

"Dostarlimab: A review of its Pharmacology and clinical use in management of cancer"

ABSTRACT

According to the World Health Organization, cancer is the biggest cause of mortality globally, accounting 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 PD-1 monoclonal antibody called dostarlimab (JEMPERLI) has been found to be effective in treatment of patients with rectal cancer, who have advanced or recurrent disease that is mismatch repair deficient (dMMR) and who have progressed during or after prior treatment with a platinum-containing regimen. This indication was quickly approved based on the rate of tumor response and the length of the response, both of which were determined using an FDA-approved test. In this review, we provide simple and comprehensible pharmacodynamic and Pharmacokinetic details of the drug to the healthcare community as we believe it would serve as quick point of reference in cases of emergency information search.

1.0. INTRODUCTION

A modest clinical experiment at the Memorial Sloan Kettering Malignant Center in Manhattan showed 100 per cent eradication 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 [1].

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Dostarlimab! In the last few 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 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 [2].

Dostarlimab, an antibody medication, has shown promising results in the experimental treatment of patients with rectal cancer, but more extensive 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.

2.0. CHEMISTRY OF DOSTARLIMAB

Dostarlimab, also known as Jemperli, is a monoclonal antibody used to treat endometrial cancer.

Other Names: TSR-042, WBP-285, dostarlimab-gxly

Drug Class: Antineoplastic

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

Molar mass: $144325.73 \text{ g}\cdot\text{mol}^{-1}$

Structural formula: Dostarlimab is a humanized IgG4 monoclonal antibody. It is a glycosylated homodimer consisting of two identical heavy chains and two identical light chains, with 12 intra-chain disulfide bonds and 4 inter-chain disulfide bonds.

Physicochemical properties: Formulated drug substance; dostarlimab is a clear to slightly opalescent, colourless to the yellow solution, essentially free from visible particles [3].

3.0. MECHANISM OF ACTION

T cells are crucial for cancer immunotherapy because they are key mediators of antitumor action, recognizing and reacting to tumour-expressing antigens. However, T cells are not as effective against cancer as one might assume [4]. This is partly 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 [5].

In addition, a transmembrane protein known as Programmed Cell Death Ligand 1 (PD-L1) is also thought 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 reduce the host immune system's response to tumour cells makes it relevant in various cancers. According to these viewpoints, 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 [6].

Dostarlimab, an IgG4-isotype humanized monoclonal antibody binds to the PD-1 receptor and prevents 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 [7].

4.0. DOSAGE AND ADMINISTRATION

Dostarlimab 500 mg should be administered every 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 [8].

5.0. PHARMACOKINETICS

Dostarlimab is given intravenously at a dose of 500 mg every three weeks. The mean maximum concentration (C_{max}) and AUC (0-tau) of dostarlimab-gxly during the first cycle are 171mcg/mL and 35,730mcg.h/mL, respectively. The average C_{max} and AUC (0-tau) at 1000 mg per six weeks are 309 mcg/mL and 95,820 mcg.h/mL, respectively. Dostarlimab has a mean terminal elimination half-life of 25.4 days. Although its metabolism has not been fully defined, it is anticipated to be broken down into smaller peptides and amino acids via catabolic processes [8].

6.0. ADVERSE EFFECTS OF DOSTARLIMAB

A medication may have side effects in addition to the intended ones. Even though not all of these side effects are likely to occur, if they do, medical treatment may be required. The following side effects have been noticed in course of treatment:

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 [9].

6.1. Incidence not known

Sore throat, sores, ulcer, or white patches in the mouth or on the lips; Blistering, peeling, or loosening of the skin; cracks in the skin; flushed, dry skin; fruit-like breath odour; increased appetite; increased thirst; enhanced urine; loss of heat from the body. Some side effects may occur that usually do not need medical attention. These side effects may disappear during treatment as your body adjusts to the medicine. Also, your health care professional may be able to tell you about ways to prevent or reduce some of these side effects. Check with your health care professional if any of the following side effects continue or are bothersome or if you have any questions about them [9].

6.2. Adverse effects of Dostarlimab based on percentage increase >10% (Higher than 10 per cent)

All grades

Lymphopenia(37%), hypoalbuminemia (30%), fatigue (48%), and nausea (48%). (30 percent), Anemia (24%), leukopenia (21%), diarrhea (26%), hyponatremia (26%), increased alkaline phosphatase (25%), increased creatinine (27%), and constipation (20%). , Vomiting (18%), elevated AST (16%), hypercalcemia (15%), elevated ALT (15%), hypokalemia (15%), decreased appetite (14%), cough (14%), itch (14%), pruritus (14%), urinary tract infection (13%), and myalgia (12%) [9].

Grade 3 or 4

Anaemia (13%)

1-10% (Lower than 10 percentage)

All grades

Urinary tract infection (2.9%), sepsis (2.9%), acute renal damage (2.9%), stomach ache (2.9 %), and Pyrrhic victory (2.9%) [9].

7.0. CONTRAINDICATIONS

This medication should not be used in the following situations. If any of the following is experienced, the doctor should be consulted:

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 [10].

8.0. USES IN SPECIAL POPULATIONS

The patient's doctor or pharmacist should find out if they are allergic to dostarlimab or if they have any other allergies before prescribing it. Inactive ingredients in this product can trigger allergic reactions or other issues. The doctor or pharmacist should verify the patient's medical history before prescribing this medication, particularly about organ transplants, stem cell transplants using donor cells, pregnancies, or plans to become pregnant. While using dostarlimab, a patient shouldn't become pregnant because it could harm the unborn child. Before starting medication, a pregnancy test should be requested. While taking this medication and four months after stopping treatment, a reliable form of birth control should be used. If pregnancy develops, the doctor should be called right away. Breastfeeding is not advised while using this medication and for 4 months after stopping treatment due to the potential risk to the baby. Before breastfeeding, a doctor should be consulted[16].

8.1. Pregnancy

Risk Summary

When given to a pregnant woman, JEMPERLI can potentially harm the fetus due to its mode of action [Clinical Pharmacology (12.1)]. No information on the use of JEMPERLI in expectant women is currently available. 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 [11].

Animal Data

No animal reproduction studies have been done to assess JEMPERLI's impact on reproduction and fetal development. The PD-1/PD-L1 pathway plays a crucial role in maintaining pregnancy by preserving the mother's immune tolerance to the fetus. JEMPERLI administration during pregnancy may increase the risk of abortion or stillbirth because blockade of PD-L1 signalling has been shown to impair tolerance to the fetus and increase fetal loss in murine models of pregnancy. PD-1 and PD-L1 17 knockout mice experienced immune-mediated disorders, contrary to reports in the literature that the blockade of PD-1/PD-L1 signalling caused malformations in the offspring of these animals. Dostarlimab-gxly's mechanism of action suggests that fetal exposure could increase the risk of immune-mediated disorders or change the immune system's normal response[11, 17].

8.2. LACTATION

Risk Summary

There is no information on dostarlimab-presence gxly's in human milk, its effects on breastfed children, or how it affects milk production. Women are advised not to breastfeed during treatment

and for 4 months following the last dose of JEMPERLI due to the possibility of serious adverse reactions in a breastfed child.

8.3. Elderly Patients

A study showed that dostarlimab monotherapy was used to treat 515 patients, 50.7% were under 65 years, 37.9% were 65-75 years, and 11.5% were 75 years or older. From the study, no overall differences were reported between elderly (≥ 65 years) and younger patients (< 65 years) [12].

9.0. TOXICITY OF DOSTARLIMAB

Immune-mediated adverse reactions also occurred in less than 5% of the patients, and the most common ones included pneumonitis (signs include cough or shortness of breath), colitis (signs include diarrhoea; also, Cytomegalovirus infection/reactivation have occurred in patients with corticosteroid-refractory immune-mediated colitis), hepatitis, endocrinopathies, and nephritis [13].

10.0. MONITORING

Reports from the European Medicines Agency show that the dostarlimab drug has been placed under a conditional approval scheme, which means that further evidence on this medicinal product is awaited.

Companies with authorization to market dostarlimab would be required to provide data from an ongoing study with patients for at least 12 months. They would also provide data from studies in patients with endometrial cancer when it is advanced or has come back and has not been treated with other cancer medicines, and the study will compare dostarlimab with other cancer medicines compared with these other cancer medicines given alone [12].

11.0. 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.

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