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Review Article

New Breakthrough In Cancer Treatment, Dostarlimab

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ABSTRACT

Dostarlimab (JEMPERLI), a PD-1 monoclonal antibody.It is used to treat adult patients with advanced or recurrent endometrial cancer who have progressed while receiving treatment with a platinum-containing regimen or after receiving prior therapy. This indication received quick approval based on the rate of tumour response and the length of the response, which were determined by an FDA-approved test. Dostarlimab, a monoclonal antibody against the programmed cell death protein (PD-1) that has shown to completely (100%) cure patients with colorectal cancer, has enchanted the medical community in this period of rapid advancement. Additionally, none of the study participants experienced any significant negative effects, according to the findings of clinical trials.It was found that Dostarlimab has also demonstrated encouraging outcomes in the treatment of breast cancer, melanoma, head cancer,neck cancer, endometrial cancer, and ovarian cancer. Based on this, we describe significant ongoing clinical trials and immunotherapy combinations to inform upcoming medical professionals and academics on the effectiveness of dostarlimab against various tumours. In this study, we give the medical community clear, understandable information about the drug's pharmacodynamic and pharmacokinetic properties in the hopes that it would be useful as a quick reference in an emergency.

INTRODUCTION

Despite decades of research in this area, cancer is still one of the deadliest diseases that humanity has ever experienced, and it is still a major health issue that causes more than 10 million deaths annually. There have been many different types of treatment implemented, including chemotherapy, radiotherapy, surgery, and immunotherapy. The extent and possibilities of immuno-oncology, the most recent area of research in this discipline, have not yet been fully explored. As a part of immunotherapy ,to treat illnesses such as cancer and large tumours particular immune system components of the patient are utilised .Use of PD-1 monoclonal antibody Dostarlimab (JEMPERLI) have been found to be beneficial in patients with rectal cancer with advanced or recurrent disease that is mismatch repair deficient (dMMR) and who

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have progressed during or after prior therapy with a platinum-containing regimen. Based on the rate of tumour response and the duration of response, this indication was swiftly authorised. A humanised mAB called dostarlimab (JemperliTM) or dostarlimab-gxly's functions as an antagonist for programmed death-1 (PD-1) receptors. For the treatment of various cancers,such as squamous cell cancer,ovarian cancer,small cell lung cancer,endometrial cancer, fallopian tube cancer, pancreatic cancer, and many more, it is being developed by GlaxoSmithKline (GSK) under a licence from AnaptysBio Inc. Dostarlimab was only just approved (22 April 2021) for persons with advanced or recurrent advanced mismatch repair-deficient endometrial cancer (dMMR), according to early results from the GARNET trial. Dostarlimab is typically provided in doses of 500 mg every three weeks (for the first four doses) and 1000 mg every six weeks (after the fourth treatment) until disease progression or any unacceptable toxicity is observed (4,5,6). Dostarlimab, also known as TSR-042 or Jemperli, is a humanised monoclonal antibody of the IgG4 isotype made in mammalian Chinese hamster ovary (CHO) cells using recombinant DNA technology. Dostarlimab binds to PD-1 on T cells and prevents interactions with its ligands, PD-L1 and PD-L2, which activate immune responses. During cancer treatment, the immunotherapy dostarlimab supports the body's own anti-tumor immune response. Depending on the cycle, it is administered every three to six weeks via intravenous infusion for more than 30 minutes.An epitope within a target molecule may be a crucial part of a therapeutic antibody as the antibodies that recognise various epitopes have different therapeutic efficacies, even though the structural reason for this is yet unknown. PD-1 and PD-L1 antibodies inhibit cells in a similar way, however they recognise different antigenic epitopes.Due to their high specificity and affinities for target cells monoclonal antibodies have been a vital therapeutic tool. Dostarlimab binds to the flexible loops of PD-1, including the BC, C'D, and FG loops, differently from Pembrolizumab or Nivolumab, according to the high-resolution structure (7). Dostarlimab was prominent by numerous in vitro and in vivo studies, as well as preclinical effects, which allowed it to be classified as an experimental novel medication. Dostarlimab does not cross-react with the mouse orthologue, and when given alone, it does not significantly stimulate cytokines (8). First, single-dose tests were conducted, then a 4-week repeat-dose study, and finally a 13-week repeat-dose research. Dostarlimab is well tolerated at doses of 30 and 100 mg/kg, with toxicity comparable to other anti-PD-1 antibodies, and it does not significantly stimulate cytokines when administered alone, according to all available evidence (9). Dostarlimab demonstrated anticancer activity as indicated by the reduction of tumour development, which was connected to increased immune cell infiltration. These results demonstrate the potent anti-PD-1 receptor antagonist properties of dostarlimab, which call for more clinical trials in cancer patients.

HISTORY:

The Drug Administration and US Food have approved the first immunotherapy drug, an anticancer cytokine known as interferon-alpha 2, in 1986. (FDA). After research revealed that IFN-a2 had a high response rate in patients with advanced HCL, it was initially licenced for the treatment of hairy cell leukaemia (HCL). FDA approval was given to IFN-a2 in 1995 to be used as adjuvant therapy for melanoma that was stage IIB/III. Interleukin-2 (IL-2) was the second anticancer cytokine FDA-approved in 1998 when it was permitted for the treatment of metastatic melanoma and renal cell carcinoma. IL-2 (a T-cell growth factor) promotes T-cell proliferation and immunological regulation. A unique class of

immunotherapeutic known as checkpoint inhibitors has recently emerged as a cornerstone in cancer treatment. Immunotherapies have long held the promise of altering the standard of care in the treatment of cancer (10). Immune checkpoint inhibitors, T-cell transfer treatment, monoclonal antibodies, vaccinations, and immune system modulators are still employed today to treat cancer. Dostarlimab, a monoclonal antibody, received accelerated approval from the FDA on August 17, 2021, for use in treating adults with dMMR recurrent or advanced endometrial cancer that has progressed despite receiving treatment or having received treatment in the past with a platinum-containing chemotherapy regimen. Dostarlimab, a PD-1 inhibitor, showed sustained activity against dMMR tumours and, in 2022, reported a 100% rectal cancer remission rate. All patients carried dMMR, a mutation that occurs in between 5% and 10% of instances of rectal cancer (this mutation is also present in endometrial, prostate, and bladder tumours). This clinical trial showed both the potential and the feasibility of treating tumours according to their genetic causes (11).

MECHANISM OF ACTION:

T-cells have the immune checkpoint receptor PD1, which blocks immunological responses that are directed specifically towards cancer. Dostarlimab, a humanised IgG4 mAB with a molecular weight of about 144 kDa, is produced from Chinese hamster ovary cells. Cytokine production and T-cell proliferation are inhibited by a binding between the PD-1 ligands (PD-L1 and PD-L2) and the PD-1 receptor on T-cells. PD-1 ligands are increased in several tumours, and signalling through this route may help to decrease active T-cell immunity. Dostarlimab, a medication, enters the picture in this situation. It suppresses the activity of the programmed cell death receptor-1 (PD-1) and prevents receptors from interacting with PD-L1 and PD-L2, which in turn stimulates T cells and improves immunity all around. Dostarlimab has been shown to bind to PD-1 receptors in humans and cynomolgus monkeys with great affinity, as evidenced by the outcomes of flow cytometry and plasmon resonance experiments. Dostarlimab also demonstrated functional antagonist activity in a human CD4+ mixed lymphocyte response assay, increasing IL-2 production. Additionally, this assay demonstrated that dostarlimab's activity was increased in the presence of TIM3 or LAG3 antibodies. Dostarlimab showed enhanced activity in the presence of antibodies, but no appreciable cytokine release was seen from human PBMCs (peripheral blood mononuclear cells) (12).

An average terminal elimination half-life of Dostarlimab is 25.4 days and has an average clearance of 0.007 L/h. There are no records of Dostarlimab overdoses. The adverse effect profile of Dostarlimab is expected to be consistent with overdose symptoms, which may involve severe immune-mediated reactions (13,14).

Medical Uses:

Dostarlimab is prescribed as a monotherapy in the European Union for the treatment of people with advanced or recurrent endometrial cancer (EC) that has progressed while receiving treatment with a platinum-containing regimen or after such treatment (15). When it comes to cancer chemotherapy, platinum-based drugs like cisplatin, carboplatin, and oxaliplatin are standard treatments (16). Additionally, solid tumours are indicated for therapy with it (17). Dostarlimab received accelerated approval from the US Food and Drug Administration (FDA) in August 2021 for people with mismatch repair deficient (dMMR) recurrent or advanced solid tumours that have progressed during or after prior treatment and who lack adequate alternative treatment choices (18,19).

SIDE EFFECTS:

Sepsis, acute renal injury, urinary tract infection, abdominal discomfort, and fever were among the serious adverse responses that occurred in more than 2% of patients (pyrexia). Dostarlimab-gxly receives fast approval from the FDA for treating dMMR endometrial cancer. American Food and Drug Administration (Press release). 22 April 2021. On April 22, 2021, the original version was archived. obtained on April 22, 2021 (17,20).

Immune -mediated adverse reaction:

A monoclonal antibody called dostarlimab binds to PD-1 and prevents it from attaching to PD-1 ligands, hence removing immune response suppression. This increases the possibility of immune-mediated adverse effects. These reactions can affect any organ or tissue in the body and can be severe or fatal. Immune-mediated pneumonitis, colitis, hepatitis, hypophysis, thyroid conditions, nephritis with renal dysfunction, and dermatological reactions are a few examples of immune-mediated adverse effects (17).

Pregnancy and Lactation:

A foetus may experience injury from dostarlimab. Based on the analysis of the immune system's mechanism in animal research, the death of the foetus may result from the immune system's response to the foetus. A human immunoglobulin G (IgG4) called dostarlimab has the potential to cross the placental barrier. Due to the possibility of drug transmission from the mother, this may put the growing foetus at danger. There is no information known about dostarlimab's presence in breast milk (17).

Hepatotoxicity:

In 15–25% of patients, dostarlimab results in modest to moderate increases in serum aminotransferase and alkaline phosphatase. 2-3% of recipients have serum ALT elevations that are greater than five times the range of the normal. Some individuals receiving dostarlimab treatment may experience immune-related liver damage (21). Jaundice, pain in the upper right abdomen, ascites, nausea/vomiting, and confusion are some signs of liver damage or acute liver failure (22).

CHEMISTRY OF DOSTARLIMAB (23):

Dostarlimab (Jemperli) is a monoclonal antibody used to treat endometrial cancer.

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

Drug Class:

Antineoplastic

Formulae:

C6420H9832N1690O2014S44

Molar mass:

144325.73g·mol−1

Structural formula:

Dostarlimab is a monoclonal IgG4 antibody that has been humanised. It is a glycosylated homodimer with four interchain disulphide bonds and 12 intrachain disulphide bonds, and it consists of two identical heavy chains and two identical light chains.

Physicochemical properties:

Dostarlimab is a synthetic medicine that has been made into a clear to slightly opalescent, colourless to yellow solution that is essentially free of visible particles.

PHARMACOKINETICS (24):

A dose of 500mg dostarlimab is administered intravenously every three weeks. Dostarlimab-mean gxly's maximum concentration (Cmax) and AUC (0-tau) during the first cycle are 171 mcg/mL and 35,730 mcg.h/mL, respectively. At 1000 mg every six weeks, the average Cmax and AUC (0-tau) are 309 mcg/mL and 95,820 mcg.h/mL, respectively. The median terminal elimination half-life of dostarlimab is 25.4 days. Its metabolism has not yet been fully characterised, although catabolic processes are expected to break it down into smaller peptides and amino acids.

DOSTARLIMAB FOR TREATING DIFFERENT CANCERS:

RECTAL CANCER:

A ground-breaking advancement in the treatment of cancer was made in June 2022. A medication during a clinical study demonstrated for the first time in the history of science the total eradication of a malignancy with no recurrence. Dostarlimab's, a mAB-based medication, was assessed for safety and effectiveness against locally advanced rectal cancer (25). Stage III rectal cancer, sometimes referred to as primary locally progressed rectal cancer, refers to solid tumours that have lymph node involvement. These tumours are distinguished by their invasion into and growth close to the mesorectal fascia. Total mesorectal resection (TME) surgery, short-course irradiation, and intensive chemotherapy are the usual treatments for these forms of colorectal cancer. Additionally, full excision of the tumour is occasionally the most advantageous and preferable approach for control and survival with locally advanced tumours (26). Radiation therapy and neoadjuvant chemotherapy are the main forms of treatment for locally advanced rectal cancer, which is then followed by surgical resection of the rectum. It has also been mentioned that a deficiency in mismatch repair is a contributing factor in some cases of rectal cancer. A prospective phase 2 study was started in individuals with mismatch repair-deficient stage II or stage III rectal adenocarcinomas by researchers working with GSK. Every three weeks for a total of six months, they received dostarlimab, a single-agent anti-PD-1 medication. Although normal surgery and chemoradiotherapy are to be performed after this treatment, patients who show a clinically complete response after receiving dostarlimab therapy won't need to have any of these procedures. This serves as the study's main endpoint as well. The study demonstrated unequivocally that a single agent, PD1, was extremely sensitive to locally progressed, mismatched repair-deficient rectal cancer and could have beneficial results; however, a longer follow-up study must be carried out to support this assertion (27). In a phase 1 nonrandomized clinical trial, dostarlimab was tested for anticancer efficacy and safety in patients with endometrial cancer that lacked adequate mismatch repair. Enrolment for patients with inadequate mismatch mutation repair endometrial cancer began on May 8, 2017, and Part 1 of this ongoing open-label, multicentre single group research started on March 7, 2016. A total of 104 women with endometrial cancer that had deficient mismatch mutation repair were included in the study. Each patient received intravenous dostarlimab at a dose of 500 mg every three weeks for the first four doses and then 1000 mg every six weeks until the disease progressed, the treatment was stopped, or the patient withdrew. This study's specific goal was to assess the antitumor activity of dostarlimab in patients with advanced or recurrent dMMR (mismatch repair deficiency) endometrial cancer (EC) using the objective response rate (ORR), which was determined by a blinded independent central review (BICR) using RECIST guidelines. Radiographic examinations were carried out 12 weeks after the first dosage of dostarlimab was administered, then every 6 weeks (around 10 days) until month 12, and then every 12 weeks after that (28). The findings of this analysis on patients with platinum-based chemotherapy and dostarlimab monotherapy-resistant recurrent or advanced dMMR EC who had progressed were associated with an ORR of 42.3% (95% CI, 30.6-54.6%) in nearly 30 patients, 29.6% in about 21 patients, and around 12.7% in 9 patients. Less than 2% of patients stopped receiving treatment due to treatment-related adverse events (TRAEs), and there were no treatment-related fatalities. These findings represent the greatest collection of information on dMMR EC treated with a PD-1 inhibitor, to the best of our knowledge (29,30).

Dostarlimab may be useful in the treatment of patients with dMMR EC, despite the GARNET

trial being a single-group study because of the antitumor activity seen in patients with dMMR EC. Dostarlimab displayed a significant ORR and a longer duration of response, highlighting its strong anticancer potential. In addition, 74% of the patients in the dMMR EC population are still alive a year after being included in the GARNET experiment. Dostarlimab has a wide range of effects, but it's dose schedule is what makes it special. After 12 weeks of first dostarlimab therapy, patients and caregivers benefit from this novel dose regimen, which may lead to fewer clinic visits and possibly lower healthcare expenses. Additionally, it has been approved for use during and after platinum-based chemotherapy in both Europe (conditional) and the USA (accelerated) for dMMR/MSI-H and dMMR endometrial cancer, respectively (31,32,33). A comparable trial was also carried out to assess the efficacy of anti-PD-1/PD-L1 axis therapy in patients with incurable endometrial cancer. This ongoing research is being done to determine the drug's safety, effectiveness, and ability to trigger an immune response that fights tumours (34).

CERVICAL CANCER:

Researchers have recently attempted to investigate the effectiveness of dostarlimab in treating locally advanced cervical cancer (LACC). Dostarlimab as a consolidation therapy after chemotherapy may improve patients' progression-free survival rates, according to their hypotheses. A randomised, phase II, open-label research was designed as maintenance therapy for patients at high risk of LACC based on this justification. This ongoing study, which had about 132 participants when it started on June 28, 2019, is a randomised one. The outcomes of this study are yet to be disclosed because of interim data (35,36).

LUNG CANCER:

Another cancer that is responsible for the majority of cancer-related deaths worldwide is lung cancer. Nearly 85% of lung cancer cases fall within the non-small cell lung cancer (NSCLC) classification, for which chemotherapy is the main form of treatment. Immune checkpoint inhibitors have transformed the way that cancer is treated in recent years. In a recent trial, 67 patients with advanced or recurrent NSCLC who had previously received platinum-based chemotherapy participated in a phase 1, multi-centre, open-label, two-part research GARNET cohort to examine the safety and antitumor efficacy of dostarlimab. Part 2 of the study, on the other hand, was conducted in two separate subparts: Part 2A evaluated the dose safety and Part 2B dealt with evaluating the clinical efficacy of the drug. Part 1 of the study was a dose escalation study and involved the evaluation of pharmacodynamics and pharmacokinetic characteristics of the drug at different doses of 1, 3, and 10 mg/kg. Dostarlimab's anticancer efficacy in patients with recurrent or advanced NSCLC was assessed using the immuno-related objective response rate (irORR) and safety as the primary endpoints. According to the scientists' evaluation using the immune-related RECIST, an irORR was defined as the percentage of patients attaining an immune-related complete response (irCR) or immune-related partial response (irPR) (irRECIST). Dostarlimab monotherapy resulted in significant antitumor activity and long-lasting responses in all PD-L1 Tumour Proportion Score (TPS) status subgroups. Dostarlimab's safety profile in NSCLC was considered to be acceptable, with minimal to manageable toxicity, and to be consistent with that of the other medications that inhibit PD-L1. In addition, dostarlimab is currently being researched as part of a combination therapy for the first-line treatment of NSCLC as well as other solid tumours (37). In addition to the studies mentioned above that focused specifically on certain types of cancer, dostarlimab is also the subject of other trials intended for advanced solid tumours. In the phase 1 GARNET study (NCT02715284), it is being

examined for both safety and efficacy in patients with advanced solid tumours. Participants in Cohort F of the GARNET trial had non-endometrial solid tumours with dMMRs or DNA polymerase epsilon (POLE) mutations; the majority of them had GI origins. Dostarlimab was given to the patients as 500 mg Q3W for four cycles, then 1000 mg Q6W until the medication was stopped. A blinded impartial central review that followed RECIST's guidelines highlighted the objective response rate (ORR) and duration of response (DOR). Around 144 individuals who received less than one dosage of the medication were included in the safety study, whereas those with quantifiable illness at baseline were included in the efficacy analysis at the 6-month follow-up (106 dMMR patients). The study's findings revealed that out of 106 patients, 99, or 93.4%, had gastrointestinal tumours. Additionally, the full response rate was approximately 7.5%, while the confirmed ORR in dMMR patients was around 38.7%. While median DOR was not obtained, the median follow-up time was 12.4 months. In addition, no deaths were brought on by the usage of drugs, and only two patients stopped taking them because to TRAE. These study findings provide evidence of dostarlimab's potential anticancer efficacy against solid tumours. Finally, other cohorts in GARNET had their safety profiles evaluated, and the findings were highly consistent with little to no immune-related TRAEs (38,39,40).

RECENTLY DRUG USED FOR THE TREATMENT OF CANCER:

There are currently more than 100 subtypes of sarcoma, a malignant solid tumour with considerable heterogeneity. Chemotherapy and surgery have been demonstrated to be an efficient therapeutic method over time, leading to a somewhat higher overall survival percentage. Additionally, dostarlimab is being used to research how it works against sarcomas. TSR-042 (dostarlimab) was tested in a phase II, single-arm, non-randomized, European multicentric study of patients with advanced/metastatic clear cell sarcoma. On February 19, 2021, the trial was launched, and about 16 patients were enrolled (41).

CONCLUSION:

Dostarlimab's strong response in patients with rectal cancer gives hope that we are on the right path to finding a dramatic match for the other cancers.A subset of 12 individuals with colorectal cancer and a mismatch repair defect participated in the clinical trial (MMRd). Radiation or chemotherapy, however, have little effect on such tumours. However, in the aforementioned trial, every single one of the 12 patients was entirely cured, indicating that immunotherapy may end up being a significant turning point in the development of cancer treatment. It is important to remember that all of the patients had the same disease stage and had not received any prior chemotherapy or surgical treatment. Although this group seems to respond well to the treatment, it is still impossible to predict if similar results would be seen in larger populations of people. To precisely assess the potency of dostarlimab, diverse samples should be used in a phase 3 clinical trial. Additionally, investigations on various cancer kinds could be conducted in various places. Since immunotherapy has not yet penetrated the larger clinical market, the idea of nanotechnology may herald a new era in oncotherapy. Dostarlimab, an immunotherapeutic drug, is unquestionably a top treatment option for colorectal cancer.

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