PHARMACY & THERAPEUTICS COMMITTEE PRODUCT EVALUATION

Rep:

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GENERIC NAME: dostarlimab-gxly

PROPRIETORY NAME: Jemperli®

INDICATION:

- a PD-1 blocking agent 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 has progressed on or following a prior platinum-containing regimen.April 22, 2021.

MECHANISM 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.

PHARMACOKINETICS

Distribution

- 5.3 L

Metabolism

- Metabolized into small peptides and amino acids

Excretion

- Total body clearance: 0.007 L/hr

Elimination Half Life

- 25.4 days

BLACK BOX WARNING: None

Warning/PRECAUTIONS

- Dermatologic: Immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis (including Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms), may occur and have been reported with PD-1/PD-L1-blocking antibodies; monitoring is recommended and treatment, interruption of therapy, or permanent discontinuation may be necessary
- Endocrine and metabolic: Immune-mediated adrenal insufficiency (primary or secondary) has been reported; monitoring is recommended and treatment, interruption of therapy, or permanent discontinuation may be necessary
- Endocrine and metabolic: Immune-mediated hypophysitis may occur; monitoring is recommended and treatment, interruption of therapy, or permanent discontinuation may be necessary
- Endocrine and metabolic: Immune-mediated thyroid disorders, including thyroiditis, hypothyroidism, and hyperthyroidism, have been reported; monitoring is recommended and treatment, interruption of therapy, or permanent discontinuation may be necessary
- Endocrine and metabolic: Type 1 diabetes mellitus, which can present with diabetic ketoacidosis, may occur; monitoring is recommended and treatment, interruption of therapy, or permanent discontinuation may be necessary

- Gastrointestinal: Immune-mediated colitis has been reported; monitoring is recommended and treatment, interruption of therapy, or permanent discontinuation may be necessary
- Hepatic: Immune-mediated hepatis has been reported; monitoring is recommended and treatment, interruption of therapy, or permanent discontinuation may be necessary
- Immunologic: Cytomegalovirus infection or reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/PD-L1-blocking antibodies; consider repeating infectious workup
- Immunologic: Fatal and other serious transplant-related complications may occur, including hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease, and steroid-requiring febrile syndrome, in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1-blocking antibody; monitoring is recommended. Consider benefit of treatment versus risk in these patients
- Immunologic: Severe or fatal immune-mediated adverse reactions may occur in any organ system or tissue; usually occurring during treatment but may occur after treatment discontinuation. Monitoring is recommended and treatment, interruption of therapy, or permanent discontinuation may be necessary
- Infusion reactions: Severe infusion-related reactions have been reported; monitoring is recommended and interruption of therapy, slowing of the infusion rate, or permanent discontinuation may be necessary
- Renal: Immune-mediated nephritis has been reported; monitoring is recommended and treatment, interruption of therapy, or permanent discontinuation may be necessary
- Reproductive: Fetal harm may occur; advise females of reproductive potential to use effective contraception during treatment and for 4 months after the last dose
- Respiratory: Immune-mediated pneumonitis has been reported; increased risk in patients with a history of thoracic radiation. Monitoring is recommended and treatment, interruption of therapy, or permanent discontinuation may be necessary

ADVERSE REACTIONS

Common

- **Gastrointestinal:** Constipation (20%), Diarrhea (26%), Nausea (30%)
- **Hematologic:** Anemia, All Grades (24%)
- **Other:** Fatigue (48%)

Serious

- **Cardiovascular:** Myocarditis, Pericarditis, Vasculitis
- **Dermatologic:** Erythroderma, Rash, Stevens-Johnson syndrome, Toxic epidermal necrolysis
- **Endocrine metabolic:** Adrenal insufficiency (0.9%), Diabetic ketoacidosis, Hyperthyroidism (1.8%), Hypoparathyroidism, Hypophysitis, Hypopituitarism, Hypothyroidism (5.6%), Thyroid dysfunction, Thyroiditis (0.5%), Type 1 diabetes mellitus
- **Gastrointestinal:** Colitis (1.4%), Duodenitis, Gastritis, Pancreatitis
- **Hematologic:** Anemia, Grades 3 or 4 (13%), Aplastic anemia, Hemolytic anemia, Hemophagocytic lymphohistiocytosis, Thrombocytopenia
- **Hepatic:** Hepatitis (0.2%), Veno-occlusive disease of the liver
- **Immunologic:** Drug reaction with eosinophilia and systemic symptoms, Graft versus host disease, Histiocytic necrotizing lymphadenitis, Sarcoidosis, Systemic inflammatory response syndrome, Transplanted organ rejection
- **Musculoskeletal:** Arthritis, Eaton-Lambert syndrome, Myasthenia gravis, Myositis, Polymyalgia rheumatica, Polymyositis, Rhabdomyolysis
- **Neurologic:** Demyelination of spinal cord, Encephalitis, Guillain-Barre syndrome, Meningitis, Myelitis, Neuropathy

- **Ophthalmic:** Iritis, Unexplained visual loss, Uveitis, Vogt-Koyanagi-Harada disease
- **Renal:** Nephritis (0.5%), Renal impairment
- **Respiratory:** Pneumonitis (1.1%)
- **Other:** Cytomegalovirus infection, Disorder characterized by fever, Steroid-requiring, Sepsis

DRUG INTERACTIONS:

- **N/A**

RECOMMENDED DOSE AND SCHEDULE

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

DOSAGE ADJUSTMENTS

- Renal: No specific adjustment recommendations are available; mild, moderate, and severe impairment and ESRD did not significantly change pharmacokinetics
- Hepatic: No specific adjustment recommendations are available; mild or moderate impairment did not significantly change pharmacokinetics
- Geriatric: No specific adjustment recommendations are available; age (up to 86 years) did not significantly change pharmacokinetics
- Immune-mediated adverse events: No dose reductions are recommended. Generally, withhold for severe (Grade 3) immune-mediated reactions. Permanently discontinue for life-threatening (Grade 4) reactions, recurrent Grade 3 reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of predniSONE equivalent/day within 12 weeks of initiating steroids. If interruption or discontinuation is required, administer systemic corticosteroid therapy (predniSONE 1 to 2 mg/kg/day or equivalent) until improvement to Grade 1 or less; upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month; consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy
- Colitis, immune-mediated (Grade 2 or 3): Withhold until complete or partial resolution to Grade 0 or 1 after corticosteroid taper. Permanently discontinue if complete or partial resolution does not occur within 12 weeks of starting steroids or inability to reduce corticosteroid dose to 10 mg or less of predniSONE equivalent/day within 12 weeks
- Colitis, immune-mediated (Grade 4): Permanently discontinue
- Endocrinopathies, immune-mediated (Grade 2, 3, or 4): If not clinically stable, withhold until complete or partial resolution to Grade 0 or 1 after corticosteroid taper. Permanently discontinue if complete or partial resolution does not occur within 12 weeks of starting steroids or inability to reduce corticosteroid dose to 10 mg or less of predniSONE equivalent/day within 12 weeks
- Exfoliative dermatologic conditions, immune-mediated (Suspected Stevens-Johnson syndrome [SJS], toxic epidermal necrolysis [TEN], or drug rash with eosinophilia and systemic symptoms [DRESS]): Withhold until complete or partial resolution to Grade 0 or 1 after corticosteroid taper. Permanently discontinue if complete or partial resolution does not occur within 12 weeks of starting steroids or inability to reduce corticosteroid dose to 10 mg or less of predniSONE equivalent/day within 12 weeks
- Exfoliative dermatologic conditions, immune-mediated (Confirmed SJS, TEN, DRESS]: Permanently discontinue
- Hepatitis with tumor involvement of the liver, immune-mediated (baseline AST and ALT less than ULN and AST or ALT increases to more than 8x ULN or total bilirubin increases to more than 3x ULN): Permanently discontinue

- Hepatitis with tumor involvement of the liver, immune-mediated (baseline AST or ALT is more than 1 and up to 3x ULN and increases to more than 5 and up to 10x ULN or baseline AST or ALT is more than 3 and up to 5x ULN and increases to more than 8 and up to 10x ULN): Withhold until complete or partial resolution to Grade 0 or 1 after corticosteroid taper. Permanently discontinue if complete or partial resolution does not occur within 12 weeks of starting steroids or inability to reduce corticosteroid dose to 10 mg or less of predniSONE equivalent/day within 12 weeks
- Hepatitis with tumor involvement of the liver, immune-mediated (AST or ALT increases to more than 10x ULN or total bilirubin increases to more than 3x ULN): Permanently discontinue
- Hepatitis with tumor involvement of the liver, immune-mediated (baseline AST and ALT less than ULN): Withhold or permanently discontinue therapy based on recommendations for hepatitis with no liver involvement
- Hepatitis with no tumor involvement of the liver, immune-mediated (AST or ALT increases to more than 3 and up to 8x ULN or total bilirubin increases to more than 1.5 and up to 3x ULN): Withhold until complete or partial resolution to Grade 0 or 1 after corticosteroid taper. Permanently discontinue if complete or partial resolution does not occur within 12 weeks of starting steroids or inability to reduce corticosteroid dose to 10 mg or less of predniSONE equivalent/day within 12 weeks
- Hepatitis with no tumor involvement of the liver, immune-mediated (AST or ALT increases to more than 8x ULN or total bilirubin increases to more than 3x ULN): Permanently discontinue
- Infusion-related reactions (Grade 1 or 2): Interrupt or slow infusion rate
- Infusion-related reactions (Grade 3 or 4): Permanently discontinue
- Myocarditis, immune-mediated (Grade 2, 3, or 4): Permanently discontinue
- Nephritis with renal dysfunction, immune-mediated (Grade 2 or 3 increased blood creatinine): Withhold until complete or partial resolution to Grade 0 or 1 after corticosteroid taper. Permanently discontinue if complete or partial resolution does not occur within 12 weeks of starting steroids or inability to reduce corticosteroid dose to 10 mg or less of predniSONE equivalent/day within 12 weeks
- Nephritis with renal dysfunction, immune-mediated (Grade 4 increased blood creatinine): Permanently discontinue
- Neurological toxicity, immune-mediated (Grade 2): Withhold until complete or partial resolution to Grade 0 or 1 after corticosteroid taper. Permanently discontinue if complete or partial resolution does not occur within 12 weeks of starting steroids or inability to reduce corticosteroid dose to 10 mg or less of predniSONE equivalent/day within 12 weeks
- Neurological toxicity, immune-mediated (Grade 3 or 4): Permanently discontinue
- Pneumonitis, immune-mediated (Grade 2): Withhold until complete or partial resolution to Grade 0 or 1 after corticosteroid taper. Permanently discontinue if complete or partial resolution does not occur within 12 weeks of starting steroids or inability to reduce corticosteroid dose to 10 mg or less of predniSONE equivalent/day within 12 weeks
- Pneumonitis, immune-mediated (Grade 3 or 4 or recurrent Grade 2): Permanently discontinue

PRODUCT AVAILABILITY & NDCs:
JEMPERLI (dostarlimab-gxly) injection is a clear to slightly opalescent, colorless to yellow solution supplied in a carton containing one 500 mg/10 mL (50 mg/mL), single-dose vial (NDC 0173-0898-03). Store vial refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze or shake

CLINICAL LITRATURE

Efficacy was evaluated based on cohort (A1) in GARNET Trial (NCT02715284), a multicenter, multicohort, open-label trial in patients with advanced solid tumors. The efficacy population consisted of 71 patients with dMMR recurrent or advanced endometrial cancer who progressed on or after a platinum-containing regimen. Patients received dostarlimab-gxly, 500 mg intravenously, every 3 weeks for 4 doses followed by 1,000 mg intravenously every 6 weeks.

The main efficacy endpoints were overall response rate (ORR) and duration of response (DOR), as assessed by blinded independent central review (BICR) according to RECIST 1.1. Confirmed ORR was 42.3% (95% CI: 30.6%, 54.6%). The complete response rate was 12.7% and partial response rate was 29.6%. Median DOR was not reached, with 93.3% of patients having durations ≥6 months (range: 2.6 to 22.4 months, ongoing at last assessment).

REFERENCES:

Product Information: JEMPERLI intravenous injection, dostarlimab-gxly intravenous injection. GlaxoSmithKline (per FDA), Research Triangle Park, NC, 2021.