Dostarlimab: Pharmacological Analysis & Clinical Applications in Therapy of Cancer

Lokesh Pramod Joshi[1*], Tejal Girish Pathak[2]

1: Student, Department of Pharmaceutics, P.G.Collge of Pharmaceutical Science & Research , Nandurbar

2: Student, Department of Pharmaceutics, P.G.Collge of Pharmaceutical Science & Research , Nandurbar

ABSTRACT :

Dostarlimab , which is sold under brand name JEMPERLI is a PD-1 monoclonal antibody which is effective for treatment of adult patient with mis-match repair deficient (dMMR), recurrent or advanced endometrialcancer that has improvement on oor upgoing therapy with platinum containing regimen. This indication was granted fast approval based on the rate of tumor respnse and duration of response by test of FDA. The clinical trial performed in June 2022 , NCT04165772 shows 100% remission rate for rectal cancer. This clinical research shows proof that we can match a tumor and the genetics of what is driving it, with therapy. This clinical research currently enrolling patients with gastric, prostate, and pancreatic cancers. Dostarlimab is being adviced for rectal cancer. The present review is an effort to share the knowledge regarding dostarlimab.

Keyword : *Anti PD-1 antibody, Dostarlimab, Clinical trials, JEMPERLI*

INTRODUCTION :

According to the World Health Organization, cancer is the biggest cause of ephemerality globaly. Calculating for almost 10 million deaths in 2020, or nearly one in every six deaths (WHO). Breast (2.26 million instances), 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). A satisfactory clinical experiment at the Memorial Sloan Kettering Malignant Center in Manhattan showed 100 per cent elimination of the cancer disease for the first time in history. Although the research was conducted on a tiny scale, it has sparked hope that the world would soon be free of the deadly cancer sickness. Dostarlimab! In the last few days, this name has come up repeatedly in all of the big medical debates. FDA approved Dostarlimab on 17 august 2021. Despite some reservations, the world regards GlaxoSmithKline's medication as a miracle. Dostarlimab, according to doctors at New York's Memorial Sloan Kettering Cancer Center, can entirely remove the disease in persons with a specific type of rectal cancer. Because we are observing an alarming surge in rectal cancer among Malayalee youth, the 'Dostarlimab' treatment will be of essential importance in research. Dostarlimab, which is an antibody medication, has shown notabl results in the experimental treatment of patients with rectal cancer, but more deep research is required to understand the effects fully. It's like a checkpoint inhibitor that directs a person's immune system to do the work instead of directly fighting the tumour.

Chemistry :

Drug class : Antineoplastic

Formula : $C_{6420}H_{9832}N_{1690}O_{2014}S_{44}$

Mol, Weight : 144325.73 $g \cdot mol^{-1}$

Physicochemical properties:

Formulated drug substance; dostarlimab is a clear to slightly opalescent, colourless to the yellow solution, essentially free from visible particles"

Pharmacological Analysis :

- **Pharmacokinetics :**
- Absorption :
  During the first cycle, and administered at 500mg intravenously every 3 weeks, the mean C_{max} and $AUC_{0\text{-}tau}$ of dostarlimab-gxly are 171 mcg/mL and 35,730 mcg.h/mL, respectively. When administered at 1000mg every 6 weeks, the mean C_{max} and $AUC_{0\text{-}tau}$ are 309 mcg/mL and 95,820 mcg.h/mL, respectively.

- Distribution :
  At steady-state, the mean volume of distribution of dostarlimab is 5.3L

- Metabolism :
  The metabolism of dostarlimab has not been characterized, but it is expected to be degraded via catabolic pathways into smaller peptides and amino acids

- Elimination :
  The elimination of dostarlimab takes long period of time. The mean terminal elimination half-life of dostarlimab is 25.4 days.

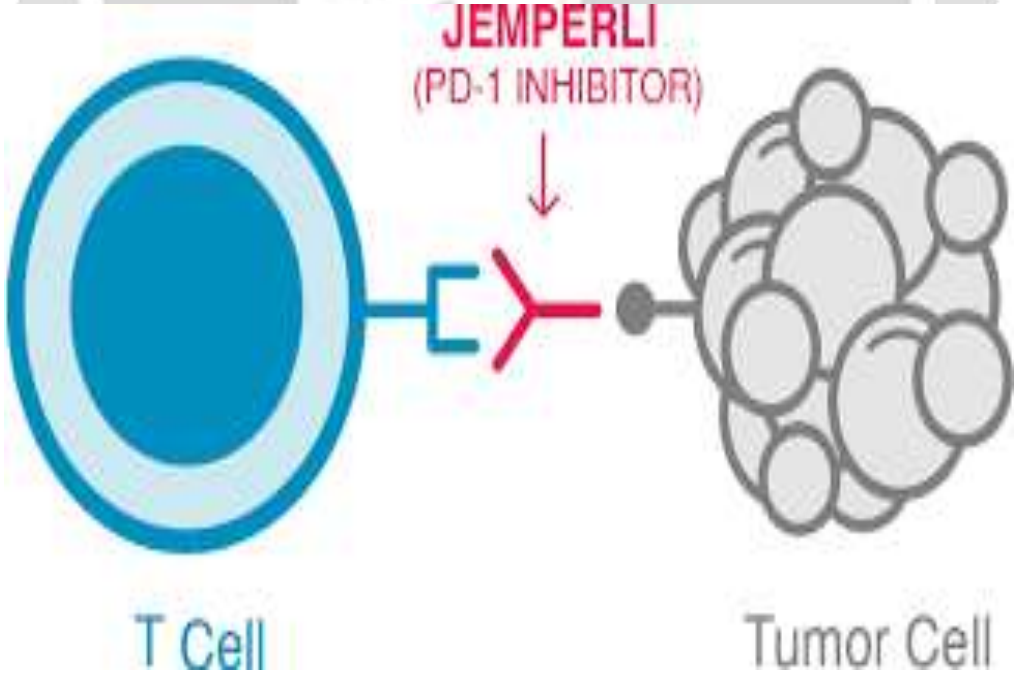
- **Pharmacodynamics :**

Mechanism of Action :

T cells are important for cancer immunotherapy because they are key mediators of antitumor action, identifying and reacting to tumour expressing antigens. However, T cells are not as effective against cancer as one might assume. “This happens due to T cells being defective or fatigued, characterized by the presence of an inhibitory Programmed Cell Death 1 (PD-1) receptor on the T-cells and as well as B-cells. PD-1 is an immune response-regulating protein found on the surface of T and B cells and it acts by reducing the T cell inflammatory activity. This stops cancer cells from being killed by the immune system”.

A transmembrane protein called as Programmed Cell Death Ligand 1 (PD-L1) is also considered to be a co-inhibitory component of the immune response. . When combined with PD-1, T cells' proliferation is inhibited, their cytokine secretion is blocked, and apoptosis is induced. The ability of PD-L1 to decrease the host immune system's response to tumour cells makes it relevant in various cancers. According to these point of view, the PD-1/PD-L1 axis plays a major role in cancer immunotherapy and is responsible for cancer immune escape. In general, macrophages, certain activated T cells, B cells, and some epithelial cells express PD-L1, especially in inflammatory situations. As an "adaptive immunological strategy" to evade antitumor responses, tumour cells also express PD-L1.

“Dostarlimab, an IgG4-isotype humanized monoclonal antibody binds to the PD-1 receptor and protects it from interacting with PD-L1 and PD-L2, thereby inhibiting the PD-1/PD-L1 immune response, including the anticancer immune response, through the PD-1 pathway”.



Dosage and administration :

The ideal dose of dostarlimab should be 500mg for three weeks until the fourth dose. Dosing schedule following the fourth dose, starting three weeks later (Dose 5 onward): every six weeks, 1,000 mg. Dostarlimab should be given intravenously for 30 minutes using Normal saline or 5% Dextrose Solution”.

Side Effects :

The main and most common side effect of dostarlimab includes fatigue, nausea, vomiting, joint and chest pain, itching, fever, anaemia, diarrhoea, constipation and hypothyroidism. While some allergics reactions such as hives, difficult breathing, swelling in your face or throat. Also some severe skin reaction like, skin pain, red or purple skin rash with blistering and peeling are to be seen. The drug dostarlimab may cause some hormone gland problems such as skin pain, red or purple skin rash with blistering and peeling, resulting in too much or too less formation of hormones by the body. Other side effects such as unexplained weight loss or weight gain, increased thirst and also increase in urination, behaviour changes, constipation are seen. "Lower back or side pain, muscle cramps and stiffness, pale skin, slow heartbeat, sore tongue, difficulty breathing, unusual bleeding or bruising, unusual tiredness or weakness, weight gain, constipation, depression, difficult, burning, or painful urination, dry skin and hair, feeling cold, frequent urge to urinate, hair loss, hoarseness or husky voice, loss of appetite" [9]. "Anxiety, irritability, lethargy, muscle twitching, nausea, nervousness, rapid weight gain, seizures, chest pain or tightness, chills, coma, confusion, cough, coughing up mucus, decreased urine output, diarrhoea, dizziness, fever, general feeling of being unwell, sweating, swelling of the face, feet, lower legs, ankles, or hands, thickening of bronchial secretions, and trouble breathing" [9]. "Anxiousness, back or leg tenderness, bloody or black stools, gum disease, swelling, blue or pale skin, blurred vision, burning, tingling, or pain in the hands, arms, feet, or legs, a burning sensation in the chest or abdomen, a change in vision, chest pain which may spread to the left arm, neck, or shoulder, Dark urine, skin darkening, drowsiness, dry mouth, eye pain, fainting, rapid heartbeat, general body swelling, inability to move the arms or legs, indigestion, joint pain, light-colored stools, lightheadedness, loss of consciousness, decreased energy, muscle cramps, anguish, tenderness, or frailty, bloody noses, tingling or numbness in the fingers, face, or feet, pains in the lower abdomen, side, or abdominal muscles, a severe headache, skin rash, erythema, soreness, or pruritus, lesions, welting, or blisters, stabbing pain, neck stiffness or back, stomach discomfort or upset, sudden numbness and weakness in the arms and legs, possibly radiating to the back, partial or mild paralysis, rapid, shallow breathing, pinpoint red spots on the skin, redness of the eye, sensation of pins and needles, sensitivity of the eye to light, and swollen, painful lymph nodes".

Adverse Reactions :

Some immune mediated adverse reactions of dostarlimab are……

- Severe or fatal immune-mediated adverse reactions can occur in any organ system or tissue
- May start at any time after initiating a programmed death 1 (PD-1)/programmed death-ligand 1 (PD-L1)–blocking antibody; may manifest during treatment and after discontinuation
- Immune-mediated pneumonitis, colitis, hepatitis, hypophysitis, thyroid disorders, thyroiditis, hypothyroidism, nephritis, or hyperthyroidism may occur
- Can cause primary or secondary adrenal insufficiency
- Type 1 diabetes mellitus reported, which can present with diabetic ketoacidosis; monitor for hyperglycemia or other signs and symptoms of diabetes; initiate treatment with insulin as clinically indicated; withhold or permanently discontinue depending on severity
- Immune-mediated rash or dermatitis (bullous and exfoliative dermatitis, SJS, TEN, DRESS syndrome) has occurred
- Monitor closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions
- If immune-mediated adverse reactions are suspected, initiate appropriate workup to exclude alternative etiologies, including infection; institute medical management promptly, including specialty consultation as appropriate

- **Other immune-mediated adverse reactions are the following**
  - Nervous system: Meningitis, encephalitis, myelitis, myasthenic syndrome/myasthenia gravis, Guillain Barre syndrome, nerve paresis, autoimmune neuropathy
  - Cardiac/vascular: Myocarditis, pericarditis, vasculitis
  - Ocular: Uveitis, iritis, other ocular inflammatory toxicities; some cases can be associated with retinal detachment; various grades of visual impairment to include blindness can occur; if uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi–Harada like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss
  - Gastrointestinal: Pancreatitis, including increases in serum amylase and lipase levels, gastritis, duodenitis
  - Musculoskeletal and connective tissue: Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica
  - Endocrine: Hypoparathyroidism
  - Other (hematologic/immune): Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenia, solid organ transplant rejection.

Contraindications :

- **Pregnancy :**

"When Dostarlimab drug was given to a pregnant woman, JEMPERLI can potentially harm the fetus due to its mode of action. information on the use of JEMPERLI in expectant women is currently unavailable. Inhibition of the PD-1/PD-L1 pathway has been shown in animal studies to increase the risk of immune-mediated rejection of the developing fetus, which can result in fetal death (see Data). Dostarlimab-gxly may pass from the mother to the growing fetus because human IgG4 immunoglobulins (IgG4) are known to cross the placental barrier. Inform women of the potential danger to an unborn child. The estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2 per cent to 4 per cent and 15 per cent to 20 per cent, respectively, in the general population of the United States"

- **Other Conditions:**

Inflammation of the kidney, high blood sugar, pregnancy, a patient who is producing milk and breastfeeding, overactive thyroid gland, low thyroid hormone levels, type 1 diabetes mellitus, severely reduced function of the cortex of the adrenal gland, interstitial pneumonitis, inflammation of the large intestine, inflammation of the liver called hepatitis, inflammation of the kidney, and inflammation of the pituitary gland.

Conclusion:

Dostarlimab, an IgG4-isotype humanized monoclonal antibody binds to the PD-1 receptor and prevents it from interacting with PD-L1 and PD-L2, inhibiting the PD-1/PD-L1 immune response, including the anticancer immune response, through the PD-1 pathway. Treatments such as Dostarlimab should become widely available, as well as access to medical teams who would help monitor patients like in the trial Stage and intervene if the tumor comes back. We believe that the future of cancer treatment is an approach based on cancer type and subtype, and such a dramatic response as seen with Dostarlimab in patients with cancer gives hope that we are on the right track to find a dramatic match for the remaining cancers.

References :

1. Chaudhary Shiva. "'First Time in History': Cancer Vanishes from Every Patient during Us's Experimental Drug Trial." Google, Google; 2022. Available:https://www.google.com/amp/s/th elogicalindian.com/amp/health/cancer-usexperimental-drug-trial-35935.
2. Joseph R. The miraculous cancer cure: All you wanted to know about dostarlimab. Lifestyle Health | English Manorama; 2022. Available:https://www.onmanorama.com/lif estyle/health/2022/06/12/miraculouscancer-cure-about-dostarlimab.amp.html
3. Wikipedia Foundation. Dostarlimab. Wikipedia; 2022. Available:https://en.m.wikipedia.org/wiki/D ostarlimab
4. Zhang Z, Liu S, Zhang B, Qiao L, Zhang Y, amp; Zhang Y. T cell dysfunction and exhaustion in cancer. Frontiers in Cell and Developmental Biology. 2020;8. Available:https://doi.org/10.3389/fcell.2020 .00017
5. Syn NL, Teng MW, Mok TS, amp; Soo RA. De-novo and acquired resistance to immune checkpoint targeting. The Lancet Oncology. 2017;18(12). Available:https://doi.org/10.1016/s1470- 2045(17)30607-1
6. Han Y, Liu D, Li L. PD-1/PD-L1 pathway: current researches in cancer. American journal of cancer research. 2020;10(3): 727–742.
7. Available:https://reference.medscape.com/ drug/jemperli-dostarlimab-4000183#6
8. FDA Approved Drug Products: Jemperli (dostarlimab-gxly) for intravenous injection.
9. Jemperli (dostarlimab) dosing, indications, interactions, adverse effects, and more; 2021.
10. Available:https://www.webmd.com/drugs/2/ drug-181367/dostarlimab-gxlyintravenous/details/list-contraindications Available:https://www.drugs.com/pregnanc y/dostarlimab.html
11. Patnaik A, Weiss GJ, Rasco DW, Blaydorn L, Mirabella A, et al. Safety, antitumor activity, and pharmacokinetics of dostarlimab, an anti-PD-1, in patients with advanced solid tumors: a dose-escalation phase 1 trial. Cancer chemotherapy and pharmacology. 2022;89(1):93–103. Available:https://doi.org/10.1007/s00280- 021-04358-3

12. Lu S, Bowsher RR, Clancy A, Rosen A, Zhang M, Yang Y, et al. An integrated analysis of dostarlimab immunogenicity. The AAPS Journal. 2021; 23(5):96. Available:https://doi.org/10.1208/s12248- 021-00624-7
13. Available:https://gskpro.com/content/dam/ global/hcpportal/en_US/Prescribing_Information/Jemperli/pdf/JEMPERLI-PI
14. Independent Digital News and Media. Dostarlimab: How does promising cancer drug work? The Independent; 2022. Available:https://www.independent.co.uk/n ews/health/cancer-trial-remissiondostarlimab-drug-treatmentb2096416.html?amp
15. Available:https://www.mayoclinic.org/drugs -supplements/dostarlimab-gxlyintravenous-route/side-effects/drg20514856
16. Markham, A. Dostarlimab: First Approval. Drugs 2021, 81, 1213–1219. [CrossRef] [PubMed]
17. Yi, M.; Zheng, X.; Niu, M.; Zhu, S.; Ge, H.; Wu, K. Combination Strategies with PD-1/PD-L1 Blockade: Current Advances and Future Directions. Mol. Cancer 2022, 21, 28. [CrossRef]
18. CHMP. Committee for Medicinal Products for Human Use (CHMP) Assessment Report. 2021. Available online: https://www. ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use-chmp-13-16-december-2021 (accessed on 20 June 2022).
19. Yap, T.A.; Bessudo, A.; Hamilton, E.; Sachdev, J.; Patel, M.R.; Rodon, J.; Evilevitch, L.; Duncan, M.; Guo, W.; Kumar, S.; et al. IOLite: Phase 1b Trial of Doublet/Triplet Combinations of Dostarlimab with Niraparib, Carboplatin-Paclitaxel, with or without Bevacizumab in Patients with Advanced Cancer. J. Immunother. Cancer 2022, 10, e003924. [CrossRef]
20. Melhem, M.; Hanze, E.; Lu, S.; Alskär, O.; Visser, S.; Gandhi, Y. Population Pharmacokinetics and Exposure–Response of Anti-Programmed Cell Death Protein-1 Monoclonal Antibody Dostarlimab in Advanced Solid Tumours. Br. J. Clin. Pharmacol. 2022, 87, 4421–4431. [CrossRef] [PubMed]
21. CHMP. ANNEX I SUMMARY OF PRODUCT CHARACTERISTICS. Available online: https://www.ema.europa.eu/en/ documents/regulatory-procedural-guideline/annex-i-summary-product-characteristics_en.pdf (accessed on 20 June 2022).
22. U.S. Food and Drug Administration. JEMPERLI Highlights of Prescribing Information. Available online: https://www.accessdata. fda.gov/drugsatfda_docs/label/2021/761174s000lbl.pdf (accessed on 20 June 2022).
23. Kasherman, L.; Ahrari, S.; Lheureux, S. Dostarlimab in the Treatment of Recurrent or Primary Advanced Endometrial Cancer. Futur. Oncol. 2021, 17, 877–892. [CrossRef] [PubMed]
24. Dong, Y.; Sun, Q.; Zhang, X. PD-1 and Its Ligands Are Important Immune Checkpoints in Cancer. Oncotarget 2017, 8, 2171. [CrossRef] [PubMed]
25. Davda, J.; Declerck, P.; Hu-Lieskovan, S.; Hickling, T.P.; Jacobs, I.A.; Chou, J.; Salek-Ardakani, S.; Kraynov, E. Immunogenicity of Immunomodulatory, Antibody-Based, Oncology Therapeutics. J. Immunother. Cancer 2019, 7, 1–9. [CrossRef]
26. Sasson, S.C.; Wilkins, L.E.; Watson, R.A.; Jolly, C.; Brain, O.; Klenerman, P.; Olsson-Brown, A.; Fairfax, B.P. Identification of Neutralising Pembrolizumab Anti-Drug Antibodies in Patients with Melanoma. Sci. Rep. 2021, 11, 1–6. [CrossRef]
27. Oaknin, A.; Gilbert, L.; Tinker, A.V.; Brown, J.; Mathews, C.; Press, J.; Sabatier, R.; O'Malley, D.M.; Samouelian, V.; Boni, V. 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. J. Immunother. Cancer 2002, 10, e003777.