Stock-exchange announcement
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Jemperli (dostarlimab-gxly) receives US FDA Breakthrough Therapy Designation for locally advanced dMMR/MSI-H rectal cancer

- Designation based on data showing no evidence of disease in 100% of all 42 patients who completed treatment with dostarlimab-gxly
- Breakthrough Therapy Designation granted to drugs with potential to show improvement over available therapies for serious conditions
- Current standard of care can be associated with significant negative quality-of-life effects, highlighting the need for new options

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GSK plc (LSE/NYSE: GSK) announced today that the US Food and Drug Administration (FDA) has granted Breakthrough Therapy Designation for *Jemperli* (dostarlimab-gxly) for the treatment of patients with locally advanced mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) rectal cancer. The Breakthrough Therapy Designation aims to expedite the development and review of drugs with the potential to treat a serious condition and where preliminary clinical evidence may indicate substantial improvement over currently available therapy.[1] This is the second regulatory designation for dostarlimab-gxly in locally advanced dMMR/MSI-H rectal cancer, following Fast Track designation for the same patient population in January 2023.[2]

Hesham Abdullah, Senior Vice President, Global Head Oncology, R&D, GSK, said: "Today's designation, which is based on the unprecedented 100% clinical complete response rate of dostarlimab-gxly reported to date, supports a path to help change the treatment paradigm for patients with locally advanced dMMR/MSI-H rectal cancer, who face long-term adverse quality-of-life effects. Our registrational AZUR-1 trial is continuing to study dostarlimab-gxly in this patient population."

The US FDA's Breakthrough Therapy Designation is supported by preliminary clinical evidence from the ongoing phase II GSK supported collaborative study with Memorial Sloan Kettering Cancer Center. In frontline locally advanced dMMR rectal cancer, the trial has shown an unprecedented 100% clinical complete response (cCR) in all 42 patients who completed treatment with dostarlimab-gxly, defined as no evidence of tumors as assessed by magnetic resonance imaging, endoscopy, PET scan and digital rectal exam. In the first 24 patients evaluated, a sustained cCR with a median follow-up of 26.3 months (95% CI: 12.4-50.5) was observed. The safety and tolerability profile of dostarlimab-gxly was generally consistent with the known safety profile of the agent. No adverse events of grade 3 or higher were reported in this trial.[3] The trial continues to evaluate enrolled patients. GSK's ongoing phase II registrational AZUR-1 trial in locally advanced dMMR/MSI-H rectal cancer aims to confirm the findings of this supported collaborative study.

The current standard of care for patients with dMMR/MSI-H locally advanced rectal cancer is initial treatment with chemotherapy plus radiation followed by surgery to remove the tumor along with portions of the intestine and/or surrounding tissue.[4] This results in initial positive outcomes for most patients, but nearly one-third ultimately die from cancer that has spread to other parts of the body (distant metastasis).[5] Additionally, the surgery and chemoradiotherapy associated with standard of care can lead to long-term negative impact on quality-of-life, including bowel, urinary and sexual dysfunction, secondary cancers and infertility.[2]

Dostarlimab-gxly is not approved anywhere in the world for the frontline treatment of locally advanced dMMR/MSI-H rectal cancer.

About dMMR/MSI-H rectal cancer
Rectal cancer is a form of cancer that starts in the rectum, the final section of the large intestine, and is often categorized as part of a group of cancers called colorectal cancer. Colorectal cancer is the third most commonly diagnosed cancer in the world. [6] In the US, it is estimated that approximately 46,220 individuals are diagnosed annually with rectal cancer. [7] Approximately 5-10% of all rectal cancers are dMMR/ MSI-H, meaning that they contain abnormalities that affect the proper repair of DNA when copied in a cell.[8] Mismatch repair deficient status is a biomarker that has been shown to predict response to immune checkpoint blockade with PD-1 therapy.[9,10] Tumors with this biomarker are most commonly found in endometrial, colorectal and other gastrointestinal cancers but may also be found in other solid tumors.[11-14]

About *Jemperli* (dostarlimab-gxly)
Jemperli, a programmed death receptor-1 (PD-1)-blocking antibody, is the backbone of GSK's ongoing immuno-oncology-based research and development program. A robust clinical trial program includes studies of *Jemperli* alone and in combination with other therapies in gynecologic, colorectal and lung cancers, as well as where there are opportunities for transformational outcomes.

In the US, *Jemperli* is indicated in combination with carboplatin and paclitaxel, followed by *Jemperli* as a single agent for the treatment of adult patients with primary advanced or recurrent endometrial cancer. This includes patients with mismatch repair proficient/microsatellite stable (MMRp/MSS) and dMMR/MSI-H tumors. *Jemperli* is also approved as a single agent for adult patients with dMMR recurrent or advanced endometrial cancer, as determined by a US FDA-approved test, that has progressed on or following a prior platinum-containing regimen in any setting and are not candidates for curative surgery or radiation. Additionally, *Jemperli* is indicated in the US for patients with dMMR recurrent or advanced solid tumors, as determined by a US FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options. The latter indication is approved in the US under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication in solid tumors may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Jemperli was discovered by AnaptysBio, Inc. and licensed to TESARO, Inc., under a collaboration and exclusive license agreement signed in March 2014. Under this agreement, GSK is responsible for the ongoing research, development, commercialization, and manufacturing of *Jemperli* and cobolimab (GSK4069889), a TIM-3 antagonist.

Indications and Important Safety Information for JEMPERLI (dostarlimab-gxly)
- JEMPERLI, in combination with carboplatin and paclitaxel, followed by JEMPERLI as a single agent, is indicated for the treatment of adult patients with primary advanced or recurrent endometrial cancer (EC).
- JEMPERLI, as a single agent, is indicated for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced:
    - EC, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen in any setting and are not candidates for curative surgery or radiation, or
    - 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. This indication is approved under accelerated approval based on tumor 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

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 2.3% (14/605) of patients, including Grade 2 (1.3%), Grade 3 (0.8%), and Grade 4 (0.2%) pneumonitis.

Immune-Mediated Colitis

- Colitis occurred in 1.3% (8/605) of patients, including Grade 2 (0.7%) and Grade 3 (0.7%) 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 0.5% (3/605) of patients.

Immune-Mediated Endocrinopathies

- Adrenal Insufficiency
  - Adrenal insufficiency occurred in 1.2% (7/605) of patients, including Grade 2 (0.5%) and Grade 3 (0.7%). 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. Grade 3 hypophysitis occurred in 0.4% (1/241) of patients receiving JEMPERLI in combination with carboplatin and paclitaxel. Grade 2 hypophysitis occurred in 0.2% (1/605) of patients receiving JEMPERLI as a single agent. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity.
- Thyroid Disorders
  - Grade 2 thyroiditis occurred in 0.5% (3/605) of patients. Grade 2 hypothyroidism occurred in 12% (30/241) of patients receiving JEMPERLI in combination with carboplatin and paclitaxel. Grade 2 hypothyroidism occurred in 8% (46/605) of patients receiving JEMPERLI as a single agent. Hyperthyroidism occurred in 3.3% (8/241) of patients receiving JEMPERLI in combination with carboplatin and paclitaxel, including Grade 2 (2.9%) and Grade 3 (0.4%). Hyperthyroidism occurred in 2.3% (14/605) of patients receiving JEMPERLI as a single agent, including Grade 2 (2.1%) and Grade 3 (0.2%). Initiate thyroid 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. Grade 3 type 1 diabetes mellitus occurred in 0.4% (1/241) of patients receiving JEMPERLI in combination with carboplatin and paclitaxel. Grade 3 type 1 diabetes mellitus occurred in 0.2% (1/605) of patients

receiving JEMPERLI as a single agent. 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. Grade 2 nephritis, including tubulointerstitial nephritis, occurred in 0.5% (3/605) of patients.

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 605 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-Barré 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, other transplant (including corneal graft) 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% (1/605) 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%), including laboratory abnormalities, in patients with EC who received JEMPERLI in combination with carboplatin and paclitaxel were decreased hemoglobin, increased creatinine, peripheral neuropathy, decreased white blood cell count, fatigue, nausea, alopecia, decreased platelets, increased glucose, decreased lymphocytes, decreased magnesium, decreased neutrophils, increased AST, arthralgia, rash, constipation, diarrhea, increased ALT, decreased potassium, decreased albumin, decreased sodium, increased alkaline phosphatase, abdominal pain, dyspnea, decreased appetite, increased amylase, decreased phosphate, urinary tract infection, and vomiting.

The most common adverse reactions (≥20%) in patients with dMMR EC who received JEMPERLI as a single agent were fatigue/asthenia, anemia, nausea, diarrhea, constipation, vomiting, and rash. The most common Grade 3 or 4 laboratory abnormalities (>2%) were decreased lymphocytes, decreased sodium, increased alanine aminotransferase, increased creatinine, decreased neutrophils, decreased albumin, and increased alkaline phosphatase.

The most common adverse reactions (≥20%) in patients with dMMR solid tumors who received JEMPERLI as a single agent were fatigue/asthenia, anemia, diarrhea, and nausea. The most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased sodium, increased alkaline phosphatase, and decreased albumin.

Please see the full US Prescribing Information for JEMPERLI, including Medication Guide.

GSK in oncology
Oncology is an emerging therapeutic area for GSK where we are committed to maximizing patient survival with a current focus on hematologic malignancies, gynecologic cancers, and other solid tumors through breakthroughs in immuno-oncology and tumor-cell targeting therapies.

About GSK
GSK is a global biopharma company with a purpose to unite science, technology, and talent to get ahead of disease together. Find out more at us.gsk.com.

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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 under Item 3.D "Risk factors" in GSK's Annual Report on Form 20-F for 2023, and GSK's Q3 Results for 2024.

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