NEW DRUG APPROVAL

Brand Name	Jemperli®
Generic Name	dostarlimab-gxly
Drug Manufacturer	GlaxoSmithKline LLC

New Drug Approval

FDA Approval Date: April 22, 2021

Review Designation: N/A; Accelerated Approval

Type of Review: N/A; Biologic License Application (BLA): 761174

Dispensing Restrictions: Specialty Pharmacy Required, Limited Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Endometrial cancer is the most common type of cancer in the uterus in the United States, affecting mainly postmenopausal women (average age of diagnosis is 60 years). Risk factors for this type of cancer include obesity, a high-fat diet, hormonal changes, type 2 diabetes, family history, endometrial hyperplasia, and a previous diagnosis of breast or ovarian cancer.

Most endometrial cancers are adenocarcinomas, and endometrioid cancer is the most common type of adenocarcinoma. There are many variants of endometrioid cancers, including adenocarcinoma (with squamous differentiation), adenoacanthoma, adenosquamous (or mixed cell) carcinoma, secretory carcinoma, ciliated carcinoma, and villoglandular adenocarcinoma.

In 2021, the American Cancer Society estimates that about 66,570 women will be diagnosed with, and about 12,940 women will die from, cancers of the uterus. About 25% to 30% of patients with advanced endometrial cancer have mismatch repair-deficient (dMMR) tumors. Mismatch repair deficiency is often associated with high microsatellite instability (MSI-H). Microsatellite instability (MSI) is the condition of genetic hypermutability (predisposition to mutation) that results from impaired DNA mismatch repair (MMR). The presence of MSI represents phenotypic evidence that MMR is not functioning normally. MSI-H and dMMR are associated with different kinds of cancers and can be identified via specific FDA-approved tests.

Efficacy

Table 1. NCT02715284: GARNET Study Design Summary	
Study Population	Phase 1 multicenter, multicohort, open-label study conducted in a cohort of 71 adult patients with mismatch repair-deficient (dMMR) recurrent or advanced EC who had progressed on or after treatment with a platinum-containing regimen. • All patients in this cohort had received prior anticancer treatment ○ 90% received prior anticancer surgery ○ 79% received prior anticancer radiotherapy ○ 40% had 2 or more lines of prior anticancer treatment. ○ 11% had received 3 regimens ○ 4% had received 4 or more prior regimens • At study entry, 66% of the patients with dMMR EC had FIGO stage IV disease ○ 70% had endometrioid carcinoma type 1 ○ 6% had serous carcinoma ○ 2.8% each had mixed and undifferentiated carcinomas • Median age, 64 years (range, 38–80 years) ○ 82% White ○ 3% Asian ○ 1% Black • ECOG status ○ 0: 32% ○ 1: 68% **Key exclusion criteria:** • Patients with prior treatment with PD-1/PD-L1–blocking antibodies or other immune checkpoint inhibitor therapy • Patients with autoimmune disease that required systemic therapy with immunosuppressant agents within 2 years
Interventions	Dostarlimab 500 mg IV every 3 weeks for 4 doses followed by 1000 mg IV every 6 weeks until disease progression or unacceptable toxicity
Endpoints	ORR and DOR as assessed by BICR according to RECIST version 1.1

Abbreviations: BICR, blinded independent central review; DOR, duration of response; EC, endometrial cancer; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; IV, intravenous; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

Efficacy Results

Efficacy results in the GARNET dMMR endometrial cancer cohort are summarized in Table 2.

Table 2. Jemperli® Efficacy Results from GARNET Study	
Endpoint	**Jemperli® (N = 71)**
Confirmed Overall Response Rate (ORR)	
ORR	42.3%
(95% CI)	(30.6, 54.6)
Complete response rate	12.7%
Partial response rate	29.6%
Duration of Response (DOR)	
Median in months	Not reached
(range)*	(2.6, 22.4+)
Patients with duration ≥6 months	93.3%

Abbreviations: CI, confidence interval; +, ongoing at last assessment.

*Median follow-up for DOR was 14.1 months, measured from time of first response.

Safety

ADVERSE EVENTS

Most common adverse reactions (≥20%) are fatigue/asthenia, nausea, diarrhea, anemia, and constipation.

WARNINGS & PRECAUTIONS

- Immune-mediated adverse reactions can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis, and immune-mediated dermatologic adverse reactions. Monitor for signs and symptoms of immune-mediated adverse reactions. Evaluate clinical chemistries, including liver and thyroid function, at baseline and periodically during treatment. Withhold or permanently discontinue Jemperli® and administer corticosteroids based on the severity of reaction.
- Infusion-related reactions: Interrupt, slow the rate of infusion, or permanently discontinue Jemperli® based on severity of reaction.
- Complications of allogeneic HSCT after PD-1/L-1–blocking antibody: Follow patients closely for evidence of transplant-related complications and intervene promptly.
- Embryo-fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.

CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS OF ACTION

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors, and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Dostarlimab-gxly is a humanized monoclonal antibody of the IgG4 isotype that binds to the PD-1 receptor and blocks its interaction with PD-L1 and

PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

Dose & Administration

ADULTS

- Dose 1 through 4: 500 mg every 3 weeks.
- Subsequent dosing beginning 3 weeks after Dose 4 (Dose 5 onwards): 1,000 mg every 6 weeks.
- Administer as an intravenous infusion over 30 minutes.

PEDIATRICS

The safety and efficacy of Jemperli® have not been established in pediatric patients.

GERIATRICS

No overall differences in safety or effectiveness were observed between these patients and younger patients. Refer to adult dosing.

RENAL IMPAIRMENT

No specific adjustment recommendations: mild, moderate, and severe impairment and ESRD did not significantly change pharmacokinetics.

HEPATIC IMPAIRMENT

No specific adjustment recommendations: mild or moderate impairment did not significantly change pharmacokinetics.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 500 mg/10 mL (50 mg/mL) clear to slightly opalescent, colorless to yellow solution in a single-dose vial for intravenous infusion after dilution.