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Pharmacodynamics and Pharmacotherapeutics of Dostarlimab

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KEYWORDS

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ABSTRACT:

Introduction: Cancer is a lethal disease in 20th century with alarming increase in 21st century. The prevalence of cancer across the globe in 2020 is 19 million, out of which the occurrence of colorectal cancer is with 10% prevalence and 9.4% mortality.

Objectives: For treating various cancers, a humanized monoclonal antibody programmed death-1 (PD-1) receptor antagonist dostarlimab has been developed. This antibody is used to treat adult patients with mismatch repair deficient and also for the advanced or recurrent endometrial cancer. T cells express the PD-1 receptors which when gets activated elicit inhibitory immune responses. Certain cancers use this mechanism by overexpressing the PD-1 ligands. This mechanism inhibits the anti-tumor immune response that usually destroys the cancer cells. Immunotherapy is one of the major strategies of cancer treatment. In the clinical trial the anti-programmed cell death protein (PD-1) monoclonal antibody has shown 100% cure for the colorectal cancer.

Conclusions: The result also confirmed that there are no side effects of the treatment in the participatory subjects. Promising results of dostarlimab has been shown in treating ovarian cancer, melanoma, endometrial cancer, breast cancer and neck cancer. This article reviews about the structure, uses, pharmacodynamics, and mechanism of action and its clinical trials of dostarlimab in cancer therapy.

Introduction

Cancer is one of the most pervasive diseases for mankind with over 10 million deaths per year even though long years of research (Siegel *et al*., 2022). For treating the cancer different therapies are in use, which includes radiation in radiotherapy, chemotherapy, surgery and immunotherapy. The newest of all these is immune-oncology, its potential and scope has to be explored.

According to this therapy to treat a range of diseases including cancer and solid tumors, the specific parts of immune system are used (Vanshikha Singh *et al*., 2022). Across the globe the prevalence of cancer in 2020 is 19 million (Hassan ul Hussain *et al*., 2022). The highly specific therapy for treating cancer is immunotherapy, which when stimulated they target only the cancerous stem cells and also the metastatic cancer cells. This therapy aims to reach the tumor cells even a surgeon might not. Cancer vaccines have also been developed as one of the strategies of immunotherapy. This has shown to have a potential to minimize the growth of tumor, still not eliminating the cancer (Vanshikha Singh *et al*., 2022). Interferon alpha, an antitumor cytokine is the first immunotherapeutic agent found in 1986.

The US Food and Drug Administration (FDA) approved the immunotherapeutic agent. To treat hairy cell leukemia (HCL) IFN-a2 was first approved and used which showed significant dose response in advanced HCL patients. IFN-a2 was approved to use as adjuvant for treating melanoma in stage IIB and III in

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1995. Later in 1998 it was licensed to treat renal cell carcinoma and metastatic melanoma. The second anticancer cytokine to be approved by FDA is interleukin-2 (IL-2), a T-cell growth factor which assists in T-cell proliferation and immunological modulation. In recent years, with the development of immunotherapies, immunotherapeutics checkpoint inhibitors have emerged to treat cancer (Eno, 2017).

1. Structural insights of the drug

The dostarlimab, humanized IgG4 mAB is derived from a Chinese hamster ovary cell which has a molecular weight of approx 144 kDa (Lu *et al.*, 2021). Dostarlimab is used as an immunotherapeutic agent that stimulates body's natural T-cell mediated anti-tumor immune response in the treatment of cancer. Dostarlimab is taken intravenously depending on the cycle over a range of 30 minutes for every three to six weeks. By grafting the heavy and light chain complementary- determining regions on the frame work of germline variable region with the nearest human species orthologs, humanized dostarlimab was obtained. This was followed by further affinity maturation using AnaptysBio SHM-XEL system by mammalian cell display and somatic hyper mutation. In collaboration with Tesaro, the AnaptysBio developed the drug Dostarlimab. In 2019, GlaxoSmithKline bought this drug (Kumar, 2021 and Bowers, 2013). The final product is a concentrate of 500mg of dostarlimab as an active ingredient infusion solution. The other constituents includes citric acid monohydrate, trisodium citrate dehydrate, L-arginine hydrochloride, sodium chloride, polysorbate 80 and water for injection. The heavy chain of dostarlimab is involved in the interaction between PD-1 and dostarlimab and the light chain governs the steric blockage of binding of PD-L1. The conformational rearrangements happen in BC, C'D, and FG loops of PD-1 by dostarlimab to attain high affinity. The R86 residue within C'D loop of PD-1 governs the binding of dostarlimab by occupying the heavy chains concave surface (Park, 2022). For human PD-1 dostarlimab has KD value of 0.3nM with a dissociation rate of 1.7 104 (s^{-1}) and association rate of 5.7105 ($M^{-1}s^{-1}$). This shows faster target association and delayed dissociation (Kumar, 2021). Dostarlimab binds to the flexible loops of PD-1, including the BC, C'D and FG loops unlike Nivolumab or Pembrolizumab as analyzed by high resolution structure analysis (Park, 2022). A variety of *in vitro* and *in vivo* experiments characterized dostarlimab. Dostarlimab does not cause cytokine stimulation even when used alone and has no cross reactivity with mouse orthologue (Kumar, 2021). When compared to other PD-1 antibodies, at a dose of 30 and 100mg/kg dostarlimab is well tolerated. This was study by single dose tests first, followed by 4 weeks repeated dose study and a 13 weeks repeated dose study (Patnaik, 2022). Tumor growth inhibition assay measured the effectiveness of anti-cancer ability of dostarlimab which is linked to the enhanced immune cell infiltration. These evidences show that dostarlimab is a strong antagonist of anti-PD-1 receptor which makes it further for clinical testing in cancer patients. Dostarlimab has 2.5 % anti-drug antibodies which is very modest immune response compare to other anti-PD-L1 medicines. It has reduced immunological reaction due to its mode of administration and product purity. Dostarlimab is neither causing any pre-existing ADAs or generation of ADAs. These finding recommends that this drug can be a novel and effective anti- PD- 1 antibody with reduced immunogenic reaction risks (Lu *et al.*, 2021).

2. Pharmacodynamics of Dostarlimab

Immunotherapy enables anti-tumor immune response endogenously to treat cancer. One such immunotherapeutic agent is dostarlimab. Depending on the cycle it is administered over a period of 30 minutes for every three to six weeks. Dostarlimab and the agents which interfere with the PD-1/PD-L1 pathway remove the important inhibitory response of the immune system. There by mediating the immune mediated adverse reaction. The adverse reaction may be severe or fatal. This immune mediated adverse reaction can occur at any time in any organ once the treatment is started. Mostly it is manifested during the therapy and also even after discontinuing the therapeutic agent. The patient under dostarlimab therapy must be monitored for the immune mediated reactions. The adverse reactions were identified if suspected and treated promptly (FDA Approved Drug Products: Jemperli (dostarlimab-gxly) for intravenous injection). Both *in vitro* and *in vivo* studies were conducted for pharmacodynamics activities of dostarlimab. In the first cycle, 500mg of dostarlimab was administered for 3 weeks intravenously. The mean Cmax and AUC0-tau of dostarlimab was found to be 171 mcg/mL and 35,730

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mcg.h/mL, respectively for the absorption of dostarlimab. For six weeks 1000mg was administered, the mean Cmax and AUC0-tau for dostarlimab are 309 mcg/mL and 95,820 mcg.h/mL, respectively (CHMP-Committee for Medicinal Products for Human Use (CHMP), 2021). 5.3 L is the mean volume distribution of the dostarlimab. The half-life of dostarlimab is 24.5 days and the Dostarlimab mean clearance is 0.007 L/h. There is no over dosage study of dostarlimab (Yap *et al*., 2022 and Melhem *et al*., 2022).

3. Mechanism of Action of Dostarlimab

Humanized monoclonal antibody, dostarlimab acts as antagonist for PD-1 receptors. For treating several cancers including ovarian cancer, small cell lung cancer, colorectal cancer, endometrial cancer and cancer of head and neck, squamous cell cancer (SCC), fallopian tube cancer, pancreatic cancer, non-small cell lung cancer (NSCLC) and other types of cancers, GlaxoSmithKline has developed dostarlimab with proper license. GARNET trail has come with the preliminary findings based on which the dostarlimab has been approved to treat adult with advanced stage of cancer and also to treat recurrent advanced mismatch repair deficient endometrial cancer in USA and EU. The general dosage of dostarlimab is 500mg every 3 weeks for the first four doses followed by 1000mg every six weeks until unacceptable toxicity is observed (FDA; CDER. Highlights of Prescribing Information Tissue, Including the Following: Immune-Mediated Pneumonitis, on 16 June 2022, GSK, on 16 June 2022, Jemperli, European Medicines Agency, on 16 June 2022). In most of the cancers the cancer specific immune response is suppressed due to the ligand binding to PD-1 receptors present in T-cells. The interaction between the PD-1 receptors on the T-cells with the PD-1 ligands inhibits the release of cytokine and the T- cell proliferation. In few tumors the up regulation of the PD-1 ligand leads to the suppression of the active T-cell immunity. Dostarlimab inhibits the interaction of the PD-1 receptors with PD-L1 and PD-L2 ligands this activates the T- Cell immune response which enhances the immunity. Results of flow cytometry and plasmon resonance show that dostarlimab binds with high affinity with PD-1 receptors in both humans and cynomolgus monkeys. Also in the human assay of CD4+ mixed lymphocyte reaction result showed increased production of IL-2 because of antagonistic effect of dostarlimab. Furthermore the results of the assay have showed improved activity of dostarlimab along with the presence of LAG3 antibodies or TIM3 antibodies. No significant increase in the release of cytokine during increased activity of dostarlimab in the presence of antibodies was observed in peripheral blood mononuclear cells in human (Lu *et al*., 2021).

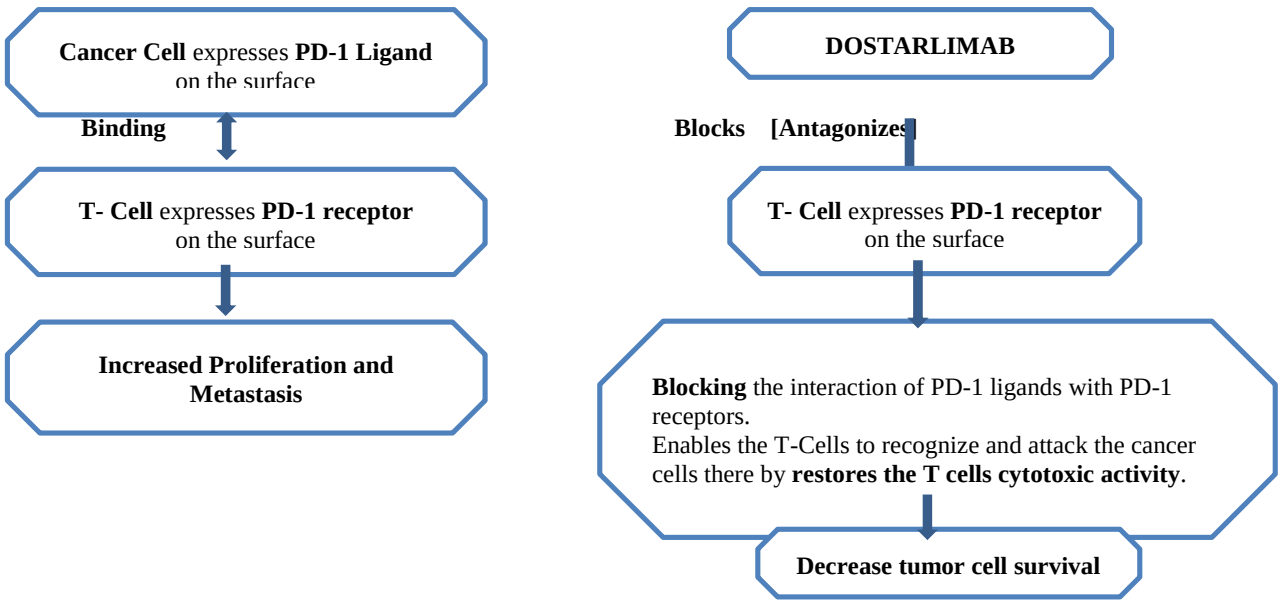

Fig 1. Illustration of mechanism of action of dostarlimab

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Patients with solid tumors underwent pharmacokinetic study for dostarlimab-gxly. It was observed that over a dose range of 1.0 -10mg/kg there is proportionate increase in mean Cmax AUC0-inf and AUC0- τ. Based on study, the mean steady-state distribution volume of dostarlimab was found to be 5.3L and also the mean steady-state clearance was found to be 0.007/L. The pharmacokinetics properties of dostarlimab had no significant clinical differences among age, gender, type of tumor, ethnicity or renal or hepatic impairment. There are no studies conducted for genotoxic and carcinogenic effect of dostarlimab. Study on sexually immature monkeys for fertility was performed; there were no significant effect on both male and female reproductive organs (Markham, 2021). GARNET trial in human was performed to study the pharmacodynamics, pharmacokinetics, clinical activity, tolerability and safety across different solid cancers for dostarlimab in NSCL, ovarian, endometrial and fallopian tube cancer. In Part 1 three weight based doses of 1,3 and 10 mg/kg were administered intravenously for every two weeks. Two fixed –dose regimens of 500mg intravenously for every three weeks in Part 2A and 1000mg intravenously for every six weeks in Part 2B. Receptor saturation has reached at 2.4g/ml dostarlimab serum concentration in Part 1. Serum median concentration was determined approximately at 40 and 50ng/ml after a single 500mg and 1000mg dose respectively (Kasherman, 2021).

4. Safety aspects of Dostarlimab

Dostarlimab demonstrated durable antitumor activity in patients with dMMR/MSI-H EC and patients with MMRp/MSS EC. The ORR in MMRp/MSS EC was lower than in dMMR/MSI-H EC. This result was consistent with the identified features of dMMR/MSI tumors, whose mutations are associated with elevated tumor-infiltrating lymphocytes, tumor neoantigen load and increased PD-1 and PD-L1 expression, which can rouse responses to immune checkpoint inhibition. Among responders (43.5% in patients with dMMR/MSI-H EC and 14.1% in patients with MMRp/MSS EC), durable responses were seen in both dMMR/MSI-H and MMRp/MSS EC; 89.4% of responders with dMMR/MSI-H EC and 63.6% of responders with MMRp/MSS EC persist in response as of the data cut-off date. The safety profile was manageable, consistent with prior experience, and similar to that of other anti–PD-1 antibodies (Oaknin *et al*., 2022).

Dostarlimab demonstrated promising antitumor activity in advanced/recurrent NSCLC that progressed following platinum-based chemotherapy, including across all PD-L1 subgroups, and has an acceptable safety profile (Moreno *et al*., 2022).

5. Dostarlimab Clinical trial

Dostarlimab was found to improve T-cell activation in a variety of in vitro functional test methods using primary human T cells. The lack of cytokine synthesis in the absence of antigen indicates that dostarlimab had no direct (nonspecific) effects on T-cell responses, despite the fact that it enhanced T-cell activation in antigen-dependent systems. In tumor models from humanized mice, dostarlimab demonstrated a strong anticancer impact in addition to a stable pharmacokinetic and pharmacodynamic profile with very little off-target effects. Its anticancer effectiveness was linked to a decrease in tumor-associated regulatory T cells Biomolecules 2022, 12, 1031 4 of 15 and an increase in tumor-infiltrating CD8+ T cells. For instance, compared to isotype control, dostarlimab therapy in vitro reduced tumor growth in the MDA-MB-436 breast cancer model (TGI of 53%) (Kumar *et al*., 2021).

Dostarlimab anti-PD-1 antibody profile was shown to be good in preclinical testing, with effective binding to PD-1 and antagonizing interactions with PD-L1 and PD-L2. Dostarlimab binds to the human PD-1 receptor with a high affinity, with a binding affinity (KD) of 300 pM. Preclinical findings for the previous approved PD-1 treatments such as Nivolumab, Pembrolizumab, and Cemiplimab have a similar binding profile. Dostarlimab was chosen for its IgG4 isotype to generate the most dependable and efficacious therapy. While anti-PD-L1 antibodies (Atezolizumab, Avelumab, and Durvalumab) are all IgG1 modalities (additional risk is possible with the continuous administration of IgG1 Fc for immunological enhancement), other anti-PD-1 antibodies (Pembrolizumab, Nivolumab, and Cemiplimab) are all IgG4 modalities.

Preclinical evidence validated Dostarlimab first-in-human dose selection and demonstrated that the medication had a wide enough safety margin to be investigated further in human dose-finding sections 1

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and 2A of the Phase 1 GARNET study. In ongoing clinical trials, dostarlimab has demonstrated both large and long-lasting responses and a reasonable safety profile with side effects similar to other anti-PD-1 therapies. There was no evidence of dose-limiting toxicity. Several clinical studies, such as RUBY (NCT03981796), FIRST (NCT03602859), IOLite (NCT03307785), MOONSTONE (NCT03307785), and several others, have demonstrated the potential of dostarlimab as an anti-PD-1 therapy. These studies are testing the drug both as a monotherapy and in combination for a range of tumor types (NCT03955471) (Costa & Vale , 2022).

The pharmacokinetics (PK) profile of dostarlimab allows for an increase in the dosing interval from three to six weeks. The investigation of Dostarlimab's pharmacodynamic action was carried out in both in vitro and in vivo experimental settings. The pharmacokinetics (PK) profile of dostarlimab allows for an increase in the dosing interval from three to six weeks. The investigation of Dostarlimab's pharmacodynamic action was carried out in both in vitro and in vivo experimental settings. Throughout the first cycle 500 mg was administered intravenously every 3 weeks, and the absorption was described by: the mean Cmax and AUC0-tau of dostarlimab as 171 mcg/mL and 35,730 mcg.h/mL, respectively. When administered at 1000 mg every 6 weeks, the mean Cmax and AUC0-tau are 309 mcg/mL and 95,820 mcg.h/mL, respectively. At steady state, the mean volume of distribution of Dostarlimab is 5.3 L. Although dostarlimab's metabolism is yet unknown, it is currently thought to be broken down into smaller peptides and amino acids by catabolic processes. The mean terminal elimination half-life of Dostarlimab is 25.4 days, and the mean clearance of Dostarlimab is 0.007 L/h. Regarding dostarlimab overdose, there are no data. The adverse effect profile of dostarlimab is likely to be consistent with overdosage symptoms, which could lead to serious immune-mediated responses.

A groundbreaking finding in the realm of cancer treatment was made in June 2022. For the very first time in science, a drug under clinical trial showed the complete eradication of a tumor with no reoccurrence. The mAB-based drug dostarlimab was evaluated for safety under efficacy against locally advanced rectal cancer. Stage III rectal cancer, sometimes referred to as primary locally advanced rectal cancer, is also suggestive of resectable tumors including lymph nodes. These tumors are characterized for invading and extending close to the meso-rectal fascia. These types of colorectal cancer are generally treated with aggressive chemoradiation, short course radiotherapy, and total meso-rectal surgery (TME) surgery. Positive outcomes from this group therapy include high survival rates and low recurrence. Furthermore, in certain instances involving locally advanced cancers, total tumor excision is the best course of action for survival and control (Singh, *et al*., 2022).

6. Trials of Dostarlimab combination therapy

There are several other immune check point inhibitors such as nivolumab, pem- brolizumab, atezolizumab, durvalumab, and avelumab that are utilized for cancer treat-ment. It is unlikely that dostarlimab will interact with other medications because it is a monoclonal antibody (mAB) rather than a cytokine modulator or a substrate of a drug transporter. However, a comparison of dostarlimab based on its pharmacodynamic and pharmacokinetic proper-ties must be conducted with other such immune checkpoint inhibitor-based therapies toobtain a clear and optimal understanding. Dostarlimab, similar to nivolumab and pem-brolizumab, specifically targets anti-PD-1 receptors, while atezolizumab, durvalumab andavelumab not only act through anti-PD-1 receptors but also block interaction with the PD-1and B7.1 receptors. Similarly, the average peak occupancy for dostarlimab is approximately 90%, while for nivolumab, it is approximately 85% (70–97%). The cumulative dose has also been recorded for these drugs: approximately 2-fold for dostarlimab, 3.7-fold for nivolumab, 2.2-fold for pem-brolizumab, around 1.91-fold for atezolizumab, and 4.3-fold and 1.25-fold for durvalumab and avelumab, respectively. Similar to the dosing schedules for nivolumab and pembrolizumab, the three-week duration guarantees patient monitoring during the start of a new treatment. For dostarlimab, a safety regimen of 500 mg IV every three weeks is often delivered, followed by 1000 mg IV every six weeks. For nivolumab and pembrolizumab, the regimens are 240 mg IV every two weeks and 200 mg IV every three weeks, respectively.

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Similarly, the dose for atezolizumab is 1200 mg or 15 mg/kg IV every three weeks; the dose for durvalumab is 1500 mg IV every four weeks; and the dose for ICI avelumab is 10 mg/kg IV every two weeks (Yap *et al*., 2022 and Melhem *et al*., 2022).

The interaction of dostarlimab with one or more chemotherapeutic medications, such as bevacizumab, cobolimab, niraparib, and many others, is also being investigated. The majority of these research, which looked at various cancer kinds, are currently in the trial stage. The combination of pembrolizumab and lanvatinib is increasingly the standard of therapy for pretreated recurrent MMR-proficient EC. Pembrolizumab and Dostarlimab have demonstrated remarkable efficacy in MMR-deficient patients. However, further research is required to comprehend the fundamental and secondary mechanisms of immunotherapy resistance as well as to apply ICI to early-stage malignancies and the first-line metastatic situation. Patients with platinum-resistant ovarian cancer have a poor prognosis and few therapy alternatives. Preclinical and clinical research in this patient population suggested that immune checkpoint medications and poly-ADP ribose polymerase inhibitors may work in concert to prevent cancer (NCT04679064). Moreover, the phase IB trial evaluates Biomolecules 2022, 12, 1031 9 of 15 the effect of Niraparib and Dostarlimab in treating patients with BRCA-mutated breast, pancreas, ovary, fallopian tube, or primary peritoneal cancer that cannot be removed by surgery (unresectable) or has spread to other places in the body (metastatic). Niraparib is an inhibitor of PARP, an enzyme that helps repair deoxyribonucleic acid (DNA) when it becomes damaged. By preventing cancer cells from fixing their damaged DNA, PARP blockade may contribute to the death of the cells. One kind of targeted treatment is PARP inhibitors. Monoclonal antibodies, like TSR-042, have the potential to boost the immune system's capacity to combat cancer and impede the growth and metastasis of malignant cells when used in immunotherapy. Giving Niraparib and TSR-042 may kill more cancer cells (NCT04673448) (Singh, *et al*., 2022). Dostarlimab has shown encouraging results, and for pre-treated recurrent MMR-proficient EC, pembrolizumab plus lenevinib is swiftly taking the place of conventional therapy.

7. Conclusions

The cancer prevalence and mortality has been increased in recent years. There are different types of treatments available for cancer which includes chemotherapy, irradiation of the cancer cells, antibody therapy, surgery etc., the most important outbreak in cancer therapy is the dostarlimab, an antibody used to treat the mismatch repair deficient in both endometrial and recurrent endometrial cancer. The over expression of PD-1 ligand by cancer cells suppresses the anti-tumor immune response which usually destroy the cancer cells. Dostarlimab antagonize (PD-1) receptor there by removing the suppression of anti-tumor immune response, which elicit the destruction of cancer cells. Immunotherapy is the major strategy in the treatment of cancer. In clinical trial dostarlimab has shown to cure colorectal cancer completely. There are no side effects with respect to this drug. This drug is promising for the treatment of ovarian, melanoma, breast and neck cancers.

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Doublet/Triplet Combinations of Dostarlimab with Niraparib, Carboplatin-Paclitaxel, with or without Bevacizumab in Patients with Advanced Cancer. J. Immunother. Cancer 2022, 10, e003924.

This article is a review paper which deals with the recent clinical findings in the area of cancer.