FDA grants accelerated approval for GSK’s JEMPERLI (dostarlimab-gxly) for women with recurrent or advanced dMMR endometrial cancer

PUBLISHED APR 22, 2021
BY GSK

For media and investors only

- GARNET study represents the largest dataset of anti-PD-1 monotherapy treatment of women with endometrial cancer

- Study results showed an overall response rate of 42%

- 93% of responders had a duration of response of ≥6 months

GlaxoSmithKline plc today announced that the US Food and Drug Administration (FDA) has approved JEMPERLI (dostarlimab-gxly), a programmed death receptor-1 (PD-1) blocking antibody, based on the company’s Biologics License Application. Dostarlimab is indicated for the treatment of adult patients with mismatch repair-deficient (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 indication is approved under 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:

> Unfortunately, as many as 60,000 women are diagnosed with endometrial cancer in the US each year and these women currently have limited treatment options if their disease progresses on or after first-line therapy. Today’s approval of dostarlimab by the FDA has the potential to transform the

> treatment landscape for these women and demonstrates our continued commitment to helping patients with gynaecologic cancers.

Around 1 in 4 women with endometrial cancer may experience a recurrence or be diagnosed with advanced disease., For women whose disease recurs after platinum-based chemotherapy, there is generally no accepted standard of care.,, Additionally, endometrial cancer has the highest rate of dMMR among tumour types, at approximately 25%,vii and increased rates of recurrence have been reported for women with dMMR endometrial cancer.

Dr Jubilee Brown, Professor and Division Director of Gynaecologic Oncology at Levine Cancer Institute, Atrium Health, and investigator on the GARNET study, noted:

> The approval of dostarlimab has the potential to change the way we've been treating dMMR advanced or recurrent endometrial cancer after standard platinum-based chemotherapy, especially given the overall response rate and durability of response that we saw in the GARNET trial.

The approval is based on results from the dMMR endometrial cancer cohort of the ongoing GARNET trial, a large, multicentre, non-randomised, multiple parallel-cohort, open-label study, representing the largest dataset to date evaluating an anti-PD-1 antibody as monotherapy treatment in women with endometrial cancer.v The approval was granted under the FDA's Real-Time Oncology Review pilot programme, and dostarlimab was initially granted breakthrough therapy designation in May of 2019 for recurrent or advanced dMMR endometrial cancer.

The primary endpoints in the GARNET trial were overall response rate (ORR) and duration of response (DOR) as assessed by blinded independent central review (BICR). Results showed an ORR of 42.3% (95% CI; 30.6-54.6) with a complete response (CR) rate of 12.7% and partial response rate (PR) of 29.6% among the 71 evaluable patients with dMMR advanced or recurrent endometrial cancer who had progressed on or after treatment with a platinum-containing regimen. Of those that responded, 93.3% demonstrated a DOR of 6 months or more. After a median follow-up of 14.1 months, the median duration of response was not reached (2.6-22.4+).

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 104 patients evaluable for safety, the most commonly reported adverse reactions (occurring in 20% or more of patients) were fatigue/asthenia (48%), nausea (30%), diarrhoea (26%), anaemia (24%) and constipation (20%). The most common Grade 3 or 4 adverse reactions (≥2%) were anaemia and transaminases increase. Dostarlimab was permanently discontinued due to adverse reactions in 5 (4.8%) patients. No deaths attributed to dostarlimab were reported in the study.

Dr Sue Friedman, Executive Director of Facing Our Risk of Cancer Empowered (FORCE), commented:

> We applaud GSK and their ongoing efforts to support women with endometrial cancer, the most common gynaecologic malignancy in the US and the sixth most common cancer in women worldwide. For many women whose disease is dMMR and has progressed after platinum-based chemotherapy, the approval of dostarlimab brings a new treatment option to an underserved patient population.

GSK is also studying dostarlimab for endometrial cancer in earlier treatment lines and in combination with other therapeutic agents for patients with advanced solid tumours or metastatic cancer as we work to expand our oncology pipeline and reinforce our portfolio of cancer treatments.

Endometrial cancer is a main type of uterine cancer that forms in the inner lining of the uterus, known as the endometrium. Endometrial cancer can be classified as mismatch repair-deficient/microsatellite instability-high (dMMR/MSI-H) or mismatch repair-proficient/microsatellite stable. There are limited treatment options for women whose disease progresses on or after first-line therapy. Nearly 60,000 new cases of endometrial cancer are expected in the US in 2021, making endometrial cancer the most common gynaecologic malignancy in the US. , Approximately 25% of women with endometrial cancer will be diagnosed with advanced disease or will experience a recurrence.,

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). GARNET is still enrolling patients.

About JEMPERLI (dostarlimab-gxly)

Dostarlimab 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.xiii In addition to GARNET, dostarlimab is being investigated in other registrational enabling studies, as monotherapy and as part of combination regimens for women with recurrent or primary advanced endometrial cancer stage III or IV non-mucinous epithelial ovarian cancer for patients with advanced solid tumours or metastatic cancer.

Dostarlimab 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: dostarlimab (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

- 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.

- This indication is approved under 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).

Important Safety Information

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. The incidence of pneumonitis in patients receiving PD-1/PD-L1 inhibitors, including JEMPERLI, may be increased in patients who have received prior thoracic radiation.

- Immune-mediated pneumonitis occurred in 1.1% (5/444) of patients, including Grade 2 (0.9%) and Grade 3 (0.2%) pneumonitis. Pneumonitis led to discontinuation of JEMPERLI in 0.7% of patients. Systemic corticosteroids were required in all patients with pneumonitis. Pneumonitis resolved in 80% of the 5 patients. Three patients reinitiated JEMPERLI after symptom improvement; of these, 33% had recurrence of pneumonitis.

- JEMPERLI can cause immune-mediated colitis. Cytomegalovirus infection/reactivation have occurred in patients with corticosteroid-

refractory immune-mediated colitis treated with PD-1/PD-L1–blocking antibodies. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

- Immune-mediated colitis occurred in 1.4% (6/444) of patients, including Grade 3 (0.7%) and Grade 2 (0.7%). Colitis did not lead to discontinuation of JEMPERLI in any patients. Systemic corticosteroids were required in 17% (1/6) of patients with colitis. Colitis resolved in 50% of the 6 patients. Of the 2 patients in whom JEMPERLI was withheld for colitis, both reinitiated JEMPERLI.

- JEMPERLI can cause immune-mediated hepatitis, which can be fatal. Immune-mediated Grade 3 hepatitis occurred in 0.2% (1/444) of patients. Systemic corticosteroids were required, and the event resolved.

Immune-Mediated Endocrinopathies

- JEMPERLI can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment per institutional guidelines, including hormone replacement as clinically indicated. Withhold JEMPERLI if not clinically stable. Adrenal insufficiency occurred in 0.9% (4/444) of patients, including Grade 3 (0.5%) and Grade 2 (0.5%). Adrenal insufficiency resulted in discontinuation in 1 (0.2%) patient and resolved in 25% of the 4 patients.

- JEMPERLI can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold JEMPERLI if not clinically stable.

- JEMPERLI can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement or medical management of hyperthyroidism as clinically indicated. Withhold JEMPERLI if not clinically stable.

- Thyroiditis occurred in 0.5% (2/444) of patients; both were Grade 2. Neither event of thyroiditis resolved; there were no discontinuations of JEMPERLI due to thyroiditis.

- Hypothyroidism occurred in 5.6% (25/444) of patients, all of which were Grade 2. Hypothyroidism did not lead to discontinuation of JEMPERLI and resolved in 40% of the 25 patients. Systemic corticosteroids were not required for any of the 25 patients with hypothyroidism.

- Hyperthyroidism occurred in 1.8% (8/444) of patients, including Grade 2 (1.6%) and Grade 3 (0.2%). Hyperthyroidism did not lead to discontinuation of JEMPERLI and resolved in 63% of the 8 patients. Systemic corticosteroids were not required for any of the 8 patients with hyperthyroidism.

- 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 0.5% (2/444) of patients; both were Grade 2. Nephritis did not lead to discontinuation of JEMPERLI and resolved in both patients. Systemic corticosteroids were required in 1 of the 2 patients experiencing nephritis.

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

- 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): Haemolytic anaemia, aplastic anaemia, 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% (1/444) of patients receiving JEMPERLI. All patients recovered from the infusion-related reactions.

- 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 after PD-1/PD-L1–Blocking Antibody:

- 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. These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1–blocking antibody prior to or after an allogeneic HSCT.

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.

- The most common adverse reactions (Grades 1-4) in ≥10% of 104 dMMR endometrial cancer patients who received JEMPERLI as monotherapy were fatigue (48%), nausea (30%), diarrhoea (26%), anaemia (24%), constipation (20%), vomiting (18%), pruritus (14%), cough (14%), decreased appetite (14%), urinary tract infection (13%), and myalgia (12%).

- JEMPERLI was permanently discontinued due to adverse reactions in 5 (4.8%) patients, including transaminases increased, sepsis, bronchitis, and pneumonitis. Dosage interruptions due to an adverse reaction occurred in 23% of patients who received JEMPERLI. Adverse reactions that required dosage interruption in ≥1% of patients who received JEMPERLI were anaemia, diarrhoea, increased lipase, and pyrexia.

Please see full Prescribing Information

GSK is focused on maximising patient survival through transformational medicines. GSK's pipeline is focused on immuno-oncology, cell therapy, cancer epigenetics 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.

GSK is a science-led global healthcare company with a special

purpose: to help people do more, feel better, live longer. For further information please visit www.gsk.com/aboutus.

Cautionary statement regarding forward-looking statements

GSK cautions investors that any forward-looking statements or projections made by GSK, including those made in this announcement, are subject to risks and uncertainties that may cause actual results to differ materially from those projected. Such factors include, but are not limited to, those described in the Company's Annual Report on Form 20-F for 2020 and any impacts of the COVID-19 pandemic.

CancerMPact® Patient Metric, Kantar. Available from www.cancermpact.com. Accessed 18 March 2020.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Uterine Neoplasms V1.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed 17 April 2020. SGO Clinical Practice Endometrial Cancer Working Group.

Burke WM, Orr J, Leitao M, et al. Endometrial Cancer: a review and current management strategies: part II. Gynecol Oncol. 2014;134(2):393-402.

Brooks RA, Flemming GF, Lastra RR, et al. Current recommendations and recent progress in endometrial cancer. CA Cancer J Clin. 2019;69(4):258-279.

Oaknin A, Tinker AV, Gilbert L, et al. Clinical activity and safety of the anti–programmed death 1 monoclonal antibody dostarlimab for patients with recurrent or advanced mismatch repair–deficient endometrial cancer: a nonrandomized phase 1 clinical trial. JAMA Oncol. 2020;6(11):1766-1772.

Le DT, Durham JN Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357(6349):409-413.

Lorenzi M, Amonkar M, Zhang J, et al. Epidemiology of microsatellite instability high (MSI-H) and deficient mismatch repair (dMMR) in solid tumor: a structured literature review. Journal of Oncology. 2020; Article ID 18079.

Backes FJ, Haag J, Cosgrove CS, et al. Mismatch repair deficiency identifies patients with high-intermediate risk (HIR) endometrioid endometrial cancer at the highest risk of recurrence: a prognostic biomarker. Cancer. 2019;125(3):398-405.

Endometrial Cancer Treatment (PDQ®) – Health Professional Version. National Cancer Institute. https://www.cancer.gov/types/uterine/hp/endometrial-treatment-pdq. Accessed May 2020.

Cancer Facts & Figures 2021. American Cancer Society. Accessed 30 March 2021. https://www.cancer.org/content/dam/cancer-org/research/cancer-....

Fung-Kee-Fung M, Dodge J, Elit L, et al. Follow-up after primary therapy for endometrial cancer: a systematic review. Gynecol Oncol. 2006;101(3):520-529.

Press release distributed by Wire Association on behalf of GSK, on Apr 22, 2021. For more information subscribe and follow us.

Media Assets

Embedded Media

Visit the online press release to interact with the embedded media.

https://wireassociation.eu/newsroom/gsk/releases/en/fda-grants-accelerated-approval-for-gsks-jemperli-dostarlimab-gxly-for-women-with-recurrent-or-advanced-dmmr-endometrial-cancer-1951

GSK

Newsroom: https://wireassociation.eu/newsroom/gsk
Website: https://www.gsk.com/
Primary Email: corporate.media@gsk.com

Social Media

Facebook - https://www.facebook.com/GSK
Twitter - http://twitter.com/GSK
Youtube - http://www.youtube.com/GSK
Linkedin - http://www.linkedin.com/company/glaxosmithkline
Instagram - https://www.instagram.com/gsk/