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REVIEW OF DOSTARLIMAB: A BREAKTHROUGH IN IMMUNO ONCOLOGY

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ABSTRACT

Overview of Dostarlimab and Immunotherapy in Cancer Treatment Immunotherapy has emerged as a transformative pillar in cancer treatment, focusing on reinvigorating the immune system to fight malignancies. Various immunotherapies, notably immune checkpoint inhibitors (ICIs), monoclonal antibodies, and chimeric antigen T-cell therapy, have shown promising efficacy by targeting immune checkpoints, including CTLA-4 and PD-1 proteins, thereby enhancing immune responses against cancer cells. Dostarlimab, a humanized IgG4 monoclonal antibody developed by GlaxoSmithKline, is a recent addition to the monoclonal antibody class. By binding to PD-1 on T cells, it prevents interactions with PD-L1 and PD-L2 on cancer cells, restoring the immune system's anti-tumor function. This drug received FDA approval for treating mismatch repair-deficient (dMMR) recurrent or advanced endometrial cancer following platinum-based chemotherapy and has demonstrated efficacy in treating various solid tumors. The mechanism of dostarlimab centers on immune checkpoint inhibition, where it blocks the PD-1/PD-L1 pathway, reversing immune suppression in cancers where PD-L1 is overexpressed. Pharmacodynamic studies show its high affinity for PD-1 in humans and primates, enhancing IL-2 production in immune assays and demonstrating a synergistic effect with LAG3 or TIM3 antibodies. Pharmacokinetic studies report dose-dependent increases in exposure metrics, confirming its effectiveness across varied doses. Clinical applications of dostarlimab extend to endometrial and rectal cancers, where it has shown efficacy in GARNET trials. Its safety profile aligns with other ICIs, reporting treatment-emergent adverse events such as fatigue, nausea, and immune-related adverse effects in a minority of cases. In trials, serious

adverse events led to treatment discontinuation in a small percentage of patients, underscoring the need for vigilant management of side effects. Ongoing clinical trials, including studies in NSCLC, continue to validate its role in the oncology landscape, with promising data supporting the integration of dostarlimab in immunotherapeutic regimens across cancer types.

KEYWORDS: Immunotherapy, Cancer treatment, Dostarlimab, PD-1/PD-L1 pathway, Immune checkpoint inhibitors (ICIs), Monoclonal antibody.

INTRODUCTION

Overview of Immunotherapy in Cancer Treatment

One of the four pillars of cancer treatment, immunotherapy, has lately come to light as a ray of hope for cancer patients. Cancer immunotherapy seeks to restore the immune system's activation, which tumor cells have repeatedly inhibited. Numerous innovative approaches using immunotherapy are being explored to either treat cancer or reduce the cytotoxic side effects that come with certain cancer treatments. Some immunotherapies, such as immune checkpoint inhibitor therapy, monoclonal antibody therapy, and chimeric antigen T-cell therapy, have attracted much attention due to their remarkable ability to trigger the immune system's reaction against cancer cells, thereby impeding the cancer's spread. Targeting checkpoint proteins like CTLA-4 and programmed cell death protein-1 (PD-1) has improved median overall survival and long-lasting effects in patients with various tumor types using immunotherapies. Checkpoint inhibitors are a new class of immunotherapeutics that have become a mainstay in cancer treatment in recent years. Since the discovery of immunotherapies, there has been a promise to transform the standard of care in cancer treatment.

Dostarlimab, received expedited clearance from the FDA on August 17, 2021, for people with dMMR recurrent or advanced endometrial cancer that has progressed after receiving platinum-containing chemotherapy regimentonment or treatment in the past. Furthermore, dostarlimab is a member of the monoclonal antibody drug class. It is a humanized IgG4 monoclonal antibody used in immunotherapy developed by GlaxoSmithKline that binds to and suppresses the PD-1 protein on cancer cells while obstructing checkpoint proteins on T cells or cancer cells. Dostarlimab, a humanized IgG4 mAb, has a molecular weight of roughly 144 kDa and is produced from Chinese hamster ovary cells. Dostarlimab was just approved (April 22, 2021) for people with advanced or recurrent advanced mismatch repair-deficient

endometrial cancer (dMMR) in the EU and USA, based on preliminary results from the GARNET trial. This medication is also used to treat a variety of tumors, such as small-cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), fallopian tube cancer, ovarian cancer, and pancreatic cancer. Adult patients with recurrent or advanced dMMR/MSI-H EC who have advanced during or following treatment with a platinum-containing regimen are eligible to receive dostarlimab as a monotherapy in the EU.

In studies involving Cynomolgus monkeys and humans, dostarlimab exhibits an excessive affinity for PD-1, as measured by floor plasmon resonance to recombinant PD-1 and float cytometry with Chinese Hamster Ovary-K1 cell lines overexpressing recombinant PD-1 or binding to local protein on peripheral blood mononuclear cells. It is created by recombinant DNA technology in the mammalian Chinese hamster Overy, which binds to T cells' PD-1 and prevents them from interacting with PD-L1 AND PD-L2, therefore triggering the immune response.

Mechanism of action immune checkpoint inhibition

A humanized monoclonal antibody (mAb) called dostarlimab (JemperliTM) or dostarlimab-gxly functions as an antagonist for programmed death-1 (PD-1) receptors. By attaching to T cell-present PD-1, it triggers immunological responses by preventing interactions with cell death protein and its ligand (PD-1 and PD-L1).

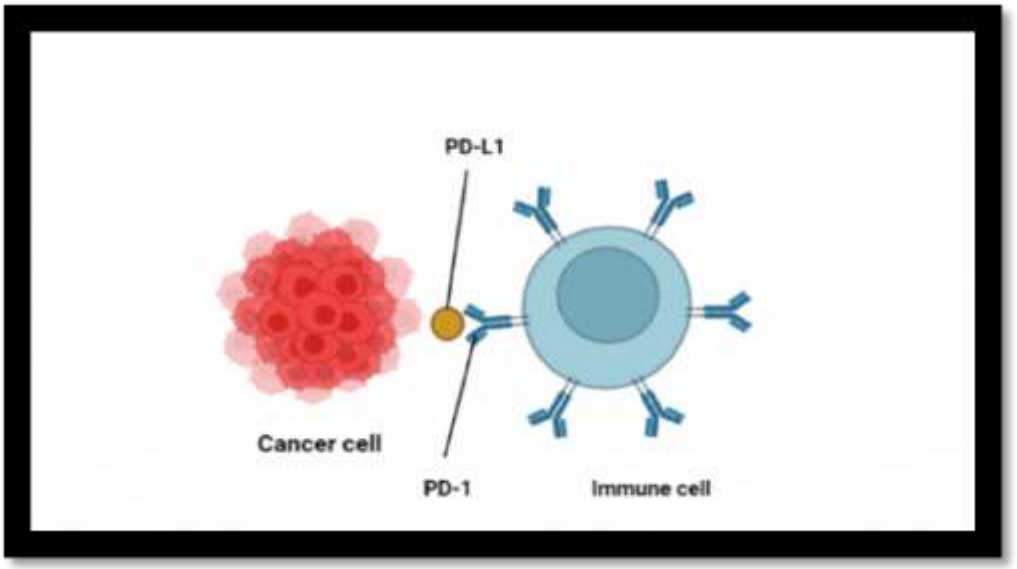
The PD-1 ligands PD-L1 and PD-L2 bind to the T cell PD-1 receptor, activating it and inhibiting T cell proliferation and cytokine production. In some malignancies, PD-1 ligands are upregulated, and signaling through this route can contribute to the suppression of active T-cell immune responses. Dostarlimab is a humanized IgG4 monoclonal antibody used for cancer surveillance. An isotype that binds to the PD-1 receptor and inhibits it from interacting with the PD-L1 and PD-L2 receptors releases the immune system's antitumor response and suppresses it through the PD-1 pathway. Studies have depicted that dostarlimab binds with PD-1 receptors of both humans and cynomolgus monkeys with high affinity, as seen from the results obtained in flow cytometry and plasmon resonance. Furthermore, dostarlimab functioned as a functional antagonist, leading to an increase in IL-2 production, as demonstrated by a human CD4+ mixed lymphocyte response assay. Additionally, this experiment demonstrated the increased activity of dostarlimab in the presence of LAG3 or TIM3 antibodies.

Dostarlimab (JEMPERLI) is a humanized anti-PD-1 immunoglobulin G4 monoclonal antibody that has high affinity binding to the PD-1 receptor, blocking interaction between PD-1 ligands, PD-L1 and PD-L2.

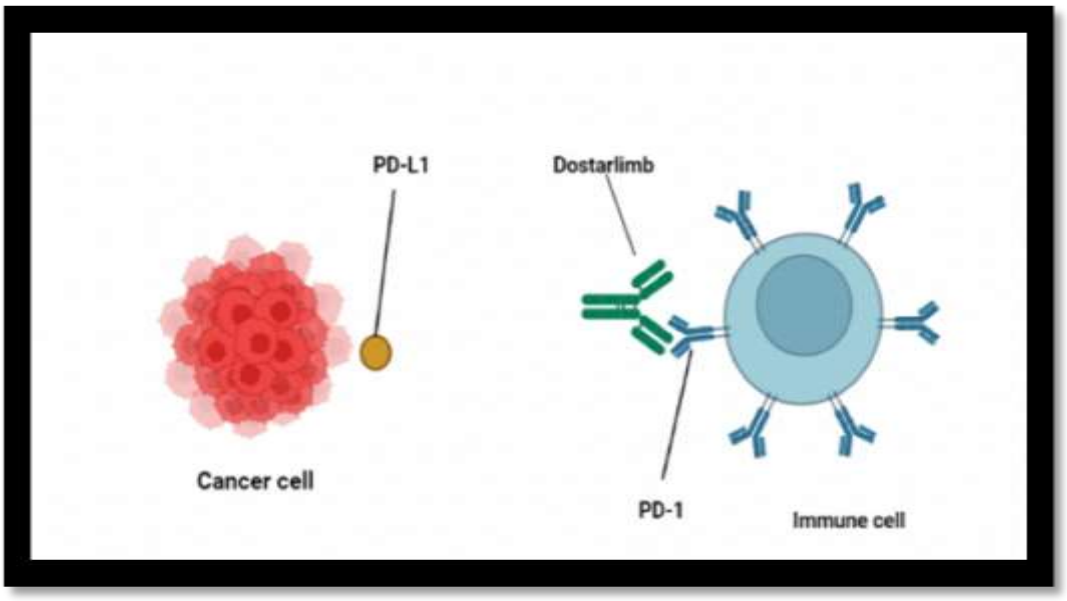
Consequently, a number of ICIs, such as durvalumab, atezolizumab, cemiplimab, nivolumab, and pembrolizumab, are currently authorized for use as monotherapies or in conjunction with chemotherapy in NSCLC. Although these drugs were first effective in treating recurrent or advanced non-small cell lung cancer (NSCLC) that had advanced following platinum-based chemotherapy, they are now also commonly used as first-line treatments for advanced NSCLC, either alone or in conjunction with other immunotherapies or chemotherapy.

Pharmacodynamics

According to flow cytometry using cell lines that overexpress recombinant PD-1, surface plasmon resonance, or binding to the native protein on peripheral blood mononuclear cells (PBMC), dostarlimab exhibited a high affinity for both human and cynomolgus monkey PD-1. Dostarlimab functioned as a potent functional antagonist in a human CD4+ mixed lymphocyte response assay, leading to increased IL-2 production. Dostarlimab's activity in this test was enhanced by the addition of anti-TIM3 or anti-LAG3 antibodies. Dostarlimab incubation of human PBMCs as a single agent did not result in significant cytokine release stimulation.



Dostarlimab binds to PD-1 and stops it from forming an ‘authentification process‘. This immune cell can now alert the rest of the immune system that cancer cells are there and must be destroyed.



When cancer cells express the protein PD-1 on their surface, immune cells with PD-1 will recognize them and link with them. The immune system is fooled into not targeting cancer cells by this 'tep connection'.

Pharmacokinetics

Dostarlimab's pharmacokinetics were investigated in 150 EC patients with various solid tumors. During the 1.0–10 mg/kg dosing range, mean Cmax, AUC0−∞, and AUC0−τ all rose in proportion. Dostarlimab's Cycle 1 mean (coefficient of variation [percent CV]) Cmax and AUC0−τ are 171 mcg/mL (20%) and 35,730 mcg*h/mL (20%) at a dosage of 500 mg once every three weeks, respectively, and 309 mcg/mL (31%) and 95,820 mcg* at a dose of 1,000 mg once every six weeks.

Clinical applications

Endometrial cancer

In women, endometrial cancer ranks sixth in terms of incidence. There were almost 400,000 new cases in 2021. Less than 20% of patients with severe and recurring disease are projected to survive for five years, and there are few therapy choices available to them. Platinum-based chemotherapy can be administered to metastasized patients. 13 months is the anticipated median progression-free survival (PFS).

Dostarlimab efficiently inhibits the interaction with PD-L1 and PD-L2 by binding to the PD-1 receptor with high affinity. In patients with advanced solid tumors, the GARNET trial (NCT02715284) aimed to ascertain the anticancer effectiveness, safety, and tolerability of

dostarlimab monotherapy. This study is focused on patients whose local immunohistochemistry tests revealed that they had dMMR tumors.

Rectal cancer

Pembrolizumab is the recommended treatment in the first line setting for patients with dMMR/MSI-H disease. Nivolumab, either by itself or in conjunction with Ipilimumab, is an alternative treatment option for patients with dMMR/MSI-H disease, regardless of whether they qualify for intensive chemotherapy.

Pembrolizumab and Nivolumab +/- Ipilimumab are two examples of immunotherapeutic regimens that are currently recommended for patients with dMMR/MSI-H chemoresistant metastatic colorectal cancer (in patients who have not previously received an ICI). Dostarlimab is also now recommended for these patients.

Ongoing clinical trial fors dostarlimab

For the first time in history, a medication undergoing clinical trials demonstrated total tumor eradication with no recurrence. Dostarlimab, a medication based on mAB, was tested for safety and effectiveness against locally advanced rectal cancer. Mismatch repair-deficient colorectal cancer responds to programmed death 1 (PD-1) blocking in the context of metastatic disease, indicating that checkpoint blockage may be useful in individuals with mismatch repair deficiency. A prospective phase 2 study was started by researchers in collaboration with GSK in patients with stage II or III rectal adenocarcinomas who lacked mismatch repair. For six months, they received dostarlimab, a single-agent anti-PD-1 mAB, every three weeks. Patients who show a clinically complete response after dostarlimab therapy would not have chemotherapy, radiation, or surgery, even though this treatment is meant to be followed by normal surgery and chemoradiotherapy. This serves as the study's main endpoint as well.

In a recent trial, 67 patients with recurrent or advanced non-small cell lung cancer (NSCLC) who had previously received platinum-based chemotherapy participated in the first-in-human, phase 1, multi-center, open-label, two-part research GARNET cohort to examine the safety and antitumor efficacy of dostarlimab.

Clinical trial and efficacy key trial

Dostarlimab's safety and effectiveness are being assessed in the GARNET trial, a Phase 1,

multicenter, open-label, two-part investigation that is the first of its kind. Dostarlimab's pharmacokinetic and pharmacodynamic characteristics were assessed in Part 1 by a dose-escalation trial (1, 3, and 10 mg/kg). Using a recommended Phase 2 dose established based on data from Parts 1 and 2A of the study, Part 2B assessed the clinical efficacy of dostarlimab within expansion cohorts based on tumor type and mutational status. Part 2A consisted of a fixed-dose safety evaluation phase.

The institutional ethics committee, the institutional review board, and/or the appropriate competent authorities at each site approved the study protocol and/or other pertinent documents.

Safety analyses

Serious adverse events (SAEs), immune-related adverse events of interest (irAEIs), and treatment-emergent adverse events (TEAEs) that happened during or up to 90 days after the completion of therapy were all included in safety assessments.

Safety profile

In April 2021, the European Medicine Agency (EMA) authorized dostarlimab for conditional marketing to treat patients with recurrent or advanced dMMR EC that had progressed following platinum-based chemotherapy. There were no differences in treatment-related adverse events (TRAEs) between the MMRp/MSS and dMMR/MSI-H cohorts.

The safety profile observed in EC cohorts was in line with the safety profile observed in GARNET for other tumor types.

The GARNET study's first safety analysis examined 34 patients' data in parts 1 (n = 21) and 2A (n = 13). Overall, there were no toxicities with dose limitations. In part 1, every patient had at least one TEAE, and 81% of those cases were thought to be connected to treatment. One patient exhibited elevated transaminases, which were thought to be connected to treatment, and 43% of patients had at least one grade ≥3 TEAE. 33% experienced severe TEAEs. Fatigue (43%), nausea (33%), decreased appetite (29%), and dehydration (29%), were the most frequent TEAEs.

83% of participants in part 2A had at least one TEAE, 50% of which were considered treatment-related, and 7% of which were grade 3 or higher. The most common TEAEs were influenza-like illness, fatigue, nausea, tachycardia, and abdominal pain, with 17% each.

Management of adverse effects

According to the GARNET study, 34% of patients with dMMR endometrial cancer receiving dostarlimab experienced serious side effects. More than 2% of patients experienced pyrexia (2.9 percent), urinary tract infection (2.9%), sepsis (2.9%), abdominal pain (2.9%), and acute renal injury (2.9%). Five (4.8%) patients were forced to discontinue Dostarlimab permanently due to side effects, including increased transaminase levels, sepsis, bronchitis, and pneumonitis. 23% of patients experienced dosage interruptions due to an adverse event, such as pyrexia, increased lipase levels, diarrhea, or anemia—all of which occur in less than 1% of patients.

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