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GSK receives FDA accelerated approval for JEMPERLI (dostarlimab-gxly) for adult patients with mismatch repair-deficient (dMMR) recurrent or advanced solid tumours

For media and investors only

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- Second FDA approved indication for dostarlimab in 2021
- GARNET study demonstrated objective response rate of 41.6% across dMMR solid tumours
- 95% of responders had a duration of response of ≥6 months

GlaxoSmithKline (GSK) plc today announced the US Food and Drug Administration (FDA) approved a new indication for JEMPERLI (dostarlimab-gxly), a programmed cell death receptor-1 (PD-1) blocking antibody, for the treatment of adult patients with mismatch repair-deficient (dMMR) recurrent or advanced solid tumours, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options. This indication received accelerated approval based on tumour response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Dr Hal Barron, Chief Scientific Officer and President R&D, GSK, said: "For patients with tumours expressing the dMMR biomarker, there continues to be a significant need for new and effective treatments. I'm excited about GSK's second oncology FDA approval this year, and the new treatment option it provides for these patients."

Mismatch repair-deficient tumours contain abnormalities that affect the proper repair of DNA when copied in a cell[i]. In the US, prevalence of dMMR across patients with solid tumours has been estimated at 14%[ii]. Mismatch repair-deficient status is a biomarker that has been shown to predict response to immune checkpoint blockade with PD-1 therapy.[iii][iv] Tumours with this biomarker are most commonly found in endometrial, colorectal and other gastrointestinal cancers, but may also be found in other solid tumours.[i][ii] [v]

Dr Jubilee Brown, Professor and Division Director of Gynecologic Oncology at Atrium Health Levine Cancer Institute, and investigator on the GARNET study, said: "Dostarlimab is an important new treatment option for patients with mismatch repair-deficient recurrent or advanced solid cancers who have progressed and have no alternative options. As we saw in the GARNET trial, of those patients who respond to treatment with dostarlimab, nearly all continued to respond for six months or longer."

This new indication follows an FDA priority review of the Biologics License Application and is based on the collective results from the dMMR endometrial cancer cohort A1 and the dMMR solid-tumour (non-endometrial cancer) cohort F of the ongoing GARNET trial. The GARNET trial is a multicentre, non-randomised, multiple parallel-cohort, open-label study. Cohort F included patients with dMMR recurrent or advanced non-endometrial cancers, with the highest prevalence in colorectal, small intestine and stomach cancers.

The major efficacy outcomes of the GARNET trial are objective response rate (ORR) and duration of response (DoR), as assessed against RECIST v 1.1 by blinded independent central review. Results in all dMMR solid tumours, including endometrial and non-endometrial solid tumours (n=209), demonstrated an ORR of 41.6% (95% CI; 34.9-48.6) with a complete response rate of 9.1% and a partial response rate of 32.5%. The median DoR was 34.7 months (range 2.6-35.8+) with 95.4% of patients maintaining a response for six months or longer. In the dMMR solid tumour non-endometrial cancer cohort (n=106), results demonstrated an ORR of 38.7% (95% CI; 29.4-48.6).

Patients received 500 mg of dostarlimab as an intravenous infusion once every three weeks for four doses, followed by 1,000 mg once every six weeks until disease progression or unacceptable toxicity. Among the 267 patients with recurrent or advanced dMMR solid tumours who were evaluable for safety, the most commonly reported adverse reactions (≥20%) were fatigue/asthenia (42%), anaemia (30%), diarrhoea (25%) and nausea (22%). The most common Grade 3 or 4 adverse reactions (≥2%) were anaemia, fatigue/asthenia, increased transaminases, sepsis and acute kidney injury. Grade 3 or 4 laboratory abnormalities (≥2%) included decreased lymphocytes, decreased sodium, increased alkaline phosphatase and decreased albumin.

In April 2021, the FDA granted accelerated approval for dostarlimab for the treatment of adult patients with dMMR recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that have progressed on or following prior treatment with a platinum-containing regimen. This approval was based on data from cohort A1, which included 71 patients with dMMR endometrial cancer.

With the dMMR solid-tumour approval, the US prescribing information for this indication includes efficacy data for an additional 32 patients in the endometrial cancer cohort A1 (n=103). The additional results for this cohort show an ORR of 44.7% (95% CI; 34.9-54.8) with a DoR range of 2.6-35.8+ months. The results of the endometrial cancer cohort of the GARNET trial represent the largest dataset to date evaluating an anti-PD-1 as monotherapy treatment for women with endometrial cancer.

As we work to expand our oncology pipeline and portfolio of cancer treatments, GSK is also studying dostarlimab in earlier lines of treatment for endometrial cancer and in combination with other therapeutic agents for patients with advanced/metastatic cancers beyond endometrial cancer.

About GARNET
The ongoing phase I GARNET trial is evaluating dostarlimab as monotherapy in patients with advanced solid tumours. Part 2B of the study includes five expansion cohorts: dMMR/MSI-H endometrial cancer (cohort A1), mismatch repair proficient/microsatellite stable (MMRp/MSS) endometrial cancer (cohort A2), non-small cell lung cancer (cohort E), dMMR/MSI-H non-endometrial or POLE-mut solid tumour basket cohort (cohort F), and platinum-resistant ovarian cancer without BRCA mutations (cohort G). Patients enrolled in cohort A1 needed to have progressed on or following prior treatment with a platinum-containing regimen, whereas, patients enrolled in cohort F needed to have progressed following systemic therapy and had no satisfactory alternative treatment options; patients with colorectal cancer must have had progressive disease after, or have been intolerant to, a fluoropyrimidine, oxaliplatin, and irinotecan.

About Mismatch Repair Deficiency
In normal cells, mismatch repair (MMR) is a process that corrects errors introduced during DNA replication via enzymes. Under normal conditions, the enzymes as part of the MMR system restore DNA integrity by detecting and fixing the erroneous strands **[vi]**. When this repair mechanism is defective, it is known as mismatch repair-deficient (dMMR). DMMR is the result of the enzymes no longer functioning properly, leading to errors in the DNA that go unchecked. A dMMR system may result in the accumulation of these errors and may lead to cancer.**[i]** **[vi]** According to results from a structured literature review and meta-analysis investigating pooled prevalence estimates of dMMR across solid tumours, prevalence of dMMR across solid tumours in the US has been estimated at 14%.**[ii]**

About JEMPERLI (dostarlimab-gxly)
JEMPERLI is a programmed death receptor-1 (PD-1)-blocking antibody that binds to the PD-1 receptor and blocks its interaction with the PD-1 ligands PD-L1 and PD-L2. **[vii]** In addition to GARNET, JEMPERLI is being investigated in other registrational enabling studies, as monotherapy and as part of combination regimens, including in women with recurrent or primary advanced endometrial cancer, women with stage III or IV non-mucinous epithelial ovarian cancer, and in patients with other advanced solid tumours or metastatic cancers.

JEMPERLI was discovered by AnaptysBio and licensed to TESARO, Inc., under a Collaboration and Exclusive License Agreement signed in March 2014. The collaboration has resulted in three monospecific antibody therapies that have progressed into the clinic. These are: JEMPERLI (GSK4057190), a PD-1 antagonist; cobolimab, (GSK4069889), a TIM-3 antagonist; and GSK4074386, a LAG-3 antagonist. GSK is responsible for the ongoing research, development, commercialization, and manufacture of each of these Products under the Agreement.

Important Safety Information for JEMPERLI

Indications
JEMPERLI is indicated for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced:

- endometrial cancer (EC), as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen, or
- solid tumours, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.

These indications are approved under accelerated approval based on tumour response rate and durability of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Important Safety Information

Severe and Fatal Immune-Mediated Adverse Reactions

- Immune-mediated adverse reactions, which can be severe or fatal, can occur in any organ system or tissue and can occur at any time during or after treatment with a PD-1/PD-L1–blocking antibody, including JEMPERLI.
- Monitor closely for signs and symptoms of immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function tests at baseline and periodically during treatment. For suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.
- Based on the severity of the adverse reaction, withhold or permanently discontinue JEMPERLI. In general, if JEMPERLI requires interruption or discontinuation, administer systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until improvement to ≤Grade 1. Upon improvement to ≤Grade 1, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroids.

Immune-Mediated Pneumonitis

- JEMPERLI can cause immune-mediated pneumonitis, which can be fatal. In patients treated with other PD-1/PD-L1–blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Pneumonitis occurred in 1.4% (7/515) of patients, including Grade 2 (1.2%) and Grade 3 (0.2%) pneumonitis.

Immune-Mediated Colitis

- Colitis occurred in 1.4% (7/515) of patients, including Grade 2 (0.8%) and Grade 3 (0.6%) adverse reactions. Cytomegalovirus infection/reactivation have occurred in patients with corticosteroid-refractory immune-mediated colitis. In such cases, consider repeating infectious workup to exclude alternative etiologies.

Immune-Mediated Hepatitis

- JEMPERLI can cause immune-mediated hepatitis, which can be fatal. Grade 3 hepatitis occurred in 0.2% (1/515) of

patients.

Immune-Mediated Endocrinopathies

- Adrenal Insufficiency
  - Adrenal insufficiency occurred in 1.4% (7/515) of patients, including Grade 2 (0.8%) and Grade 3 (0.6%). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment per institutional guidelines, including hormone replacement as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity.
- Hypophysitis
  - JEMPERLI can cause immune-mediated hypophysitis. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity.
- Thyroid Disorders
  - Thyroiditis occurred in 0.4% (2/515) of patients; both were Grade 2. Hypothyroidism occurred in 7.2% (37/515) of patients, all of which were Grade 2. Hyperthyroidism occurred in 1.9% (10/515) of patients, including Grade 2 (1.7%) and Grade 3 (0.2%). Initiate hormone replacement or medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity.
- Type 1 Diabetes Mellitus, Which Can Present with Diabetic Ketoacidosis
  - JEMPERLI can cause type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity.

Immune-Mediated Nephritis with Renal Dysfunction

- JEMPERLI can cause immune-mediated nephritis, which can be fatal. Nephritis occurred in 0.4% (2/515) of patients; both were Grade 2.

Immune-Mediated Dermatologic Adverse Reactions

- JEMPERLI can cause immune-mediated rash or dermatitis. Bullous and exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS), have occurred with PD-1/PD-L1–blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes. Withhold or permanently discontinue JEMPERLI depending on severity.

Other Immune-Mediated Adverse Reactions

- The following clinically significant immune-mediated adverse reactions occurred in <1% of the 515 patients treated with JEMPERLI or were reported with the use of other PD-1/PD-L1–blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.
  - Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy
  - Cardiac/Vascular: Myocarditis, pericarditis, vasculitis
  - Ocular: Uveitis, iritis, other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur
  - Gastrointestinal: Pancreatitis, including increases in serum amylase and lipase levels, gastritis, duodenitis
  - Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica
  - Endocrine: Hypoparathyroidism
  - Other (Hematologic/Immune): Autoimmune hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenia, solid organ transplant rejection

Infusion-Related Reactions

- Severe or life-threatening infusion-related reactions have been reported with PD-1/PD-L1–blocking antibodies. Severe infusion-related reactions (Grade 3) occurred in 0.2% (1/515) of patients receiving JEMPERLI. Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion or permanently discontinue JEMPERLI based on severity of reaction.

Complications of Allogeneic HSCT

- Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after treatment with a PD-1/PD-L1–blocking antibody, which may occur despite intervening therapy. Monitor patients closely for transplant-related complications and intervene promptly.

Embryo-Fetal Toxicity and Lactation

- Based on its mechanism of action, JEMPERLI can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with JEMPERLI and for 4 months after their last dose. Because of the potential for serious adverse reactions from JEMPERLI in a breastfed child, advise women not to breastfeed during treatment with JEMPERLI and for 4 months after their last dose.

Common Adverse Reactions

- The most common adverse reactions (≥20%) in patients with dMMR EC were fatigue/asthenia, nausea, diarrhea, anemia, and constipation. The most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased sodium, decreased leukocytes, decreased albumin, increased creatinine, increased alkaline phosphatase and increased alanine aminotransferase.

- The most common adverse reactions (≥20%) in patients with dMMR solid tumours were fatigue/asthenia, anemia, diarrhea, and nausea. Most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased sodium, increased alkaline phosphatase, and decreased albumin.

Please see full Prescribing Information

GSK in Oncology
GSK is focused on maximising patient survival through transformational medicines. GSK's pipeline is focused on immuno-oncology, cell therapy, tumour cell targeting therapies and synthetic lethality. Our goal is to achieve a sustainable flow of new treatments based on a diversified portfolio of investigational medicines utilising modalities such as small molecules, antibodies, antibody drug conjugates and cells, either alone or in combination.

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