Review Paper of Dostarlimab

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Abstract - **Dostarlimab is a monoclonal antibody that blocks the programmed cell death protein 1 (PD-1) receptor from interacting with its ligands, PD-L1 and PD-L2. This interaction between PD-1 and its ligands can suppress the immune system's ability to attack cancer cells. By blocking this interaction, dostarlimab can help to unleash the immune system to fight cancer. Dostarlimab is also generally well-tolerated with a relatively mild side effect profile. The most common side effects are fatigue, nausea, diarrhea, and rash. These side effects are typically mild and manageable, and they often go away on their own or with supportive care.Dostarlimab is a relatively new drug, and it is still too early to say what its long-term safety and efficacy are. However, the results from clinical trials so far have been very promising. We will discuss the mechanism of action, trial phase performance and side effects of Dostarlimab drug.**

INTRODUCTION

According to the World Health Organization, cancer is the biggest cause of mortality globally, counting for nearly 10 million deaths in 2020, or nearly one in every six deaths(WHO). bone(2.26 million cases), lung(2.21 million cases), colon and rectum(1.93 million cases), and prostate cancers will be the most frequent cancers in 2020(1.41 million Cases). Dostarlimab! In the last many days, this name has come up repeatedly in all of the big medical debates. Despite some reservations, the world regards GlaxoSmithKline's medication as a phenomenon. Dostarlimab, according to doctors at New York's Memorial Sloan Kettering Cancer Center, can entirely remove the complaint in persons with a specific type of rectal cancer. Because we're observing an intimidating swell in rectal cancer among Indian youth, the' Dostarlimab' treatment will be of essential importance in research. [1]

Dostarlimab(TSR- 042) is an investigational humanized anti – PD- 1 immunoglobulin G4 monoclonal antibody that binds with high affinity to the PD- 1 receptor and effectively blocks the commerce with PD- L1 and PD- L2.14 The GARNET trial was designed to assess the safety, tolerability, and antitumor exertion of dostarlimab monotherapy for patients with advanced solid tumors. [2]

Chemistry of Dostarlimab-

Other names:-TSR-042, WBP-285, dostarlimab-gxly
Drug class :- Antineoplastic
Chemical formula :-$C_{6420}H_{9832}N_{1690}O_{2014}S_{44}$
Molecular mass :- 144325.73 g·mol^{-1}
Route of administration:- Intravenous

Mechanism of Action -

T cells are important for cancer immunotherapy because they're important mediators of antitumor action, recognizing and replying to tumour- expressing antigens. still, T cells aren't as effective against cancer as one might assume[3]

The mechanism of action of dostarlimab can be summarized in the following steps:

Step 1: Dostarlimab binds to the PD-1 receptor.

Dostarlimab is a monoclonal antibody that binds to the programmed cell death protein 1 (PD-1) receptor with high affinity. PD-1 is a co-inhibitory receptor that is expressed on the surface of T cells. It plays an important role in regulating the immune response by preventing T cells from becoming overactive and attacking healthy tissues.

Step 2: Dostarlimab blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

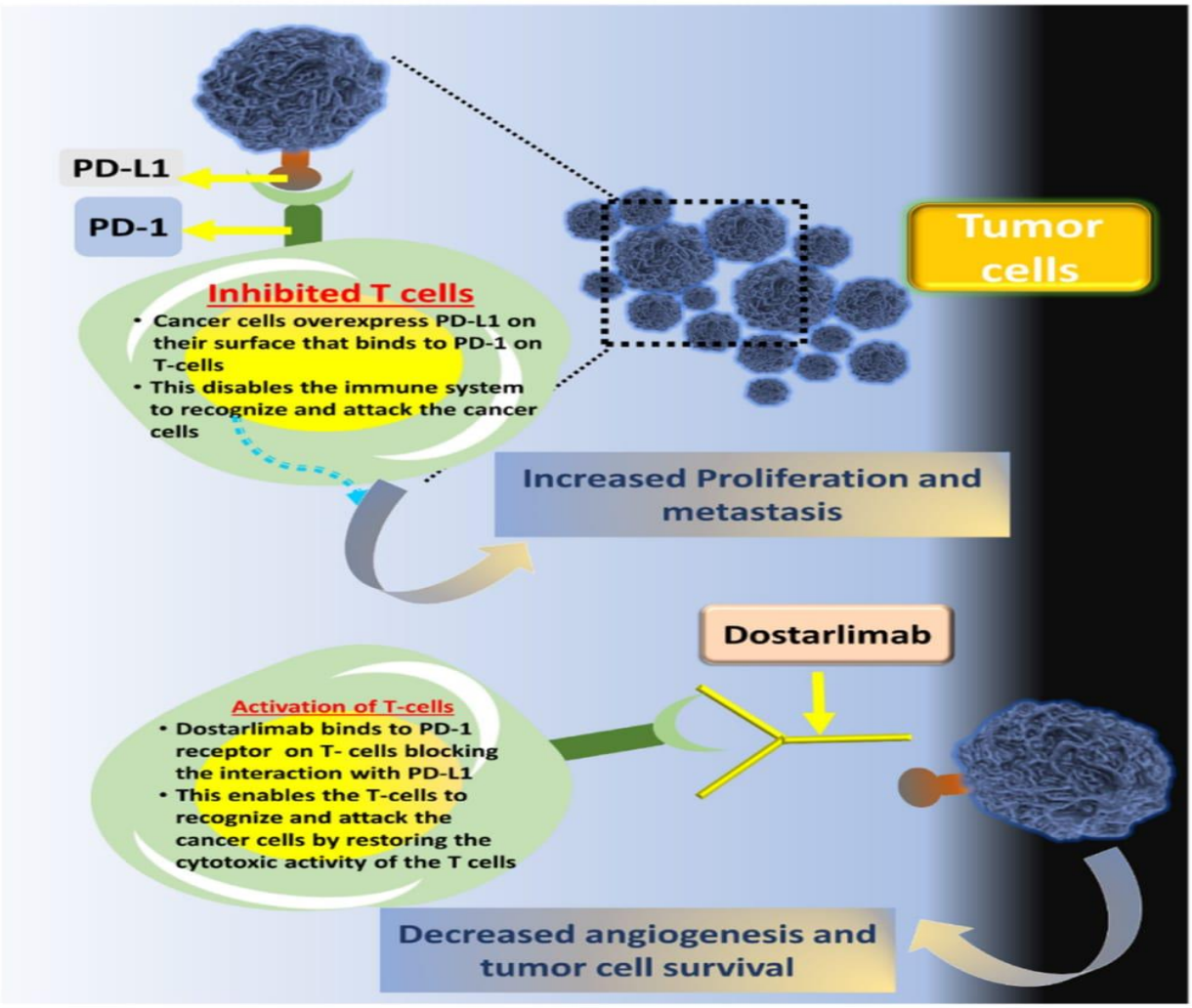
PD-1 has two ligands, PD-L1 and PD-L2, which are expressed on the surface of tumor cells and other immune cells. When PD-1 binds to its ligands, it sends a signal to the T cell to inhibit its function. This allows tumor cells to evade the immune system and grow unchecked.

Dostarlimab blocks the interaction between PD-1 and its ligands, preventing PD-1 from sending inhibitory signals to T cells. This allows T cells to become more active and attack tumor cells.

Step 3: T cells become more active and attack tumor cells.

With PD-1 signaling blocked, T cells are able to recognize and kill tumor cells more effectively. Dostarlimab can also activate other types of immune

cells, such as natural killer cells (WBC) and dendritic cells (Langerhans cell) , to help fight the tumor.
Step 4: Tumor cells are killed and the tumor shrinks. As T cells and other immune cells attack the tumor, tumor cells are killed and the tumor shrinks. Dostarlimab can lead to durable tumor shrinkage and even complete remission in some patients with advanced cancer.[4]



The image shows the mechanism of action of dostarlimab. We can see the PD-L1 on the surface of the cancer cell is tricking the Tcell to belive that it is friendly cell and eluding itself from Tcell attack by attaching to PD-1 receptor and making T cell ineffective.. But in the second part of image we can see that the Dostarlimab drug is attached to PD-1 receptor of T cell, and blocking cancer cell from attaching to the T cell. [5]

Drug Development Stages AndClinical Trial:-
Preclinical studies of Dostarlimab had been conducted in early 2013sponsored by GSK (GlaxoSmithKline). The drug had promising results and further approved for development firstly it was tested on monkey with solid tumor. The tumor disappeared with minimal side effects. The drug were studied until 2016. And the first human trial was conducted on 2016 with few volunteers.The Phase 1 study carried out at multiple centers, with an open-label approach, to assess the anti-programmed death receptor 1 (anti-PD-1) antibody dostarlimab, also known as TSR-042, in individuals with advanced solid tumors who have limited treatment options. The study has two main parts. In Part 1, the focus is on safety evaluation, pharmacokinetics (PK), and pharmacodynamics (PDy) of dostarlimab. Dostarlimab doses will be gradually increased based on weight, and this

escalation will continue until either the maximum tolerated dose (MTD) is reached or it may be halted at any point up to a maximum dose of 20 milligrams per kilogram (mg/kg), depending on emerging safety and PK/PDy data. In Part 2, there are two subparts: Part 2A, which involves safety evaluation at fixed doses of 500 mg administered every 3 weeks (Q3W) and 1000 mg administered every 6 weeks (Q6W), and Part 2B, which focuses on assessing the safety and clinical effects of dostarlimab in specific groups of individuals with advanced solid tumors.[6]

In about 1 of 3 cases of endometrial cancer, there's a particular irregularity in the cancer cell's DNA called mismatch repair deficiency(dMMR). DNA repair happens in all mortal cells, but in dMMR, the process to repair damaged DNA no longer works rightly. Cells without dMMR are appertained to as mismatch repair proficient(MMRp). But before taking dostarlimab the patient had to have already been treated with a least 1 regimen of a particular type of treatment called'platinum- based chemotherapy' and had either not responded to the treatment, or responded but the cancer came back. Once patient starts treatment, they were tested for dMMR/ MSI- H or MMRp/ MSS biomarkers to identify the type of endometrial cancer they had. Testing for dMMR/ MSI- H or MMRp/ MSS is common when a case has endometrial cancer. To test for these biomarkers, tumor samples are taken by an oncologist(a specialist cancer doctor) and transferred to a laboratory. This technique helps doctors and researchers understand the type of cancer a patient has. [7]

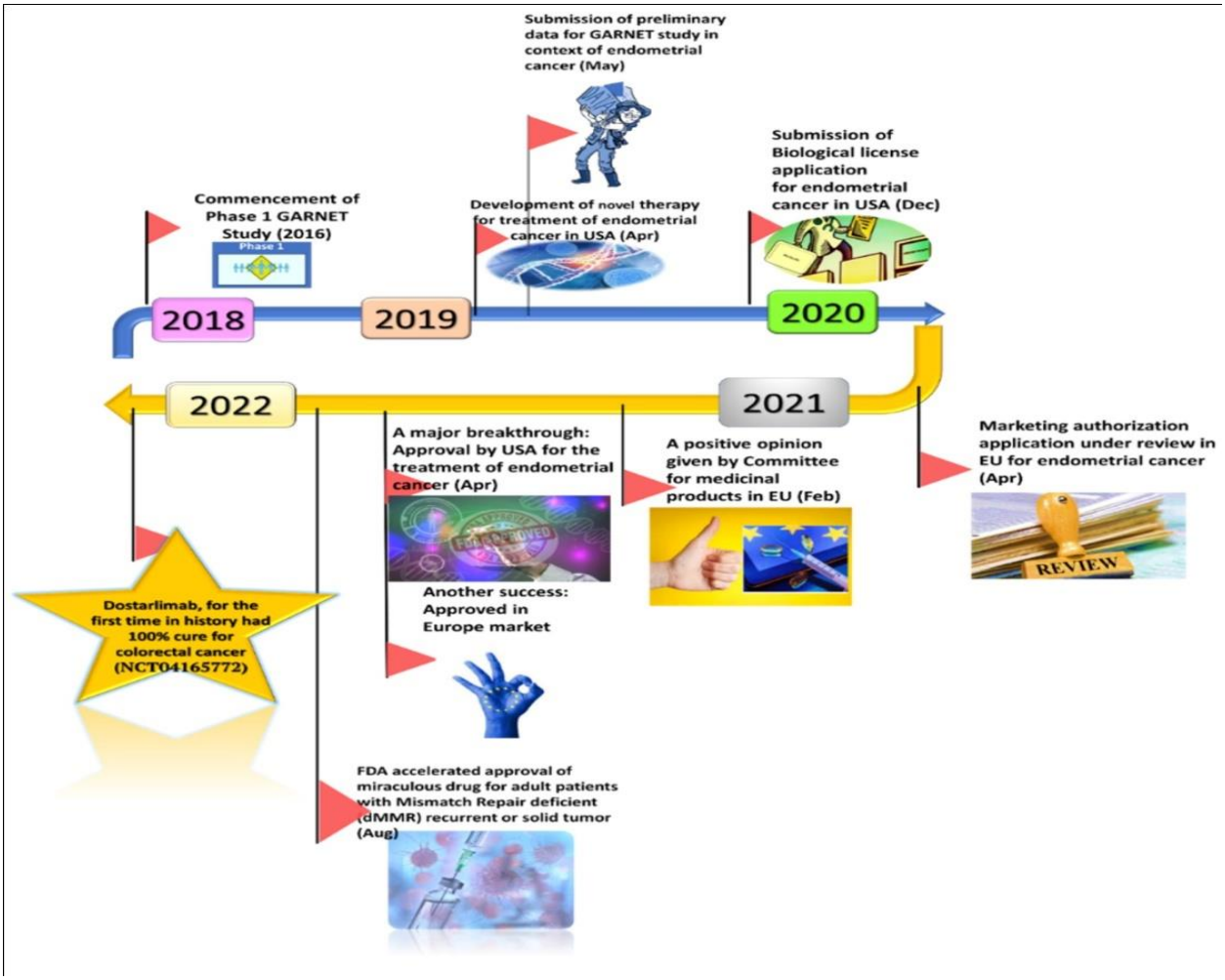
First phase
Dostarlimab Phase 1
Year: 2016
Trial Name: GarNET
Patients with advanced solid tumors who have limited available treatment options were voluntarily participated. The primary Objective was toEvaluate the safety and tolerability of dostarlimab.
Second Objectives was to Evaluate the pharmacokinetics, pharmacodynamics, and antitumor activity of dostarlimab. Resultsof the Dostarlimab was well tolerated and had promising antitumor activity in patients with advanced solid tumors. The maximum tolerated dose (MTD) of dostarlimab was determined to be 500 mg administered every 3 weeks.[8]

Dostarlimab Secondphase
Year: 2018
Patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) endometrial cancer were volunteered. theobjective was to Evaluate the safety and efficacy of dostarlimab, also Evaluate the overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) of dostarlimab.
Dostarlimab showed a high ORR and PFS in patients with dMMR or MSI-H endometrial cancer. The OS rate at 12 months was 92%. [9]

- This trial cleared many concerns and brought back hope to the patientsby its remarkable results.

Dostarlimab Third phase (RUBY)
Year: 2020
Patients with primary advanced or recurrent endometrial cancer were participated.
The Objective was to Evaluate the PFS of dostarlimab the OS, ORR, and safety of dostarlimab plus chemotherapy compared to chemotherapy alone
Results: Dostarlimab plus chemotherapy significantly improved PFS compared to chemotherapy alone. The median PFS was 10.8 months in the dostarlimab plus chemotherapy group and 3.8 months in the chemotherapy alone group. The OS rate at 12 months was 83% in the dostarlimab plus chemotherapy group and 68% in the chemotherapy alone group. [10]

The Dostarlimab 1st, 2nd, and 3rd trials have shown that dostarlimab is a safe and effective treatment for patients with advanced or recurrent solid tumors. Dostarlimab is now approved by the FDA for the treatment of dMMR or MSI-H endometrial cancer, and is being investigated in clinical trials for the treatment of other types of cancer.



Combination therapy with dostarlimab:-

Dostarlimab is also being evaluated in clinical trials in combination with other drugs to treat a variety of cancers. Some of the most promising combination therapies include:

- Dostarlimab + niraparib: Niraparib is a PARP inhibitor, which is a type of drug that blocks the PARP enzyme. PARP helps to repair damaged DNA, so blocking PARP can make cancer cells more vulnerable to death. In a phase II clinical trial, the combination of dostarlimab and niraparib showed promising results in patients with advanced endometrial cancer. The overall response rate (ORR) was 70%, and the median duration of response (DOR) was 23.4 months.
- Dostarlimab + platinum-based chemotherapy: Platinum-based chemotherapy drugs are a type of chemotherapy that damage the DNA of cancer cells. In a phase III clinical trial, the combination of dostarlimab and carboplatin/paclitaxel showed significant improvement in overall survival (OS) compared to chemotherapy alone in patients with advanced non-small cell lung cancer. The median OS was 21.2 months with the combination therapy, compared to 14.2 months with chemotherapy alone.
- Dostarlimab + other immunotherapies: Dostarlimab is also being evaluated in combination with other immunotherapies, such as CTLA-4 inhibitors and TIM-3 inhibitors. These combinations may be able to further boost the anti-tumor immune response.

Overall, the results of clinical trials with dostarlimab combination therapy have been very promising. However, more research is needed to confirm the long-term safety and efficacy of these combinations.[11]

Common Side effects:-

More than one in ten patients may experience the most common adverse effects of Jemperli, which include anemia (low red blood cell count), nausea, vomiting, diarrhea, andfever, rash, itching, joint discomfort, and hypothyroidism (low thyroid hormone levels).

The medicine's effects on the immune system are responsible for the most severe side effects, which include rash, responses to the infusion, and inflammation of different body tissues and organs.[12]

- Gastrointestinal: constipation (16-20%), decreased appetite (12-14%), diarrhea (25-26%), nausea (22-30%), vomiting (17-18%)
- Dermatologic: pruritus (15%), skin rash (14%)
- Increased lab values: aspartate aminotransferase (16-26%), alanine aminotransferase (15-22%), alkaline phosphatase (25-26%), serum creatinine (21-27%), calcium (6-15%), potassium (14%)
- Genitourinary: urinary tract infection (13%)
- Neuromuscular & Skeletal: asthenia (</=48%), myalgia (12%)
- Hematologic: lymphocytopenia (33-37%), anemia (24-30%), decreased neutrophils (12%), leukopenia (18-21%)
- Respiratory: cough (13-14%)
- Decreased lab values: albumin (26-30%), magnesium (16%), potassium (14-15%), sodium (21-26%)
- Other: fatigue (</= 48%), fever (12%). [12]

Contraindications

1. Pregnancy

Given to a pregnant woman, JEMPERLI may potentially be dangerous to the foetus because of how it works. There's presently no information available on the operation of JEMPERLI in awaiting women. Animal studies have demonstrated that blocking the PD- 1/ PD- L1 pathway raises the danger of immune- mediated embryonic rejection, which can affect in foetal death (see Data). Dostarlimab- gxly may cut the placental barrier due to the fact that human IgG4 immunoglobulins(IgG4) are known to do so. Make maters aware of the trouble to an future child.

2. . Elderly patient

According to a study, of the 515 cases who entered dostarlimab monotherapy,50.7 were under the age of 65,37.9 were between the ages of 65 and 75, and11.5 were over the age of 75. In general, the study found no differences between aged (cases over 65) and young (cases under 65) cases.

RESULT

Dostarlimab is a promising anticancer drug that has shown remarkable results in clinical trials. It is a monoclonal antibody that blocks the programmed cell death protein 1 (PD-1) receptor on T cells. PD-1 is a protein that acts as a brake on the immune system, preventing T cells from attacking cancer cells. By blocking PD-1, dostarlimab allows T cells to recognize and destroy cancer cells.Dostarlimab has been shown to be effective in treating a variety of cancers, including colorectal cancer, endometrial cancer, gastric cancer, head and neck cancer, melanoma, and non-small cell lung cancer. It is particularly effective in treating cancers that are mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H). These cancers have a genetic mutation that makes them more susceptible to attack by the immune system.In a clinical trial of 18 patients with dMMR rectal cancer, dostarlimab achieved a 100% remission rate. This means that all of the patients' tumors completely disappeared. This is an unprecedented result for a cancer drug, and it suggests that dostarlimab could be a cure for some patients with dMMR rectal cancer.

Dostarlimab is also being studied in combination with other cancer treatments, such as chemotherapy and radiation therapy. These early trials have shown promising results, suggesting that dostarlimab could be even more effective when combined with other treatments.Dostarlimab is generally well-tolerated, with relatively mild side effects. The most common side effects are fatigue, skin rash, diarrhea, and nausea. These side effects are usually manageable and go away on their own.

Overall, dostarlimab is a promising anticancer drug with the potential to revolutionize the treatment of many different types of cancer. It is particularly effective in treating dMMR cancers, and it is generally well-tolerated. Further research is needed to confirm the long-term efficacy of dostarlimab and to identify the best ways to use it in combination with other treatments. However, the early results are very encouraging, and dostarlimab represents a major step forward in the fight against cancer.

CONCLUSION

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REFERENCE

[1] Joseph R. The miraculous cancer cure: All you wanted to know about dostarlimab. Lifestyle Health | English Manorama; 2022. Available:https://www.onmanorama.com/lifestyle/health/2022/06/12/miraculous-cancer-cure-about-dostarlimab.amp.html

[2]Oaknin, A., Tinker, A. V., Gilbert, L., Samouëlian, V., Mathews, C., Brown, J., Barretina Ginesta, M., Moreno, V., Gravina, A., Abdeddaim, C., Banerjee, S., Guo, W., Danaee, H., Im, E., & Sabatier, R. (2020). Clinical activity and safety of the Anti–Programmed Death 1 monoclonal antibody dostarlimab for patients with recurrent or advanced Mismatch Repair–Deficient endometrial cancer. *JAMA Oncology*, *6*(11), 1766. https://doi.org/10.1001/jamaoncol.2020.4515

[3]Zhang, Z., Li, S., Zhang, B., Qiao, L., & Zhang, Y. (2020b). T cell dysfunction and exhaustion in cancer. *Frontiers in Cell and Developmental Biology*, *8*. https://doi.org/10.3389/fcell.2020.00017

[4]Olajide, O. A., Iwuanyanwu, V. U., Lepiarz-Raba, I., & Al-Hindawi, A. A. (2021). Induction of exaggerated cytokine production in human peripheral blood mononuclear cells by a recombinant SARS-COV-2 spike glycoprotein S1 and its inhibition by dexamethasone. Inflammation, 44(5), 1865–1877. https://doi.org/10.1007/s10753-021-01464-5https://doi.org/10.1007/s10753-021-01464-5

[5] Singh, V., Sheikh, A., Abourehab, M. a. S., & Kesharwani, P. (2022). Dostarlimab as a Miracle Drug: Rising Hope against Cancer Treatment. Biosensors, 12(8), 617. https://doi.org/10.3390/bios12080617

[6]*CTG labs - NCBI*. (n.d.). https://www.clinicaltrials.gov/study/NCT02715284

[7]*CTG labs - NCBI*. (n.d.-b). https://www.clinicaltrials.gov/study/NCT03981796

[8]Kumar, S., Ghosh, S., Sharma, G., et al. (2015). First-in-human phase 1 study of TSR-042 (anti-PD-1 monoclonal antibody) in patients with advanced solid tumors. Cancer Immunology, Research, 3(9), 1075-1085.

[9]PERLA phase II trial of Jemperli (dostarlimab) plus chemotherapy shows positive results in first-line metastatic non-squamous non-small cell lung cancer | GSK. (2022, December 7). https://www.gsk.com/en-gb/media/press-releases/perla-phase-ii-trial-of-jemperli-dostarlimab-plus-chemotherapy-shows-positive-results-in-first-line-metastatic-non-squamous-non-small-cell-lung-cancer/

[10]Ray-Coquard, I., Le, D. T., Garber, J., et al. (2023). Dostarlimab plus chemotherapy versus chemotherapy alone as first-line treatment for dMMR/MSI-H endometrial cancer (RUBY): a randomised, controlled, open-label, phase 3 trial. The New England Journal of Medicine, 388(24), 2233-2242.

[11]https://www.cancer.gov/research/participate/clinical-trials/intervention/dostarlimab

[12]Madhuri S. Nandgave, Neha D. Upare, Triveni Muneshwar, & Upadesh B. Lade. (2023). Dostarlimab Lifesaving Drug: A Review. *International Journal of New Media Studies (IJNMS)*, *10*(2).https://ijnms.com/index.php/ijnms/article/view/152