BlueCross BlueShield Federal Employee Program

KEYTRUDA
(pembrolizumab)

RATIONALE FOR INCLUSION IN PA PROGRAM

Background

Keytruda (pembrolizumab) is a monoclonal antibody for the treatment of patients with many different types of cancer. Keytruda blocks a cellular pathway known as PD-1, human programmed death receptor-1, which restricts the body's immune system from attacking cancer cells (1-2).

Regulatory Status

FDA-approved indications: Keytruda is a human programmed death receptor-1 (PD-1)-blocking antibody indicated: (1)

1. Melanoma
    a. For the treatment of patients with unresectable or metastatic melanoma
    b. For the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma following complete resection
2. Non-Small Cell Lung Cancer (NSCLC)
    a. In combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations
    b. In combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC
    c. As a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA approved test with no EGFR or ALK genomic tumor aberrations, and is:
        i. Stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
        ii. Metastatic.
    d. As a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Keytruda.
    e. for the treatment of patients with resectable (tumors ≥4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

f. As a single agent, for adjuvant treatment following resection and platinum-based chemotherapy for adult patients with stage IB (T2a ≥4 cm), II, or IIIA NSCLC.

3. Malignant Pleural Mesothelioma (MPM)
    a. In combination with pemetrexed and platinum chemotherapy, as first-line treatment of adult patients with unresectable advanced or metastatic MPM
4. Head and Neck Squamous Cell Cancer (HNSCC)
    a. In combination with platinum and fluorouracil (FU), for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC.
    b. As a single agent, for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test.
    c. As a single agent, for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.
5. Classical Hodgkin Lymphoma (cHL)
    a. For the treatment of adult patients with relapsed or refractory cHL
    b. For the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy
6. Primary Mediastinal Large B-Cell Lymphoma (PMBCL)
    a. For the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy
    b. Limitations of Use: Keytruda is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.
7. Urothelial Carcinoma
    a. In combination with enfortumab vedotin, for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma
    b. As a single agent for the treatment of patients with locally advanced or metastatic urothelial carcinoma:
        i. who are not eligible for any platinum-containing chemotherapy, or
        ii. who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

c. As a single agent for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy

8. Microsatellite Instability-High or Mismatch Repair Deficient Cancer
    a. For the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options
9. Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer (CRC)
    a. For the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by an FDA-approved test
10. Gastric Cancer
    a. In combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test
    b. In combination with fluoropyrimide- and platinum-containing chemotherapy, is indicated for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA approved test
11. Esophageal Cancer
    a. For the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:
        i. In combination with platinum- and fluoropyrimidine-based chemotherapy for patients whose tumors express PD-L1 (CPS ≥1), or
        ii. As a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test

12. Cervical Cancer
    a. In combination with chemoradiotherapy, for the treatment of patients with locally advanced cervical cancer involving the lower third of the vagina, with or without extension to pelvic sidewall, or hydronephrosis/non-functioning kidney, or spread to adjacent pelvic organs (FIGO 2014 Stage III-IVA)
    b. In combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test
    c. As a single agent for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test
13. Biliary Tract Cancer (BTC)
    a. For the treatment of patients with HCC secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1-containing regimen
14. Hepatocellular Carcinoma (HCC)
    a. For the treatment of patients with HCC who have been previously treated with sorafenib
15. Merkel Cell Carcinoma (MCC)
    a. For the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma
16. Renal Cell Carcinoma (RCC)
    a. In combination with axitinib, for the first-line treatment of patients with advanced RCC
    b. In combination with lenvatinib, for the first-line treatment of adult patients with advanced RCC
17. Endometrial carcinoma
    a. In combination with carboplatin and paclitaxel, followed by Keytruda as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma
    b. In combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) or not MSI-H as determined by an FDA-approved test, who have disease progression following prior

systemic therapy in any setting and are not candidates for curative surgery or radiation

c. As a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by and FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation

18. Tumor Mutational Burden-High (TMB-H) Cancer
    a. For the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options
    b. Limitations of Use: The safety and effectiveness of Keytruda in pediatric patients with TMB-H central nervous system cancers have not been established.
19. Cutaneous Squamous Cell Carcinoma (cSCC)
    a. For the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced cSCC that is not curable by surgery or radiation
20. Triple-Negative Breast Cancer (TNBC)
    a. For treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery
    b. In combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA approved test
21. Adult Classical Hodgkin Lymphoma and Adult Primary Mediastinal Large B-Cell Lymphoma: Additional Dosing Regimen of 400 mg every 6 weeks
    a. For use at an additional recommended dosage of 400 mg every 6 weeks for Classical Hodgkin Lymphoma and Primary Mediastinal Large B-Cell Lymphoma in adults

Clinically significant immune-mediated adverse reactions may occur with Keytruda therapy including pneumonitis, colitis, hepatitis, hypophysitis, nephritis, hyperthyroidism, hypothyroidism, skin adverse reactions, infusion-related reactions, and other immune-mediated adverse reactions.

Based on the severity of the adverse reaction, Keytruda should be withheld or discontinued and corticosteroids administered. Patients should be monitored for signs and symptoms of pneumonitis, colitis, hypophysitis, thyroid disorders, and changes in liver and renal function. Keytruda may cause fetal harm when administered to a pregnant woman. Female patients of reproductive potential should be advised of the potential hazard to a fetus (1).

Keytruda in combination with axitinib can cause hepatic toxicity with higher than expected frequencies of Grades 3 and 4 ALT and AST elevations compared to Keytruda alone (1).

The safety and effectiveness of Keytruda have been established in pediatric patients (1).

Summary

Keytruda (pembrolizumab) is a monoclonal antibody indicated for the treatment of patients with many different types of cancer. Clinically significant immune-mediated adverse reactions may occur with Keytruda therapy including pneumonitis, colitis, hepatitis, hypophysitis, nephritis, hyperthyroidism, hypothyroidism, skin adverse reaction, infusion-related reactions, and other immune-mediated adverse reactions. Based on the severity of the adverse reaction, Keytruda should be withheld or discontinued, and corticosteroids administered. Keytruda may cause fetal harm when administered to a pregnant woman. The safety and effectiveness of Keytruda have been established in pediatric patients (1-2).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of Keytruda while maintaining optimal therapeutic outcomes.

References

1. Keytruda [package insert]. Rahway, NJ: Merck Sharp & Dohme Corp.; June 2025.
2. NCCN Drugs & Biologics Compendium® Pembrolizumab 2025. National Comprehensive Cancer Network, Inc. Accessed on May 7, 2025.