Dostarlimab: A novel approach to Cancer Therapy

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Abstract

Recently, monoclonal antibodies used in immunotherapy for the treatment of cancer have demonstrated clinical success, particularly when used with the antigens programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1). D dostarlimab inhibits PD-L1 and PD-L2 interactions as well as exchange with adaptive immunity by binding to human PD-1. A s a result of recent clinical trials demonstrating that it is successful in treating mismatch repair deficiency (dMMR) in patients with endometrial cancer, Dostarlimab gets authorised in the United States and the European Union in 2021 . This article provides an exhaustive overview of dostarlimab, its therapeutic effect, and its promising applications. Dostarlimab could be a suitable replacement for umpteen cancer treatments, which frequently have detrimental impact on patients' lives.

Keywords: Dostarlimab, cancer, tumour, colorectal cancer, deficient mismatch repair

Introduction

Cancer/tumors are unchecked cell growths in one area of the body that can spread to other body areas and contain trillions of cells. Depending on their capacity to metastasis, tumors are divided into cancerous (malignant tumors) and non-cancerous (benign tumors). [1] One of the deadliest diseases of the 20th century, cancer has alarmingly escalated in the 21st century to the point that every fourth person is now likely to contract it. [2] [4][6][7] According to GLOBOCAN 2020, there were 19 million new cancer cases and almost 10 million cancer-related deaths in 2020. [9][10].

Despite decades of research in this area, cancer continues to be one of the deadliest diseases that humanity has ever experienced, causing more than 10 million deaths annually [3][18]. It

is now possible to receive treatment using a variety of methods, such as immunotherapy, radiotherapy, and chemotherapy [5].[16][17]. The extent and possibilities of immuno-oncology, the most recent area of research in this discipline, have not yet been fully explored.[8] As part of immunotherapy, particular immune system components of the patient are utilised to treat a variety of illnesses, such as cancer and largely solid tumours. [11][12][13][14] Cancer immunotherapy seeks to reactivate the immune system, which tumour cells have in multiple ways suppressed [15].

Endometrial carcinoma (EC) is a condition in which the uterine lining is home to malignant cells. (endometrium).[19] There are four stages in EC, from the cancer remaining localised in the endometrium to it spreading to other body organs.[20] If this disease is identified early enough, it can be treated.

Studies on dostarlimab and pembrolizumab show encouraging outcomes of the tumours responding effectively to the treatments in people with chemo resistant MSI-high tumours.[20]

The mechanism of action of the novel medicine dostarlimab, which was previously used to treat endometrial malignancies, is consistent with that of existing inhibitors. In a recent clinical experiment, it was discovered that dostarlimab completely cured all CRC patients who received it, with no patients experiencing any grade 3 or above adverse events.[26]

Solid tumors, which can appear anywhere including the bones, muscles, and organs, are tumours without any liquid or cysts. Sarcomas and carcinomas are the two most prevalent varieties of solid tumours. For individuals who have exhausted all other treatment choices, dostarlimab may be used to treat recurrent or advanced tumors[21].

History

The US Food and Drug Administration approved the first immunotherapy drug, an anticancer cytokine known as interferon-alpha 2 (IFN-a2), in 1986. IFN-a2 was initially licenced for the treatment of hairy cell leukaemia (HCL) after research shown that patients with advanced HCL responded to the drug with a high rate. IFN-a2 was given FDA approval in 1995 to be used as adjuvant therapy for melanoma that was stage IIB/III.[22]

Dostarlimab, a monoclonal antibody, received accelerated approval from the FDA on August 17, 2021, for adults with advanced or recurrent endometrial cancer that has progressed despite

current or prior treatment with a chemotherapy regimen that contains platinum. Tumors that exhibit the Deficient mismatch repair (dMMR) or microsatellite instability high (MSI-H) biomarker have abnormal DNA repair mechanisms functioning.[23] Colorectal cancer (CRC) has an incidence of 10% and a mortality rate of 9.4% among the 19 million cancer cases recorded globally in 2020.[25] These cancers lack the genes necessary to correct any incorrect activity and sustain cell health. In 2022, dostarlimab, a PD-1 inhibitor, revealed a 100% remission rate for rectal cancer [4] and showed a long-lasting effect on dMMR tumours. 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 tumors. This clinical trial demonstrated that it is possible to match a tumour's genetic makeup with its therapeutic targets.[24] The major milestones in the history of Dostarlimab are shown in figure 1.

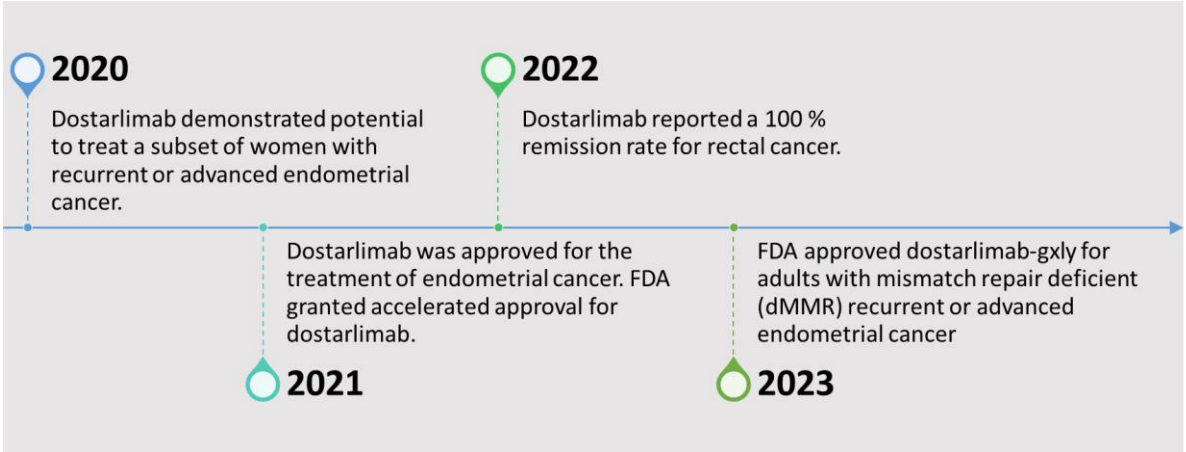

Figure 1:Journey of Dostarlimab

Dostarlimab: Monoclonal Antibodies

In the field of immune-oncology, monoclonal antibodies (mAbs) are regarded as effective therapeutic agents. Although they have been successful, it is concerning that some patients have encountered problems with their clinical application.

One of these is the development of immunogenicity because of the production of antidrug antibodies against exogenous treatments.

The pharmacokinetics, safety, and efficacy of medications may be affected by antidrug antibodies. Critical product factors (e.g., primary sequence, T and B cell epitopes, expression system, glycosylation, aggregation, degradation, post-translational modification, formulation,

and impurities) and patient-related factors (e.g., human leukocyte antigen type, immune competence, disease, concomitant medicines), dose regimen, route of administration, and antidrug antibody development are all influenced by these factors.

Antibody-mediated disorders such as infusion responses, anaphylaxis, hypersensitivity reactions, and ADA-mediated diseases cause antidrug antibodies to modify drug clearance and influence drug safety. Antidrug antibodies known as neutralising antibodies work by interfering with the targeted drug binding, which decreases the effectiveness. Immunological reactions are still seen with antibodies that have been partially or totally humanised, even though they are less likely to occur.

Dostarlimab: a promising drug in the treatment of rectal and endometrial cancer

Dostarlimab or dostarlimab-gxly functions as an antagonist for programmed death-1 (PD-1) receptors. For the treatment of various cancers, including endometrial cancer, colorectal cancer, ovarian cancer, cancer of the head and neck, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), squamous cell cancer (SCC), fallopian tube cancer, pancreatic cancer, and many more, it is being developed by GlaxoSmithKline (GSK) under a licence from AnaptysBio Inc. According to early findings from the GARNET trial, dostarlimab was just recently granted a licence in the EU and USA (as of April 22, 2021) for patients with advanced or recurrent mismatch repair-deficient endometrial cancer (dMMR). [27].

Dostarlimab is an experimental humanised anti-PD-1 that is being explored for gynaecological tumours as well as lung cancer or melanoma, both as a monotherapy and in combination with other treatments. Preliminary findings demonstrate a strong affinity against PD-1 with encouraging clinical action, particularly in endometrial cancer.[37]

It is known that an epitope within a target molecule may be a crucial part of a therapeutic antibody because antibodies that recognise various epitopes have different therapeutic efficacies, albeit the structural reason for this is yet unknown. [28] PD-1 and PD-L1 antibodies inhibit cells in a similar way, but they recognise different antigenic epitopes. Monoclonal antibodies have long been a vital therapeutic tool due to their high specificity and affinities for their targets.[29][30]

A PD-1 receptor-blocking antibody called JEMPERLI binds to the PD-1 receptor and prevents it from interacting with the PD-1 ligands PD-L1 and PD-L2. In addition to GARNET, JEMPERLI is being researched in other registrational enabling studies as monotherapy and in

combination regimens, including in patients with other advanced solid tumours or metastatic cancers, women with recurrent or primary advanced endometrial cancer, women with stage III or IV non-mucinous epithelial ovarian cancer, and women.[31]

Mechanism of action

In a recent study, a stable Chinese hamster ovary (CHO) cell line was used to create the anti-programmed cell death protein 1 (PD 1) immunoglobulin G4 (IgG4) humanised monoclonal antibody (mAb) known as dostarlimab. The PD 1 receptor on T cells is where the PD 1 ligands, PD L1 and PD L2, bind. This binding prevents T cells from proliferating and from producing cytokines. Some cancers exhibit upregulation of PD 1 ligands, and signalling through this route may help to impair active T cell immune surveillance of tumours. Dostarlimab is an IgG4-isotype humanised monoclonal antibody (mAb) that binds to PD 1, inhibiting the binding of PD L1 and PD L2 and inhibiting the PD 1 pathway-mediated immune response, including the anticancer immune response. Blocking PD 1 activation reduced tumour growth in syngeneic murine tumour models [32,33,34].

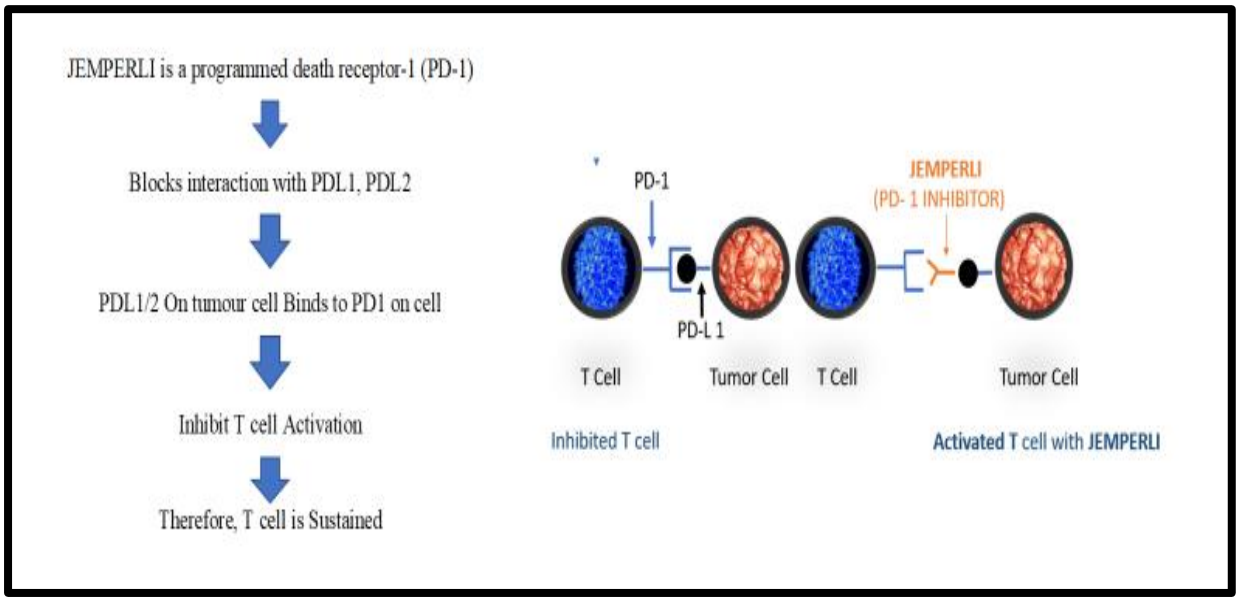

Figure 2: Mode of action of Dostarlimab

Pharmacokinetic properties of Dostarlimab

Absorption	Estimates of absorption are not applicable because dostarlimab is delivered intravenously.

Distribution	Dostarlimab mean volume of distribution in steady state is roughly 5.3 L (CV% of 12.3%).
Biotransformation	Dostarlimab is an IgG4 therapeutic monoclonal antibody that is anticipated to undergo fluid-phase or receptor-mediated endocytosis and be lysosomal catabolized into small peptides, amino acids, and small carbohydrates. The breakdown products either return to the nutrient pool or are excreted by the kidneys without having any biological consequences.
Elimination	At steady state, the mean clearance is 0.007 L/h (with a CV% of 31.3%). At steady state, the t1/2 is 25.4 days (with a CV% of 24.0%). [35][36]

Table 1: Pharmacokinetic Properties of Dostarlimab

Recently approved drugs for CRC by FDA

The US Food and Drug Administration (FDA) has currently authorised the use of the following five PD-1/PD-L1 inhibitors for the treatment of CRC: Durvalumab, atezolizumab, nivolumab, pembrolizumab, and avelumab. [38]

Atezolizumab: 7.10 months were the median overall survival time (6.05–10.05)

Nivolumab: Only one metastatic colorectal cancer (mCRC) patient (1/14; 17%) showed a long-lasting full response for six months in a phase 1 study of nivolumab in 39 patients with treatment-resistant solid tumours. [39]

Pembrolizumab: According to research published in the New England Journal of Medicine, the median progression-free survival was 16.5 months (95% CI: 5.4-32.4).

Avelumab: In a phase 2 study of avelumab monotherapy, the median progression-free survival and overall survival were reported to be 3.9 and 13.2 months, respectively. [40]

Combination Study

In a recent open-label clinical research of phase 2, dostarlimab was evaluated as a single neoadjuvant therapy for CRC. [41][42] Patients with stage 2 or 3 CRC who tested positive for

dMMR were included in the experimental trial. The first-ever total removal of tumours with no return of cancerous cells was shown in a clinical experiment. In 12/12 patients, complete remission of the locally progressed malignancy was recorded. [43] [44][45][46]

Different clinical trials are being conducted for the effect of combinations of Dostarlimab. Table 2 summarizes these trail studies.

Target Population	Combination	Clinical Trial
Endometrial cancer	Dostarlimab and Niraparib	NCT03016338
Head and neck cancer	Dostarlimab and Niraparib	NCT04313504
Localized unresectable adult primary liver cancer	Dostarlimab and TSR-022	NCT03680508
Melanoma stage III or IV	Dostarlimab and TSR-022	NCT04139902
Endometrial or Ovarian carcinosarcoma [49]	Dostarlimab and Niraparib	NCT03651206
Recurrent Ovarian cancer	Dostarlimab and Niraparib	NCT03806049
Stage III or IV nonmucinous [50]	Standard of care ± Dostarlimab and Niraparib	NCT03602859
Advanced (unresectable) or metastatic solid tumor [51]	Dostarlimab and TSR-022(Anti-TIM-3)	NCT02817633
Advanced (unresectable) or metastatic solid tumor [52]	Dostarlimab and Anti-LAG-3	NCT03250832
Mainly NSCLC or any other metastatic cancer [53]	Dostarlimab and TSR-022 (Combination), Platinum-based doublet chemotherapy, bevacizumab and niraparib	NCT03307785
Recurrent ovarian cancer	Dostarlimab, Niraparib and Bevacizumab	NCT03574779
Advanced and metastatic NSCLC [54]	Niraparib + Pembrolizumab/Dostarlimab	NCT03308942
Ovarian Advanced cancer	Dostarlimab and Niraparib	NCT03955471
Triple negative breast cancer [55]	Dostarlimab and Niraparib plus radiation therapy	NCT04837209
Advanced non small cell lung cancer [57]	Dostarlimab and Cobolimab	NCT04655976
Metastatic Non squamous Nonsmall Cell Lung cancer [56]	Dostarlimab and Chemotherapy (Pemetrexed, cisplatin, and carboplatin)	NCT04581824
Relapsed / Refractory Multiple Myeloma [58]	Dostarlimab and Belantamab mafodotin	NCT04126200

Table 2: Clinical Trials Testing the Combination of Drug Dostarlimab with other therapies [47] [48] [59]

Major applications of Dostarlimab

1. The PD-1 inhibitor Dostarlimab is used in cancer immunotherapy.

2. Dostarlimab has demonstrated excellent results in the treatment of locally advanced rectal cancer [60].
3. Authorized in April 2021 for the treatment of adult patients with advanced or recurrent endometrial cancer that is mismatch repair deficient (dMMR).
4. Approved in August 2021 for the treatment of adult patients with advanced or recurrent solid cancers that are mismatch repair-deficient (dMMR) [61]
5. The drug dostarlimab is used to treat solid tumours and endometrial cancer. [62]

Conclusion

A recently developed drug called dostarlimab blocks a specific cancer cell protein that, when produced, can reduce the immune system's capacity to fight cancer. In the fight against cancer, a small immunotherapy drug trial is having a significant impact. After six months of an experimental treatment called dostarlimab, tumours disappeared. These revolutionary findings point to a potential substitute for many cancer treatments, which frequently have negative effects on patients' quality of life.

Future Applications

Dostarlimab has drawn much of attention as a result of its cancer treatment breakthrough. It must be studied in more cancer types while adjusting the dosing quantity. To combat drug resistance in cancer, this medication can be used in combination with additional therapies. Priority should be paid to minimising the drug's negative effects, which are many and have not yet been linked to a particular mechanism of action. This knowledge may help Dostarlimab develop into a more effective and safe cancer treatment. [64]

Until the current experiment, cancer was thought to be an untreatable disease that killed millions of people worldwide. Even though Cercek et alstudy .'s [63] represented a significant advancement in the field of oncology, the trial's sample size was incredibly tiny, which made it less trustworthy despite all the sincere manoeuvres carried out during the trial [11]. Also, the follow-up time wasn't lengthy enough. Hence, additional studies with longer follow-up times are necessary to examine the duration of the treatment response and tumour recurrence.

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