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ANTINEOPLASTIC DRUG

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Abstract

Dostarlimab (JEMPERLI) is a PD-1 monoclonal antibody for the treatment of adult patients, with mismatch repair deficient (dMMR), recurrent or advanced endometrial cancer that has progressed on or following prior therapy with a platinum-containing regimen. As determined by an FDA-approved test this indication was granted rapid approval based on the rate of tumor response and the duration of the response. Continued approval for this indication is conditioned on further confirmatory trials demonstrating and documenting clinical benefit. In June 2022, the clinical trial NCT04165772 reported a 100% remission rate for rectal cancer. This clinical trial brought proof that we can match a tumor and the genetics of what is driving it, with therapy. This clinical trial continues to enroll patient and is currently enrolling patients with gastric, prostate, and pancreatic cancers. Dostarlamib is being recommended for rectal cancer. The focus of this review is to summarize the existing knowledge regarding Dostarlimab and explore the possibilities of mono- and combination therapies.

Keywords: anti-PD-1 antibody; clinical trials; dostarlimab; immunotherapy.

Introduction

In 1986, the first immunotherapy agent, an antitumor cytokine designated interferon-alpha 2 was approved by the US Food and Drug Administration (FDA). IFN-a2 was first approved for the treatment of hairy cell leukemia (HCL) after studies showed that it had a high response rate in patients with advanced HCL. In 1995, the FDA approved IFN-a2 for use as adjuvant therapy for stage IIB/III melanoma. When it was licensed for the treatment of metastatic melanoma and renal cell carcinoma in 1998, interleukin-2 (IL-2), a T-cell growth factor that aids in immunological modulation and T-cell proliferation, became the second anticancer cytokine approved by the FDA. Since the development of immunotherapies a promise of revolutionizing the standard care in cancer treatment has existed and, in recent years, a novel class of immunotherapeutics known as checkpoint inhibitors has emerged as a cornerstone in cancer treatment. To this day, different types of immunotherapies are used to treat cancer: immune checkpoint inhibitors, T-cell transfer therapy, monoclonal antibodies, vaccines, and immune system modulators.

On 17 August 2021, the FDA granted accelerated approval to Dostarlimab, a monoclonal antibody, for adults with dMMR recurrent or advanced endometrial cancer that has progressed despite ongoing or prior treatment with the platinum-containing chemotherapy regimen, Tumors that exhibit the dMMR or MSI-H biomarker have an abnormal function of DNA repair mechanisms. Genes that should repair any improper activity to maintain cell health are absent in these types of cancer. Dostarlimab, an inhibitor of PD-1, demonstrated a long-lasting effect on dMMR tumors, and in 2022, reported a 100% remission rate for rectal cancer [4]. All patients had dMMR, a mutation present in 5 and 10% of rectal cancer cases (this mutation is also present in endometrial, prostate, and bladder tumors). This clinical trial brought the promise and the proof that we can match a tumor and the genetics of what is driving it, with therapy.

Dostarlimab

Dostarlimab, sold under the brand name **Jemperli**, is a monoclonal antibody used as a medication for the treatment of endometrial cancer Dostarlimab is a programmed death receptor-1 (PD-1)–blocking monoclonal antibody.

The most common side effects reported in the US include fatigue/asthenia, nausea, diarrhea, anemia, and constipation. Additional side effects reported in the European Union include vomiting, joint pain, itching, rash, fever, and hypothyroidism (low levels of thyroid hormones).

Dostarlimab was approved for the treatment of endometrial cancer in both the United States and the European Union in April 2021.

Based on the GARNET trial, Dostarlimab (Jemperli) gained accelerated approval from the Food and Drug Administration (FDA) in April 2022. Jemperli's mechanism of action allows it to act directly on cancerous cells. Follow-up appointments accompanying long-term treatments or long-term post-operative therapies are not necessary with dostarlimab.

Inhibitors of PD-1/PD-L1 and dMMR

Cancer immuno-therapy has seen significant clinical success driven by ICBs that restore T-cell activation. ICBs act in multiple ways to alter T-cell function, including the downregulation of inhibitory signaling. One target of ICBs is programmed cell death protein 1 (PD-1). Multiple malignancies have high levels of PD-L1 and PD-L2, which suppress T cells. Monoclonal antibodies that target PD-1 or PD-L1 (PD-(L)1) disrupt the interaction between PD-1 on T cells and PD-L1 on cancer cells, restoring T-cell activity. The PD-L1 inhibitor has been licensed as an immunotherapeutic for a variety of malignancies.

Anti–PD-(L)1 pathway-targeted treatments have been demonstrated to be well tolerated and have consistent safety profiles as a pharmacological class, and when used to treat dMMR-MSI-H, PD-1/PD-L1 inhibitors showed favorable clinical results, including a higher response rate. However, not all drugs entitled of PD-1/PD-L1 inhibitors have the same success rate in treating tumors with dMMR. In Sclafani's review, it is highlighted that the administration of Pembrolizumab to patients with dMMR metastatic colorectal cancer was correlated with a poor prognosis. Numerous studies have demonstrated the wide range of immunotherapy, prognosis, and chemotherapy sensitivity in individuals with dMMR/MSI malignancies, and the detection limitation contributes to the difficulty of treatment. Moreover, it is necessary to quantify the frequency of missmatch repairs. A lower or higher frequency will require a different treatment. However, it remains unclear how the same PD-1/PD-L1 inhibitors (or even different ones) cause variable therapeutic responses in patients with a different frequency of mismatch repairs. At last, it appears Dostarlimab that shows durable antitumor activity in patients with dMMR/MSI-H.

Combination Studies

Based on the enormous success of antibodies targeting PD-1 or its ligand PD-L1, the low response rate of -PD-1/PD-L1 therapy must be addressed. For most cancer patients, the PD-1/PD-L1 pathway is not the only mechanism limiting antitumor immunity and inhibiting the PD-1/PD-L1 axis is insufficient to generate an effective antitumor immune response. Some combination therapies, such as PD-1/PD-L1 plus chemotherapy, radiation, angiogenesis inhibitors, targeted therapy, additional immune checkpoint inhibitors, co-stimulatory molecule agonists, interferon gene stimulator agonists, fecal microbiota transplantation, epigenetic modulators, or metabolic modulators exhibit better response rates and superior anticancer efficacies

Combination techniques have been developed to generate synergistic effects or to diminish primary or secondary resistance to PD-L1 inhibitors due to the complexity of immune response activation and the multiple mechanisms leading to resistance to PD-(L)1 inhibitors. Combinations with CTLA-4, TIGIT, IDO, and PVRIG are being evaluated in early clinical trials to

block other immune checkpoints (NCT03015129, NCT04570839, NCT04106414, NCT03667716), and future findings will give insight into their therapeutic utility in this environment. In the recurrent scenario, angiogenesis and PARP inhibitors are investigated, whereas chemotherapy is investigated in the first-line setting.

Medical uses

In the United States, dostarlimab is indicated for the treatment of adults with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen. Platinum-based agents such as cisplatin, carboplatin and oxaliplatin are mainstays of treatment when it comes to cancer chemotherapy treatment. It is also indicated for the treatment of solid tumors.

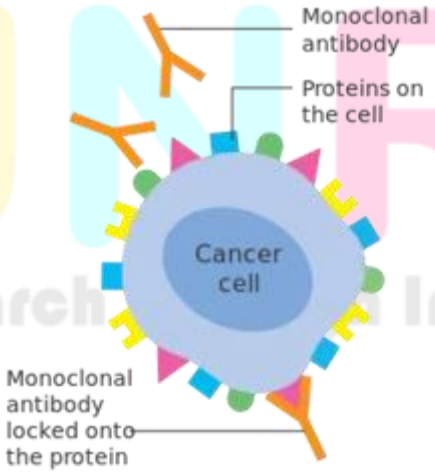
In the European Union, dostarlimab is indicated as monotherapy for the treatment of adults with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.

In August 2021, the US Food and Drug Administration (FDA) granted accelerated approval to dostarlimab for adults with mismatch repair deficient (dMMR) recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.

Endometrial cancer

Endometrial cancer (EC) is a disease where cancerous cells reside in the lining of the uterus (endometrium). There are four stages in EC, ranging from staying settled in the endometrium to the cancer spreading to other organs in the body. This disease can be treated if discovered at the beginning of development. In those with chemoresistant MSI-high tumors, studies conducted on dostarlimab and pembrolizumab display promising results of the tumors reacting well to the therapies.

Solid tumors



monoclonal antibody attached to a cancer cell CRUK 070 from Cancer Research UK.

Solid tumors are tumors that do not contain any liquid or cysts, which can occur in many places including bones, muscles and organs. The most common types of solid tumors are sarcomas and carcinomas. Dostarlimab can used to treat recurrent or advance tumors for patients who have tried alternative treatment options.

Side effects

Serious adverse reactions in >2% of patients included sepsis, acute kidney injury, urinary tract infection, abdominal pain, and fever (pyrexia). Immune-mediated adverse reactions can occur including pneumonitis, colitis, hepatitis, endocrine disease (endocrinopathies), and nephritis.The most common side effects reported while taking this medication during a trial were dyspnea, asthenia, fatigue, and nausea.

Symptoms of overdose are similar to the side effect profile of the medication, so it could involve significant immune-mediated reactions.

Immune-mediated adverse reactions

Dostarlimab is a monoclonal antibody that binds to PD-1 to block it from binding PD-1 ligands to remove inhibition of immune response. With this, it causes risk for immune-mediated adverse reactions. These reactions can be severe or fatal and occur in any part of the body: organs or tissues.

Examples of immune-mediated adverse reactions include immune-mediated pneumonitis, colitis, hepatitis, adrenal insufficiency, hypophysitis, thyroid disorders, nephritis with renal dysfunction, and dermatologic reactions.

Pregnancy and lactation

Dostarlimab can cause harm to a fetus. The death of the fetus can occur from the immune system's reaction to the fetus through the examination of its mechanism in animal studies. Dostarlimab is a human immunoglobulin G (IgG4), which could permeate through the placental barrier. This may risk harm to the developing fetus as the drug may be passed on from the mother. Data is not available regarding the presence of dostarlimab in breastmilk.

Hepatotoxicity

Dostarlimab causes mild to moderate elevations to serum aminotransferase and alkaline phosphatase in 15-25% of recipients. Serum ALT elevation above five times the normal range occurs in 2-3% of recipients. Some people treated with dostarlimab can develop immune related liver injury.

Some symptoms of liver injury or acute liver failure can include jaundice, pain in the upper right abdomen, ascites, nausea/vomiting, and disorientation or confusion.

Pharmacology

Dostarlimab is a humanized IgG4 monoclonal antibody that was derived from a mouse antibody which was humanized via Complementarity Determining Region (CDR) grafting. Its serum half-life is 25.4 days.

Other PD-1 antibodies included nivolumab (Opdivo) and pembrolizumab (Keytruda), both of which have uses in many different types of cancers which include classical Hodgkin lymphoma, renal cell carcinoma, and breast cancer. Another PD-1 antibody is cemiplimab (Libtayo) which was approved for treatment of squamous cell carcinoma, basal cell carcinoma and non-small cell lung cancer.

Mechanism of Action

Dostarlimab binds to the PD-1 receptor, with high affinity, to block its activity with PD-1 ligands (PD-L1) and PD-L2). PD-1 is a co-inhibitory receptor that is an important checkpoint protein for regulating T-cell tolerance. When PD-1 is constantly stimulated by PD-1 ligands, which are highly expressed in cancer cells, it allows cancer cells to dodge T-cell mediated immune responses. Therefore, blocking the binding of PD-1 to these ligands can allow T-cells to function normally and prevent tumor cells from bypassing immune surveillance. In mouse tumor models, it was shown that inhibiting PD-1 activity decreased tumor growth.

Efficacy

In the GARNET Trial, dostarlimab achieved favorable results in decreasing the size of the tumor in those with endometrial cancer. The study observed people with endometrial cancer from seven different countries and the size of the tumor was reduced in 42% of the population studied.

Dostarlimab exhibits better efficacy than other PD-1 inhibitors, such as avelumab and durvalumab, in dMMR advanced endometrial cancers. Efficacy of the drug is measured by the response rate, which is 47% for dostarlimab.

History

In 2020, dostarlimab, a PD-1inhibitor, was undergoing phase I/II and phase III clinical trials.

In 2020, the manufacturer, Tesaro, announced preliminary successful results from the phase I/II GARNET study.

In 2020, the GARNET study announced that dostarlimab had promising potential to treat a specific subset of individuals with recurrent or advanced endometrial cancer.

In April 2021, dostarlimab was approved for the treatment of recurrent or advanced endometrial cancer with mismatch repair deficient (dMMR), which are genetic abnormalities that disrupt DNA repair, in individuals who had previously been treated with platinum-containing regimens.

In April 2021, the Food and Drug Administration granted accelerated approval to dostarlimab-gxly (Jemperli, GSK). Efficacy was evaluated based on cohort (A1) in GARNET Trial (NCT02715284), a multicenter, multicohort, open-label trial in participants with advanced solid tumors.

In 2022, an early clinical study of dostarlimab reported a 100% remission rate in 14 patients with rectal cancer who had mismatch repair deficiency, a type of genetic mutation that only affects 5-10% of cases.

Society and culture

Dostarlimab is the international nonproprietary name (INN), and the United States Adopted Name (USAN).

Legal status

In February 2021, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion, recommending the granting of a conditional marketing authorization for the medicinal product Jemperli, intended for the treatment of certain types of recurrent or advanced endometrial cancer. The applicant for this medicinal product is GSK (Ireland) Limited. Dostarlimab was approved for medical use in the European Union in April 2021.

Economics

In the United States, dostarlimab is an expensive medication, costing around US$11,000 per dose.

For patients with endometrial cancer it is estimated cost of dostarlimab is $104,000 in the first 6 months. This only includes the cost of accessing the medication and not the doctor's fee or infusion cost or imaging. Thus those who are uninsured will most likely have trouble getting treatment with Dostarlimab.

Among those who are insured, those who have Medicaid insurance are less likely to receive full care for gynecologic cancer. Those insured through private insurance still experience economical hardships while getting treatment. Uninsured patients do not tend to get screened regularly, which results in late diagnosis of the disease.