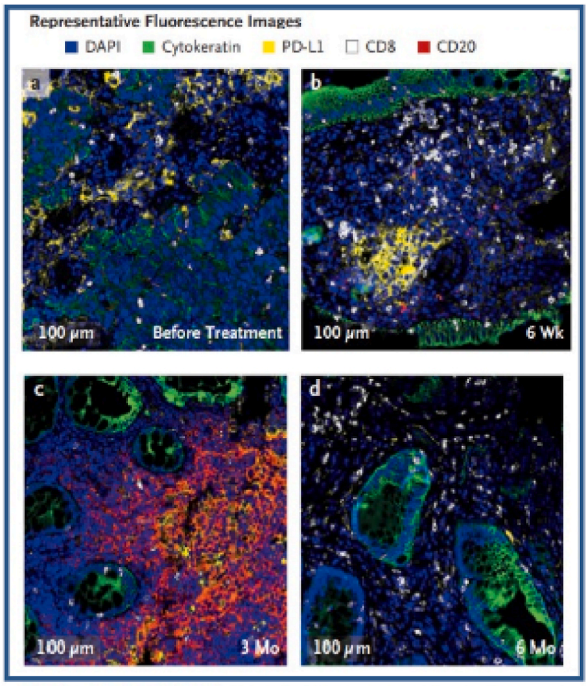


Fig. 7. (a–d). A fluorescent image, it was discovered that the concentration of PD LX1 (represented in yellow) gradually decreased once dostarlimab therapy began and was nil after 6 months [13].

plotted in Fig. 8. It is clear that after a certain period of Dostarlimab therapy, the PD L1 concentration began to decrease significantly and eventually became NIL.

It is also clear that the degradation slope varies between patients, owing to differences in immune response and tumour stage at the time Dostarlimab therapy was initiated.

6. Conclusion

In mismatch repair-deficient (cells with mutations in certain genes involved in fixing mistakes produced when DNA is replicated in a cell) rectal cancer, the single-agent dostarlimab responded dramatically. Pathological imaging and analysis are also used to show how the dostarlimab therapy treated the 12 patients. It should also be noted that this therapy is only appropriate for cancers caused by mismatch repair deficiencies; dostarlimab, the monoclonal antibody sold under the brand name Jemperli, costs around 3.5 lakhs per

Table 1
The maximum concentration of acellular mucin among the four patients were considered 100 %.

Time in days	Percentage of acellular mucin			
	Patient 1	Patient 2	Patient 3	Patient 4
0	80	100	90	70
30	60	70	70	60
60	55	65	55	58
90	40	60	40	48
120	35	48	28	30
150	15	30	0	24
180	0	18	0	18
210	0	0	0	15
240	0	0	0	0

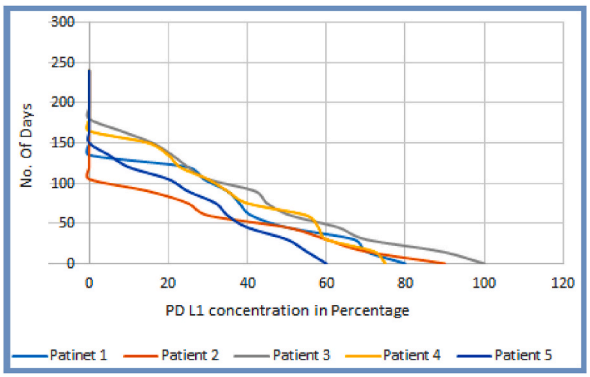


Fig. 8. Dostarlimab treatment lowered the levels of PD L1.

vial in India, which is quite expensive; the economic feasibility will be considered in future research to find any other cheaper alternative of equivalent chemical composition. The recommended clinical trial only included twelve patients, but in the future, the same procedure could be done with a greater number of patients to confirm overall success. When weighing the risks and advantages of this medicine, the most common side effects mentioned were fatigue, asthenia, nausea, diarrhoea, anaemia, constipation, vomiting, joint pain, itching, rash, fever, and hypothyroidism, among others. Furthermore, the study did not reveal the drug's long-term detrimental effects, which must be confirmed in order to verify its usefulness in the near future. The mitogen-activated protein kinase (MAPK) signalling pathway is especially essential because it may transform extracellular responses to intracellular responses, which can then be used to regulate cell proliferation via phosphorylation. So there will undoubtedly be an opportunity to examine the effect of dostarlimab therapy on the MAPK pathway, which may also be useful in the treatment of endometrial hyperplasia.

Funding

Not applicable.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Sitangshu Sekhar Biswas: Conceptualization. **Sarath BabuV:** Project administration, Conceptualization. **Abhipsa Chakraborty:** Supervision, Resources. **Amarnath Chakraborty:** Methodology, Investigation. **Hasheetha Jayashankar:** Formal analysis, Data curation. **Kudiyarasan Swamynathan:** Writing - review & editing, Writing - original draft, Software, Resources.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

The authors sincerely thank Rajalakshmi Medical College, Chennai, Tamil Nadu, India and The Jawaharlal Institute of Postgraduate Medical Education & Research is a medical school located at Pondicherry to do the further image processing and to estimate the concentration of PD L1 to ensure the success of the therapy.

References

[1] A. Oaknin, A.V. Tinker, L. Gilbert, et al., Clinical activity and safety of the anti–programmed death 1 monoclonal antibody dostarlimab for patients with recurrent or advanced mismatch repair–deficient endometrial cancer: a nonrandomized phase 1 clinical trial, JAMA Oncol. 6 (11) (2020) 1766–1772, https://doi.org/10.1001/jamaoncol.2020.4515.

[2] A. Oaknin, L. Gilbert, A.V. Tinker, R. Sabatier, V. Boni, D.M. O'Malley, S. Ghamande, L. Duska, P. Ghatage, W. Guo, E. Im, B. Pothuri, LBA36 Safety and antitumor activity of dostarlimab in patients (pts) with advanced or recurrent DNA mismatch repair deficient (dMMR) or proficient (MMRp) endometrial cancer (EC): results from GARNET, Ann. Oncol. 31 (4) (2020) S1166, https://doi.org/10.1016/j.annonc.2020.08.2266.

[3] B. Costa, N. Vale, Dostarlimab: a review, Biomolecules 12 (2022) 1031, https://doi.org/10.3390/biom12081031.

[4] Kasherman Lawrence, Soha Ahrari, Stephanie Lheureux, Dostarlimab in the treatment of recurrent or primary advanced endometrial cancer, Future Oncol. 17 (NO. 8) (Nov. 2020), https://doi.org/10.2217/fon-2020-0655.

[5] Thierry Andre, Dominique Berton, Giuseppe Curigliano, Susan Ellard, Jose Manuel Trigo Pérez, Hendrik-Tobias Arkenau, Cyril Abdeddaim, Victor Moreno, Wei Guo, Im Ellie, Naureen Starling, Safety and efficacy of anti–PD-1 antibody dostarlimab in patients (pts) with mismatch repair-deficient (dMMR) solid cancers: results from GARNET study, J. Clin. Oncol. 39 (3) (January 20, 2021). https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.3_suppl.9.

[6] Hassan ul Hussain, Muhammad Husban Burney, Syeda Tayyaba Rehan, Mohammad Mehedi Hasan, Dostarlimab: a breakthrough in the field of oncology, Annals of Medicine and Surgery 80 (2022), https://doi.org/10.1016/j.amsu.2022.104046.

[7] Chen Gong, Ying Jin, Wen-Long Guan, Rong-Xin Zhang, Wei-Wei Xiao, Pei-Qiang Cai, Min Liu, Jun-Zhong Lin, Fu-Long Wang, Cong Li, Ting-Ting Quan, Shao-Yan Xi, Hui-Zhong Zhang, Zhi-Zhong Pan, Feng Wang, Rui-Hua Xu, Neoadjuvant PD-1 blockade with sintilimab in mismatch-repair deficient, locally advanced rectal cancer: an open-label, single-centre phase 2 study, The Lancet Gastroenterology & Hepatology, (2023), https://doi.org/10.1016/S2468-1253(22)00439-3. Available online.

[8] K. Powell, T. Olivier, V. Prasad, A novel trial methodology to test interventions with very large effect sizes: the case of dostarlimab in mismatch repair-deficient, locally advanced rectal cancer, Trials 23 (1044) (2022), https://doi.org/10.1186/s13063-022-06988-1.

[9] V. Singh, A. Sheikh, M.A.S. Abourehab, P. Kesharwani, Dostarlimab as a miracle drug: rising hope against cancer treatment, Biosensors 12 (2022) 617, https://doi.org/10.3390/bios12080617.

[10] Busayo Odunayo Akodua, Azike Ruth Chinazor, Ikalo David Oseghale, Regina Titilayo Oddiri, George Chigozie Njokue, Dostarlimab GodwinOkoye, A review of its pharmacology and clinical use in management of cancer, International Research Journal of Oncology6 (3) (2022) 44–49. https://journalirjo.com/index.php/IRJO/article/view/106/211.

[11] Andres Redondo, Alejandro Gallego, Marta Mendiola, Dostarlimab for the treatment of advanced endometrial cancer, Expet Rev. Clin. Pharmacol. 15 (1) (2022) 1–9. https://www.tandfonline.com/doi/full/10.1080/17512433.2022.2044791.

[12] A. Oaknin, L. Gilbert, A.V. Tinker, Safety and antitumor activity of dostarlimab in patients with advanced or recurrent DNA mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) or proficient/stable (MMRp/MSS) endometrial cancer: interim results from GARNET—a phase I, single-arm study, Journal for ImmunoTherapy of Cancer 10 (2022), e003777, https://doi.org/10.1136/jitc-2021-003777.

[13] A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J. Garcia-Aguilar, M. Gonen, M. Gollub, M.R. Weiser, K.A. Schalper, L.A. Diaz Jr., PD-1 blockade in mismatch repair-deficient, locally advanced rectal cancer, N. Engl. J. Med. 386 (25) (2022 Jun 23) 2363–2376. Jun 5. PMID: 35660797; PMCID: PMC9492301.

[14] Odunayo Akodu, Busayo, Ruth Chinazor, , Azike and David Oseghale, Ikalo, Titilayo Oddiri, Regina, Chigozie Njoku, George and Okoye, Dostarlimab Godwin, A review of its pharmacology and clinical use in management of cancer, International Research Journal of Oncology 6 (3) (2022) 44–49. http://europeanrepository.uk/id/eprint/31.