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A Review on Dostarlimab: A New FDA Approved Drug for Endometrial Cancer

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Abstract

Endometrial carcinoma is the most common gynecological cancer and mainly affects women in the postmenopausal age group. Each year in India, 122,844 women are diagnosed with cervical cancer and 67,477 die from the disease. The main feature of this drug is that the disease can be cured without surgery or chemotherapy. The emergence of this new drug could improve the state of cancer treatment and therefore offer hope for better control of the disease.

Introduction

Dostarlimab is an anti-PD1 monoclonal antibody used in the treatment of maladaptive repair deficient endometrial cancers. Dostarlimab is a humanised IgG4 monoclonal antibody directed against the human programmed death receptor1 (PD1).6 PD1 receptors are found on T cells and, when activated, serve to inhibit immune responses some tumours exploit this system by overexpressing PD1 ligands, thereby effectively inhibiting the antitumor immune response that would typically attempt to destroy cancer cells. Agents acting on the PD1 pathway, such as nivolumab and pembrolizumab, facilitate endogenous immune-mediated antitumor activity and may therefore be used to treat a wide variety of cancers, including those of the skin, lung, kidney and liver[1].

In April 2021, dostarlimab received accelerated FDA approval as dostarlimabgxly (Jemperli) from GlaxoSmithKline for the treatment of adult patients with recurrent or advanced mis-match repair deficiency (dMMR) endometrial cancer who experience disease progression despite treatment with platinum-containing chemotherapy regimens. Since this accelerated approval was only granted for the treatment of dMMR endometrial cancers, it was approved alongside a diagnostic device associated with the VENTANA MMR RxDx Panel to be used to select appropriate

patients for treatment.[5] The aim of our study is to evaluate the efficacy and safety of Dostarlimab for Endometrial Cancer.

1. Indication

Dostarlimabgxly is indicated for the treatment of adult patients with recurrent mismatch repair deficiency (DMMR) advanced endometrial cancer that has progressed despite current or previous treatment with a platinum-containing chemotherapy regimen.[5]

2. Dostarlimab Chemistry

Dostarlimab is an Immunoglobulin G4, anti-programmed cell death protein 1 (PDCD1) (humanised clone ABT1 gamma4-chain), disulfide with humanised clone ABT1 kappa-chain, dimer with molecular formula C6420-H9832-N1680-O2014-S44 (non-glycosylated)

3. Mechanism of Action

Jemperli (dostarlimabgxly) is an antibody that blocks the programmed death receptor1 (PD1).Binding of PD1, PDL1 and PDL2 ligands to the PD1 receptor present on T cells inhibits T cell proliferation and cytokine production.Upregulation of PD1 ligands occurs in some tumours, and signalling through this pathway may contribute to inhibition of active immune surveillance of T-cell tumors.Dostarlimabgxly is a humanised IgG4 isotype monoclonal antibody that binds to the PD1 receptor and blocks its interaction with PDL1 and PDL2, releasing inhibition of the PD1 pathway-mediated immune response, including the antitumor immune response. Dostarlimab is a monoclonal antibody directed against PD1 that binds to the receptor prevents interactions with PDL1 and PDL2, thus allowing the antitumor immune response to proceed unimpeded.[6]

4. Administration

The recommended dose as monotherapy is 500mg dostarlimab every 3 weeks for 4 cycles followed by 1000mg every 6 weeks for all cycles there after Jemperli is for intravenous infusion only. It should be administered by IV Infusion using an intravenous infusion pump over 30 minutes.

5. Pharmacokinetics

During the first cycle, when administered at 500 mg 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 1000 mg every 6 weeks, the mean Cmax and AUC0-tau are 309 mcg/mL and 95,820 mcg.h/mL, respectively.The mean terminal elimination half-life of dostarlimab is 25.4 days. At steady-state, the mean volume of distribution of dostarlimab is 5.3L and the mean clearance of dostarlimab is 0.007 L/h.The dostarlimab is metabolised into small peptides and amino acids by catabolic pathways. Its clearance is about 0.007L/hr

6. Pre-Clinical Studies

The nonclinical characterization of dostarlimab (TSR-042), a humanised anti-PD-1 antibody, which binds with high affinity to human PD1 and effectively inhibits its interaction with its ligands, PDL1 and PDL2. Dostarlimab enhances effector T-cell functions, including cytokine production, in vitro. Since dostarlimab does not bind mouse PD-1, its single-agent antitumor activity was evaluated using humanised mouse models. In this model system, dostarlimab demonstrated antitumor activity as assessed by tumour growth inhibition, which was associated with increased infiltration of immune cells. Single-dose and four -week repeat-dose toxicology studies in cynomolgus monkeys indicated that dostarlimab was well tolerated.In a

clinical setting, based on data from the GARNET study, dostarlimab (Jemperli) has been approved for the treatment of adult patients with mismatch repair–deficient recurrent or advanced endometrial cancer that had progressed on or following prior treatment with a platinum-containing regimen.[4]

7. Clinical Trials

According to a study conducted in United States, people in the clinical trial had previously received treatments such as chemotherapy, radiotherapy and invasive surgery, which can lead to intestinal, urinary and sexual dysfunctions. All 18 patients are expected to undergo these surgeries as the next step in the research. However, they were surprised to learn that no further therapy was needed. Experts were stunned by the results of the studies, saying complete remission in a single patient is "unheard of"[7] .

For patients with endometrial malignancies with insufficient mismatch mutation repair after prior platinum-based chemotherapy, dostarlimab was linked to clinically significant and long-lasting antitumor efficacy with a favourable safety profile 3 . Both dMMR/MSI-H (ORR 43.5%) and MMRp/MSS EC (ORR 14.1%) tumour models of dostarlimab showed persistent anticancer activity with a tolerable safety profile [2].

8. FDA Approval

On August 17, 2021, the FDA approved dostarlimab- gxly(brand name Jemperli) for adult cases with mismatch repair-deficient intermittent or advanced solid tumours, as determined by an FDA-approved test, that have progressed on or following previous treatment and who have no satisfactory indispensable treatment options.March nineteen, 2019 Data from the GARNET study indicates Robust activity of Dostarlimab in patients with advanced or recurrent endometrial cancer.April 28, 2020 GSK Presents new data from the GARNET study demonstrates potential of Dostarlimab to treat a subset of women with recurrent or advanced endometrial cancer.January 16, 2021 GSK presents positive efficacy data of Dostarlimab in mismatch repair-deficient(dMMR) solid cancers at ASCO gastrointestinal cancers Symposium.April 22,2021 FDA approves Jemperli (Dostarlimab- gxly) for women with recurrent or advanced dMMR Endometrial cancer.August 17, 2021 GSK receives FDA accelerated approval for jemperli (Dostarlimab- gxly) for adult patients with mismatch repair-deficient (DMMR) recurrent or advanced solid tumors [7].

9. Adverse Effect

The most common adverse effects include fatigue, lymphopenia, hypoalbuminemia, nausea, increased creatinine, hyponatremia, diarrhoea, increased ALP, Anaemia, leukopenia, constipation, vomiting, increased AST, hypercalcemia, increased ALT, hypokalemia, decreased appetite, cough, pruritus, urinary tract infection, myalgia.Immune mediated adverse reactions (such as, immune mediated pneumonitis,colitis, hepatitis, endocrinopathies,Nephritis with renal dysfunction, rash or dermatitis bullous and exfoliative dermatitis, DRESS syndrome, SJS). Nervous system involvement include Meningitis, encephalitis, myelitis, myasthenic syndrome.

10. Drug Interaction

10.1 Antibiotics may reduce the therapeutic effect of immune checkpoint inhibitors.

10.2 Risk c- monitor therapy

10.3 Corticosteroids(systemic): may diminish the therapeutic effect of immune checkpoint inhibitors.Risk D- consider therapy modification

10.4 Efgartigimod alfa- may diminish the therapeutic effect of Fc receptor binding agents. Risk C- monitor therapy

10.5 Ketoconazole (systemic)- immune checkpoint inhibitors may enhance the hepatotoxic effect of ketoconazole. Risk C- Monitor therapy

10.6 Inhibitors of the proton pump(PPIs and PCABs)- may diminish the therapeutic effect of immune checkpoint inhibitors. Risk C-Monitor therapy.

11. Cautions

May cause severe or dangerous infusion-related reactions; monitor for signs and symptoms of infusion related reactions. Severe infections (sepsis, herpes encephalitis, mycobacterial infections) resulting in retroperitoneal harm were reported; most typical infection was higher tract infections; monitor for signs and symptoms of infection. and Can cause foetal harm[8].

12. Elderly

No dose adjustment is recommended for those who are aged 65 years or over. There is limited clinical data with dosatarlimab in patients aged 75 years and over.

13. Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment. There is limited data in patients with severe renal impairment or End stage disease undergoing dialysis.

14. Hepatic Impairment

No dosage adjustment is recommended in patients with mild hepatic impairment. There is limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment.

15. Hepatic Impairment

No dosage adjustment is recommended in patients with mild hepatic impairment. There is limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment.

16. Paediatric Population

The safety and efficacy of jenperli in children and adolescents aged under 18 years have not been established. No data is available.

Limitations

Limited knowledge regarding the long term efficacy of Dostarlimab and long term adverse effects of Dostarlimab are still needed to monitor. Dostarlimab is expensive, so it is not affordable for everyone.

Conclusion

Recent approval of dostarlimab provides a range of treatments for cancer (endometrium and colorectal). It heals much faster and has fewer side effects than other treatments. Dostarlimab as a single agent results in sustained antitumor activity in patients with advanced or recurrent endometrial cancer with mismatch repair deficiency / microsatellite instability-high or mismatch repair capacity / mismatch stability disease.

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Abbreviations

1. ALP- Alkaline Phosphatase
2. ASCO-American Society of Clinical Oncology
3. AST- Aspartate Transaminase
4. dMMR- Deficient mis-match repair
5. DRESS- Drug reaction with eosinophilia and systemic symptoms
6. FDA- Food and Drug administration
7. IgG4- Immunoglobulin G4
8. ORR- Overall Response Rate
9. PD1- Programmed Death-1
10. SJS- Stevens-Johnson syndrome