Dostarlimab: The Miraculous New Drug For Cancer

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A trial on colorectal patients in the US found that cancer could be treated without chemotherapy or surgery. The world is sitting up and taking note of Dostarlimab which has been called a wonder drug. Dostarlimab, sold under the brand name Jemperli, is a monoclonal antibody used as a medication for the treatment of rectal cancer. It is developed by a biotech company out of Massachusetts called Tesaro before being acquired by GlaxoSmithKline in 2019, dostarlimab is also known by the brand name Jemperli. Stay informed about local news and weather.
INTRODUCTION:
The FDA has granted an accelerated approval to dostarlimab-gxly for the treatment of adult patients with mismatch repair-deficient recurrent or advanced solid tumors, as determined by an FDA-approved test, who have progressed on or following previous treatment and who have no satisfactory alternative options. Dostarlimab was developed by Tesaro and sold to GlaxoSmithKline in 2019. In 2020, the GARNET study announced that dostarlimab was demonstrating potential to treat a subset of women with recurrent or advanced endometrial cancer. In April 2021, dostarlimab was approved for the treatment of recurrent or advanced endometrial cancer with deficient mismatch repair (dMMR), which are genetic abnormalities that disrupt DNA repair. On 22 April 2021, the Food and Drug Administration granted accelerated approval to dostarlimab-gxly (Jemperli, GlaxoSmithKline). Dostarlimab-gxly injection is used to treat endometrial cancer (cancer of the lining of the uterus or womb) that is mismatch repair deficient (dMMR) in patients whose cancer has returned, or it has spread or cannot be removed by surgery. Efficacy was evaluated based on cohort (A1) in GARNET Trial (NCT02715284), a multicenter, multicohort, open-label trial in participants with advanced solid tumors.\(^1\)

![Figure-1: Colorectal cancer](image)

Dostarlimab [CAS: 2022215-59-2] is a drug with laboratory-produced molecules and it acts as substitute antibodies in the human body. Reportedly, all 18 rectal cancer patients were given the same drug and as a result of the treatment, cancer was completely obliterated in every patient. The cancer is undetectable by physical exam; endoscopy; positron emission tomography or PET scans or MRI scans. Protein
formula: $\text{C}_{6420}\text{H}_{9832}\text{N}_{1680}\text{O}_{2014}\text{S}_{44}$. Protein Average Weight: 144000.0 Da (non-glycosylated).

**Medical Uses:** 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. On 17 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.

**Pharmacodynamics:** Dostarlimab is an immunotherapy that facilitates the body's endogenous anti-tumor immune response in the treatment cancer. It is administered over a span of 30 minutes via intravenous infusion every three to six weeks depending on the cycle. Agents that interfere with the PD-1/PD-L1 pathway, including dostarlimab, remove an important immune system inhibitory response and may therefore induce immune-mediated adverse reactions which can be severe or fatal. These reactions can occur in any organ system and can occur at any time after starting therapy, and while they most often manifest during therapy they may also appear after discontinuing the causative agent. Patients receiving therapy with dostarlimab should be monitored closely for evidence of an underlying immune-mediated reaction and evaluated and treated promptly if an immune-mediated reaction is suspected.[2]

**Mechanism of action:** Approximately 13-30% of recurrent endometrial cancers involve microsatellite instability (MSI) or mismatch repair deficiency (dMMR). The mutations resulting in dMMR endometrial cancers are primarily somatic in nature (~90%), although 5-10% of cases involve germline mutations. Cancers that have mutations resulting in dMMR can upregulate the expression of programmed death receptor-1 (PD-1) ligands 1 and 2 (PD-L1 and -L2) - PD-1 is found on T-cells and, when activated, inhibits their proliferation and the production of cytokines. The binding of these ligands to PD-1 thereby functions as an immune checkpoint that downregulates the anti-tumor immune response. Dostarlimab is a monoclonal antibody targeted against PD-1 - it binds to the receptor and prevents interactions with PD-L1 and PD-L2, thus allowing the anti-tumor immune response to proceed unimpeded.
Absorption: During the first cycle, and administered at 500mg intravenously every 3 weeks, the mean Cmax and AUC0-tau of dostarlimab-gxly are 171 mcg/mL and 35,730 mcg.h/mL, respectively. When administered at 1000mg every 6 weeks, the mean Cmax and AUC0-tau are 309 mcg/mL and 95,820 mcg.h/mL, respectively.

Volume of distribution: At steady-state, the mean volume of distribution of dostarlimab is 5.3L.

Metabolism: The metabolism of dostarlimab has not been characterized, but it is expected to be degraded via catabolic pathways into smaller peptides and amino acids.

Half-life: The mean terminal elimination half-life of dostarlimab is 25.4 days.

Clearance: At steady-state, the mean clearance of dostarlimab is 0.007 L/h.

Toxicity: There are no data regarding overdose with dostarlimab. Symptoms of over dosage are likely to be consistent with the adverse effect profile of dostarlimab and may therefore involve significant immune-mediated reactions.

Side effects: Serious adverse reactions in >2% of patients included sepsis, acute kidney injury, urinary tract infection, abdominal pain, and pyrexia. Immune-mediated adverse reactions can occur including pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis, vomiting, joint pain, itching, rash, fever etc.

What are the findings? In an unprecedented first of its kind, every single person in a 12-person group of people with cancer had their tumours vanish fully after being administered an experimental cancer treatment drug treatment called Dostarlimab. The US Food and Drug Administration (FDA) had given the experimental drug Dostarlimab-gxly, a drug candidate created by GlaxoSmithKline, approval for use in patients with recurrent tumours, in August 2021. The trial was performed at the Memorial Sloan Kettering Cancer Center in New York. Single dose dostarlimab was administered every three weeks for six months in patients with mismatch repair–deficient stage II or III rectal adenocarcinoma. This treatment was to be followed by standard chemo radiotherapy and surgery. All 12 patients underwent the course of treatment as well as six months of follow-up care. At the end of the period, tumours in all 12 patients had vanished completely. In May 2022, another treatment procedure had been administered for the first time, with a genetically modified virus CF33-hNIS which would target, infect, and kill cancer cells while leaving healthy cells untouched.
Is Dostarlimab actually very effective? Dostarlimab is not a new drug but a combination of drugs that are already approved for use in immunotherapy. There is a possibility that Dostarlimab may improve the outcome and survival rate in rectal cancer patients but to say it as a magic drug for cancer is completely going overboard.

How does this drug cure? PD1 is a protein that regulates immune function and can sometimes keep T cells from killing cancer cells. The therapy in the trial used PD1 blockades, allowing T cells to kill cancer cells. ‘Mismatch repair deficient’ cancer is most common among colorectal, gastrointestinal, and endometrial cancers. Patients suffering from this condition lack the genes to correct typos in the DNA that occur naturally while cells make copies. Immunotherapy belongs to a category called PD1 blockades that are now recommended for the treatment of such cancers rather than chemotherapy or radiotherapy.[4]

Will Indian patients get access to the drug? At present, Indian doctors seem to be generally wary of prescribing Dostarlimab for their patients. Experts have termed as optimistic the findings of an ongoing trial—a group of rectal cancer patients showed no signs of a tumour after taking the drug for six months. None of the participants reported any severe side-effects either. Yet, doctors say they want to assess the duration of the response.

What do we know about the clinical trial? Cancer was treated in all the patients and could not be detected by physical examination, endoscopy, positron emission tomography, or magnetic resonance imaging. Thus, there is a thought that cancer can be treated without chemotherapy or surgery.

Dosage and administration: Select patients for treatment with JEMPERIL based on presence of dMMR in tumor specimens. Because the effect of prior chemotherapy on test results for dMMR in patients with high grade gliomas is unclear, it is recommended to test for this marker in the primary tumor specimen obtained prior to initiation of temozolomide chemotherapy in patients with high-grade gliomas.

Recommended Dosage: Dose 1 through Dose 4: 500 mg every 3 weeks. Subsequent dosing beginning 3 weeks after Dose 4 (Dose 5 onwards): 1000 mg every 6 weeks. Administer JEMPERIL as an intravenous infusion over 30 minutes. Treat patients until disease progression or unacceptable toxicity.[5]
Preparation and Administration:

Preparation for Intravenous Infusion

- Visually inspect the solution for particulate matter and discoloration. The solution is clear to slightly opalescent, colorless to yellow. Discard the vial if visible particles are observed.
- Do not shake.
- For the 500-mg dose, withdraw 10 mL of JEMPERLI from a vial using a disposable sterile syringe made of polypropylene and dilute into an intravenous infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a final concentration between 2 to 10 mg/mL (maximum 250 mL). JEMPERLI is compatible with an infusion bag made of polyolefin, ethylene vinyl acetate, or polyvinyl chloride with di(2-ethylhexyl) phthalate (DEHP).
- For the 1,000-mg dose, withdraw 10 mL from each of 2 vials (withdraw 20 mL total) and dilute into an intravenous bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a final concentration between 4 to 10 mg/mL (maximum 250 mL).
- Mix diluted solution by gentle inversion. Do not shake.
- Discard any unused portion left in the vial.

Storage of Infusion Solution: Store in the original carton until time of preparation in order to protect from light. The prepared dose may be stored either: At room temperature for no more than 6 hours from the time of preparation until the end of infusion. Under refrigeration at 2°C to 8°C (36ºF to 46ºF) for no more than 24 hours from time of preparation until end of infusion. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Discard after 6 hours at room temperature or after 24 hours under refrigeration. Do not freeze.
Administration: Administer infusion solution intravenously over 30 minutes through an intravenous line using tubing made of polyvinyl chloride or platinum cured silicon; fittings made of polyvinyl chloride or polycarbonate; and a sterile, non-pyrogenic, low-protein binding, 0.2-micron, in-line or add-on filter. JEMPERLI must not be administered as an intravenous push or bolus injection. Do not co-administer other drugs through the same infusion line.

Is it too early to celebrate? Cancer specialists said initial signals show how precision medicine is building the future but they need to test more patients from different areas and other types of cancers.

CONCLUSION:
Dostarlimab is an immunotherapy drug typically used to treat endometrial cancer. This study was the first time it was used to battle rectal cancer tumors. Usually, patients with rectal cancer must endure surgery and chemotherapy — but there was no need for either of those after patients took the drug. Two years later, each of the patients is cancer free, with no trace of cancer whatsoever anywhere in their bodies. The results that have their physicians equally as excited, and ready to see how else this drug could help.

REFERENCES: