Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of Keytruda® (pembrolizumab) and KEYTRUDA QLEX™ (pembrolizumab and berahyaluronidase alfa-pmph) approved by the Food and Drug Administration (FDA) for the treatment of various cancers.

Background Information

Keytruda® (pembrolizumab), a human programmed death receptor-1 (PD-1) blocking antibody. Keytruda QLEX (pembrolizumab and berahyaluronidase alfa-pmph) shares all FDA-approved **solid tumor indications** with intravenous Keytruda (pembrolizumab) for adult and pediatric patients 12 years and older. **Intravenous Keytruda (pembrolizumab) has two hematologic malignancy indications that Keytruda QLEX does not have**: relapsed or refractory classical Hodgkin lymphoma (cHL) and relapsed or refractory primary mediastinal large B-cell lymphoma (PMBCL). The following are the FDA indications and NCCN compendia uses for Keytruda:

Anal Cancer

The NCCN Drugs and Biologics Compendia and the NCCN CPG for anal cancer offered a NCCN 2A recommendation for the use of Keytruda as a single agent for subsequent treatment of metastatic squamous cell carcinoma of the anal canal as a treatment option. The NCCN Panel recommendation is based on unpublished preliminary results reported from the KEYNOTE-28 trial, a multi-cohort, phase 1b trial for PD-1 positive squamous cell carcinoma of the anal canal (Ott, 2017). Ott and colleagues (2017) concluded that further studies of PD-1 and PD-L1 inhibitors is warranted for treatment of squamous cell carcinoma of the anal canal. Most anal cancer treatments are extrapolated from colorectal treatment guidance.

Biliary Tract Cancer

Biliary Tract Cancer Keytruda, in combination with gemcitabine and cisplatin, is indicated for the treatment of patients with locally advanced unresectable or metastatic biliary tract cancer (BTC). The NCCN Drugs and Biologics Compendia and the NCCN CPG for biliary tract cancers offered level 1 and 2A recommendations for the use of Keytruda as the primary treatment for unresectable and metastatic disease in combination with gemcitabine and cisplatin (NCCN category 1) or for MSI-H/dMMR tumors using pembrolizumab as a single agent. Also, as subsequent therapy for biliary tract cancer with disease progression in MSI-H/dMMR tumors or TMB-H tumors using pembrolizumab as a single agent.

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

Breast Cancer

Keytruda is FDA indicated in combination with chemotherapy for the treatment of patients with locally recurrent, unresectable, or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 Combined Positive Score (CPS) ≥10 as determined by an FDA-approved test. Keytruda is also approved for use in combination with chemotherapy as neoadjuvant treatment, followed by single agent use in the adjuvant setting after surgery.

Cervical Cancer

Keytruda is FDA indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 Combined Positive Score (CPS) ≥1 as determined by an FDA-approved test. Keytruda is also indicated in combination with chemotherapy, with or without bevacizumab, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 CPS≥1. Keytruda is also indicated by the FDA (January 2024) in combination with chemoradiotherapy, for the treatment of patients with FIGO 2014 Stage III-IVA cervical cancer.

Central Nervous System Cancers

NCCN provides a 2A recommendation for the use of Keytruda as a single agent in recurrent or refractory hypermutant tumor pediatric diffuse high-grade glioma.

Colorectal Cancer

Colorectal cancer refers to malignancies originating from the large intestine (colon) or the rectum. The term colorectal cancer does not include anal cancer. Howe

Keytruda is FDA approved for the treatment of unresectable or metastatic microsatellite instability-high or mismatch repair deficient colorectal cancer (MSIH/dMMR).

NCCN Drugs and Biologics Compendium and the NCCN Clinical Practice Guidelines (CPG) on colon cancer and rectal cancer lists off-label use of Keytruda for individuals with unresectable metachronous metastases or unresectable advanced or metastatic colorectal cancer. The recommendations were based on 2A category of evidence and uniform consensus.

The NCCN panel recommends use of Keytruda or nivolumab as treatment options in patients with metastatic MMR- deficient colorectal cancer in second- or third-line therapy. Patients progressing on either of these drugs should not be offered the other.

Cutaneous Squamous Cell Carcinoma (cSCC)

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

Basal cell and cutaneous squamous cell cancers are together known as non-melanoma skin cancers (NMSCs) or keratinocyte carcinoma.

Keytruda is FDA approved to treat individuals with locally advanced, recurrent or metastatic cutaneous (skin) squamous cell carcinoma that is not curable by surgery or radiation.

Endometrial Cancer

Keytruda received accelerated FDA approval for the treatment of endometrial cancer in combination with lenvatinib (Lenvima) in those with advanced disease that is *not* microsatellite instability-high or mismatch repair deficient (MSI- H/dMMR) who have disease progression following prior systemic therapy and are not eligible for surgery or radiation. NCCN placed this indication as a 1 category.

Keytruda also received accelerated FDA approval for the treatment of advanced endometrial cancer that is MSI-H or dMMR as determined by an FDA approved test, as a single agent, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

Esophageal Cancer

Esophageal cancer can be classified as squamous cell carcinoma or adenocarcinoma. Compared to adenocarcinoma, squamous cell carcinoma has a poorer prognosis.

Keytruda is FDA indicated for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 10], with disease progression after one or more prior lines of systemic therapy. Keytruda (pembrolizumab) is also FDA indicated for the treatment of 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 in combination with platinum- and fluoropyrimidine–based chemotherapy.

Gastric or Gastroesophageal Junction Adenocarcinoma

Gastroesophageal junction adenocarcinoma, a form of cancer that is located in the region where the esophagus joins the stomach, is also rare, but equally lethal. Five-year survival rates for both cancers are relatively low for esophageal cancer and for gastric cancer. Treatments are aimed at extending OS, while also providing palliative and supportive care.

In November 16, 2023 the FDA approved Keytruda in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma. Keytruda is also indicated for use with trastuzumab plus platinum and fluoropyrimidine-based chemotherapy as first line treatment in locally advanced

unresectable or metastatic HER2 positive gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 (CPS $\geq$ 1) as determined by an FDA-approved test.

Gestational Trophoblastic Neoplasia

The NCCN Drug and Biologics Compendia and the NCCN CPG for gestational trophoblastic neoplasia offer a category 2A recommendation for Keytruda as a single agent in the treatment of recurrent or progressive intermediate trophoblastic tumor following treatment with a platinum/etoposide-containing regimen and as a single agent for individuals with methotrexate-resistant high-risk disease. Though there is insufficient published evidence, due to the rarity of this disease the committee used clinical judgement to support the use of Keytruda for this condition.

Head and Neck Squamous Cell Cancer (HNSCC)

Head and neck cancer usually begins in the squamous cells that line moist, mucosal surfaces inside the head and neck (for example, inside the mouth, nose and throat), and is commonly referred to as squamous cell carcinoma of the head and neck. Head and neck cancers can also begin in the salivary glands, but these are much less common (NCI, 2018).

Keytruda is FDA indicated for the treatment of patients with recurrent, unresectable, or metastatic head and neck squamous cell carcinoma (HNSCC) as first-line monotherapy whose tumors express PD-L1 with CPS greater than or equal to 1, as first-line in combination with platinum and fluorouracil, and as monotherapy in those with disease progression on or after platinum-containing chemotherapy. NCCN also provides similar recommendation for Keytruda in HNSCC, with an additional recommendation for use of Keytruda with platinum and fluorouracil as a subsequent therapy option. However, published studies are lacking at this time.

NCCN also provides a 2A recommendation for use of Keytruda as monotherapy for first or subsequent line therapy in combination with platinum-containing chemotherapy and docetaxel for recurrent, unresectable, or metastatic HNSCC.

Hepatocellular Carcinoma

Hepatocellular carcinoma is the most common form of liver cancer. Chronic infections with hepatitis B virus (HBV) or hepatitis C virus are the most common causes of liver cancer. (ACS, 2018).

Keytruda is FDA indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

Hodgkin Lymphoma (Keytruda QLEX does not share this indication)

Hodgkin lymphoma is a type of malignancy which starts in the lymphocytes, a type of white blood cell that fights infection. Hodgkin lymphoma most commonly affects people between the ages of 15 and 40 and people older than age 55. In Hodgkin lymphoma, cells in the lymphatic system grow abnormally and may spread beyond the lymphatic system. As the disease progresses, it compromises the body's ability to fight infection. Many initial signs and symptoms may be similar to those of influenza, such as fever, fatigue and night sweats. Eventually, tumors develop. Hodgkin lymphoma is distinguished by the presence of abnormal Reed-Sternberg cells with the majority of cases expressing CD15 and CD30 on immunohistochemistry testing of tissue. In developed countries, classical Hodgkin lymphoma accounts for approximately 95% of all Hodgkin disease (ACS, 2018).

Keytruda is FDA indicated for the treatment of adult with relapsed or refractory classical Hodgkin lymphoma (cHL), and pediatrics with refractory cHL, or those who have relapsed after 2 or more prior lines of therapy.

NCCN Drugs and Biologics Compendium and the NCCN CPG for Hodgkin disease includes a 2A recommendation for off-label use of Keytruda as an additional therapy option when used as a single agent for individuals with relapsed or refractory cHL.

NCCN also provides a 2A recommendation for off-label use of Keytruda as an additional therapy option when used as monotherapy for relapsed or refractory primary cutaneous anaplastic large cell lymphoma (ALCL).

Malignant Pleural Mesothelioma

Malignant mesothelioma is a rare cancer where malignant cells are found in the lining of the chest or abdominal cavity. Malignant pleural mesothelioma is the most common type, difficult to treat because the majority of individuals have advanced disease at presentation. The NCCN CPG for malignant pleural mesothelioma (2019) reported the median overall survival for the disease to be approximately 1 year, with cure rare.

The recently updated NCCN CPG for malignant pleural mesothelioma (2019) includes a category 2A recommendation for use of Keytruda as subsequent systemic therapy for the treatment of malignant pleural mesothelioma, a highly aggressive cancer with poor prognosis and limited treatment options. The recommendation is based on preliminary results from the KEYNOTE-028 study, a non-randomized, open-label, phase 1b trial that evaluated the clinical safety and activity of Keytruda in individuals with malignant pleural mesothelioma.

Melanoma

BRAF gene mutations are seen most commonly in melanoma, occurring in approximately 50% of cutaneous melanomas. Mutations of the BRAF gene have been associated with shorter progression-free intervals and overall decreased survival. When discovered early, melanoma can usually be cured with surgery. Once metastasis occurs, the prognosis is usually poor. In the metastatic stage of melanoma (stage IV), the average survival rate is about 6

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

months with a 1-year mortality rate of 75%. Treatment of metastatic melanoma may include lymphadenectomy, immunotherapy, radiation therapy, chemotherapy or participation in a clinical trial.

Keytruda is FDA indicated for the treatment of patients with unresectable or metastatic cutaneous melanoma and for the adjuvant treatment of adult or pediatric patients 12 years of age or older with Stage IIB, Stage IIC or Stage III melanoma following complete resection.

NCCN Drugs and Biologics Compendium and the NCCN CPG on cutaneous melanoma include Category 2A recommendations for use of Keytruda as a single agent in first-line, second-line or subsequent therapy for disease progression or following maximal clinical benefit from BRAF targeted therapy for individuals with a performance status of 0-2.

NCCN Drug and Biologics Compendium and the NCCN CPG for uveal melanoma, the NCCN panel offers recommendations (category 2A) for use of Keytruda in the treatment of unresectable disease. The NCCN panel recommendation for use of Keytruda as a single agent is based on case series that evaluated Keytruda as a treatment option for uveal melanoma. Eggermont and colleagues reported results from the KEYNOTE-054 study (NCT02362594), a randomized phase 3 trial designed to evaluate Keytruda versus placebo after completion of resection of high-risk stage III melanoma. In summary, the authors concluded that: “as adjuvant therapy for high-risk stage III melanoma, 200 mg of Keytruda administered every 3 weeks for up to 1 year resulted in significantly longer recurrence-free survival than placebo, with no new toxic effects identified.”

NCCN also provides a category 2A recommendation for use of Keytruda (pembrolizumab) as single-agent treatment for brain metastases in patients with BRAF non-specific melanoma.

Merkel Cell Carcinoma

MCC is an uncommon type of skin cancer, also known as neuroendocrine carcinoma with up to 97% of cases primarily in the epidermis of the skin. An overall 5-year survival rate for MCC was reported at nearly 60%.
Keytruda is FDA indicated for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC).

Microsatellite Instability-High Cancer

Keytruda is FDA indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient.

- Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.

The safety and effectiveness of Keytruda in pediatric patients with MSI-H central nervous system cancers have not been established.

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

In the NCCN Drugs and Biologics and NCCN CPG for testicular cancer offer a category 2A recommendation for use of Keytruda as a single agent as palliative treatment in individuals with MSI-H/dMMR or tumor mutation burden-high (TMB-H) tumors and progression after treatment with high dose chemotherapy or third-line therapy. The recommendation is based on a small phase II study (Le, 2015; Le, 2017). In summary, the authors conclude that Keytruda may be a treatment option, however, they suggest participation in a clinical trial as the preferred treatment option. The phase 2 Keynote-158 study for those with TMB-H tumors with advanced solid tumors (Marabelle, et.al. 2020) investigated the efficacy of immunotherapy in testicular cancer, 12 patients with nonseminoma GCTs who progressed after first-line cisplatin base therapy and at least one high-dose or conventional dose chemotherapy were treated with Keytruda. Two patients achieved stable disease, but no partial or complete responses were observed.

NCCN Drugs and Biologics Compendium and the NCCN CPG for bone cancer – Ewing sarcoma and osteosarcoma offers NCCN 2A recommendation for use of Keytruda when used as a single agent for unresectable or metastatic, MSI-H or dMMR tumors with disease progression with prior treatment or when the individual has no satisfactory alternative treatment options, in line with current FDA approval.

In the recent NCCN Drugs and Biologics compendium and the NCCN CPG for ovarian cancer the NCCN panel lists NCCN 2A recommendations for use of Keytruda as a single-agent therapy for persistent disease or recurrence if MSI-H or dMMR, based on preliminary analysis from the KEYNOTE-028 study which led to the FDA approval for treatment of unresectable or metastatic solid tumors (dMMR/MSI-H only).

NCCN provides a category 2A recommendation for use of Keytruda in small bowel adenocarcinoma (including ampullary adenocarcinoma) as subsequent therapy for disease progression as a single-agent (in certain circumstances) if microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR) or tumor mutational burden-high (TMB-H ≥ 10 mut/Mb). At this time this data is extrapolated on first-line use of checkpoint inhibitors in colorectal cancer. There is no direct evidence for efficacy support in usage as subsequent therapy or in disease progression.

Neuroendocrine and Adrenal Tumors

NCCN 2A considers Keytruda for the management of mismatch repair deficient (dMMR) or microsatellite instability- high (MSI-H) unresectable/metastatic adrenocortical tumors that have progressed following prior treatment and have no satisfactory alternative treatment options. NCCN also offers a 2A recommendation for use of Keytruda in locoregional unresectable or metastatic adrenocortical carcinoma as single agent or in combination with mitotane.

Classical Hodgkin Lymphoma, Non-Hodgkin Lymphoma, Primary Mediastinal Large B-Cell Lymphoma (Keytruda QLEX does not share this indication)

Keytruda is FDA indicated for the treatment of adult and pediatric patients with refractory primary mediastinal large B- cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy. Keytruda is not

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy. NCCN also provides a 2A recommendation for the use in PMBCL as monotherapy or in combination with brentuximab vedotin.

Keytruda is FDA indicated for relapsed or refractory classical Hodgkin lymphoma or refractory primary mediastinal large B-Cell lymphoma.

Non-Small Cell Lung Cancer (NSCLC)

Lung cancer is the leading cause of death from cancer worldwide, with advanced NSCLC representing the majority (85%) of these cases. It has been estimated that only 15.7% of all individuals with lung cancer will survive 5 years or more following diagnosis (NCI, 2018).

Keytruda is FDA indicated:

- In combination with pemetrexed and platinum chemotherapy, for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.
- In combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.
- As a single agent, is indicated for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥50%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.
- As a single agent, is indicated 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.
- As a single agent, is indicated for the first-line treatment of patients with stage III NSCLC, who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC, and whose tumors express PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.
- for adjuvant treatment following resection and platinum-based chemotherapy for stage IB (T2a ≥4 cm), II, or IIIA non-small cell lung cancer (NSCLC).

The updated NCCN Drugs and Biologics Compendium and the NCCN CPG on NSCLC offers recommendations for use of Keytruda for use as first-line therapy for PD-L1 positive NSCLC with PD-L1 expression positive (≥ 50%) and EGFR, ALK, ROS1 negative or unknown disease (Category 1) (Reck,2016). The panel includes category 1 recommendations for use of Keytruda as a subsequent therapy for disease progression in individuals with NSCLC tumors with PD-L1 expression levels ≥ 1%, when Keytruda not previously given. The panel recommendations are based on preliminary results from one phase 1 study (KEYNOTE-001) and a phase 2/3 trial (KEYNOTE-010) that

evaluated use of Keytruda as subsequent therapy for metastatic NSCLC. In the NCCN clinical practice guideline for NSCLC the panel defines continuation maintenance therapy as "the use of at least one of the agents that was given in the first-line regimen". The NCCN panel includes category 1 recommendations for nonsquamous NSCLC continuation maintenance therapy for use of Keytruda in combination with pemetrexed if given first-line as part of pembrolizumab/carboplatin/pemetrexed or pembrolizumab/cisplatin/pemetrexed regimen. For squamous cell NSCLC the panel offers a category 2A recommendation for use of Keytruda as a single agent as continuation maintenance therapy, if given first-line as part of pembrolizumab/carboplatin/paclitaxel regimen. NCCN also provides a category 2A recommendation for use of Keytruda (pembrolizumab) as single-agent treatment for brain metastases in patients with PD-L1 positive NSCLC.

NCCN also provides a recommendation for use of Keytruda as treatment for recurrent, advanced, or metastatic NSCLC in combination with pemetrexed and either carboplatin or cisplatin for nonsquamous cell histology, or carboplatin and either paclitaxel or albumin-bound paclitaxel for squamous cell histology as first line or subsequent therapy in those with BRAF, NTRK, MET, or ROS1 mutations. The recommendation was based on studies (Gandhi 2018, Paz-Ares 2018) that excluded individuals with EGFR and ALK mutations, but it is unknown if those with other sensitizing mutations were included to support such use.

Penile Cancer

NCCN 2A recommendation to use as a single agent (preferred) as subsequent-line systemic therapy if unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumor that has progressed following prior treatment and no satisfactory alternative treatment options. There are no randomized clinical trials due to the rarity of penile cancer in industrialized countries. The NCCN Panel strongly recommends consideration of clinical trial participation as data are limited in the second-line setting

Primary Cutaneous Lymphomas (Mycosis Fungoides/Sezary Syndrome) (Keytruda QLEX does not share this indication)

In the NCCN Drugs and Biologics Compendia and the NCCN CPG for Primary Cutaneous Lymphomas, the panel includes a NCCN 2A recommendation for use as systemic therapy of Keytruda as primary treatment in stage III Mycosis Fungoides or stage IV Sezary Syndrome. The recommendation was based on a small phase II trial of 24 patients (21 had stage III or IV), with an overall response rate of 38% (2 complete responses and 7 partial responses). The authors concluded that more studies are needed to determine potential biomarkers for response and assess whether PD-1/PD-L1 therapy can actually negatively affect the disease since there is theoretical concern that PD-1 blockade could accelerate growth of the malignancy (Khodadoust 2020).

Renal Cell Carcinoma

Keytruda received FDA approval for use in combination with axitinib (Inlyta), as first-line treatment of those with advanced renal cell carcinoma. Keytruda is also FDA approved as adjuvant treatment in those with renal cell carcinoma at intermediate-high, or high risk of recurrence following nephrectomy, or following nephrectomy and

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

resection of metastatic lesions. Patients defined as being at intermediate or high risk of recurrence in the Keynote-564 study met at least one of the following criteria:

- Tumor: pT3 or pT4, M0
- Node: Positive
- Histology: Sarcomatoid or Grade 4 with at least pT2
- Metastasis: M1, no evidence of metastasis

The NCCN provides similar recommendations, with an additional recommendation for subsequent therapy; however, published studies supporting this are lacking. NCCN also provides a recommendation for use of Keytruda for relapse or stage IV kidney cancer in combination with lenvatinib (preferred) as first-line therapy for clear cell histology and favorable or poor/intermediate risk.

Soft Tissue Sarcoma

NCCN considers Keytruda useful in certain circumstances as first line or subsequent therapy for various types of soft tissue sarcoma, including of the extremity/body wall, head/neck, retroperitoneal/intra-abdominal, angiosarcoma, and alveolar soft part sarcoma. NCCN also provides a 2A recommendation for use in combination with Inlyta for the use in alveolar soft part sarcoma.

Solid Tumors

Keytruda is FDA granted approval for expanded use in adults or children for the treatment of unresectable or metastatic solid tumors (dMMR/MSIH only) (which can be found in biliary, bladder, breast, colorectal, endometrial, esophageal, gastric/gastroesophageal junction, pancreatic, prostate, renal cell, retroperitoneal adenocarcinoma, sarcoma, small cell lung, small intestine and thyroid) with *disease progression following prior treatment* and no other satisfactory alternative treatment options identified. The approval included coverage in treatment of individuals with unresectable or metastatic colorectal cancer (dMMR/MSIH only) with disease progression following treatment with fluoropyrimidine, oxaliplatin, and irinotecan. The FDA approval was based on tumor response rate and durability of response. NCCN provides additional recommendations for certain solid tumors (occult primary, pancreatic, and small bowel adenocarcinoma) that are dMMR/MSIH for Keytruda as first-line therapy; however, supporting literature is lacking. The recommendation is based on a small phase II study (Le, 2015, 2017), which studied Keytruda's use as subsequent therapy.

Keytruda is also FDA approved for solid tumors with tumor mutational burden-high (TMB-H), defined as greater than or equal to 10 mutations per megabase (mut/Mb), as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory treatment options.

NCCN provides a 2A recommendation for Keytruda for progressive locally advanced or metastatic well-differentiated grade 3 neuroendocrine tumors with unfavorable biology. This is supported by the KEYNOTE-158 study where 7 out of 233 individuals had NETs. An objective response was seen in 34.3% of the 233 individuals.

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

T cell Lymphomas (Keytruda QLEX does not share this indication)

In the NCCN CPG for T-Cell Lymphomas the NCCN panel included a category 2A recommendation for extranodal NK/T-Cell lymphoma as a treatment option for Keytruda in relapsed or refractory disease following therapy in a clinical trial. The NCCN Panel concluded that use of Keytruda in "clinical trial is the preferred relapsed/refractory option in the absence of a clinical trial, Keytruda is an appropriate option."

Thymic Carcinoma

NCCN provides a 2A category recommendation for Keytruda as subsequent therapy for unresectable or metastatic thymic carcinoma. This is based on two phase II trials (Giaccone 2018, Cho 2019) which demonstrated positive overall response rate (22.5% and 15.4%, respectively). NCCN caveats this a warning that immunotherapy, including Keytruda, can be associated with a high rate of severe immune-related adverse events, including myocarditis. For this reason, Keytruda is not recommended in those with thymomas. Additionally, NCCN also recommends use of Keytruda in individuals who cannot tolerate first-line combination regimens.

Urothelial Carcinoma/Bladder Cancer

Urothelial carcinoma is the most common type of bladder cancer. The ACS estimates that in 201 there will be approximately 80,470 new cases of bladder cancer (incidence about four times higher in men than in women) and 17,670 deaths from bladder cancer (about 12,870 in men and 4800 in women) in the United States (ACS, 2019).

Keytruda is FDA indicated:

- In combination with enfortumab vedotin, for the treatment of adult patients with locally advanced or metastatic urothelial cancer.
- For the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- For the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy.
- 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.

Vulvar Cancer (Squamous Cancer)

NCCN provides a category 2A recommendation for use of Keytruda as useful in certain circumstances as a single agent for second-line treatment of advanced, recurrent, or metastatic squamous cell vulvar cancer if disease progression on or after chemotherapy in patients whose tumors express PD-L1 (Combined Positive Score ≥1). The

recommendation was based on a small ongoing basket study that included individuals with cervical cancer (Chung 2018, Marabelle 2020). Therefore, there is lack of supporting data for such use at this time.

Abbreviations:

Abbreviation	Name
ALK	Anaplastic Lymphoma Kinase
cHL	Classical Hodgkin Lymphoma
CPC	Circulating Plasma Cells
CRC	Colorectal Cancer
cSCC	Cutaneous Squamous Cell Carcinoma
dMMR	Mismatch Repair Deficient Cancer
ECOG	Eastern Cooperative Oncology Group (ECOG) Performance Status
EGFR	Epidermal Growth Factor Receptor
GEJ	Gastroesophageal Junction
HCC	Hepatocellular Carcinoma
HNSCC	Head and Neck Squamous Cell Cancer
MCC	Merkel Cell Carcinoma
MSI-H	Microsatellite Instability-High Cancer
NSCLC	Non-Small Cell Lung Cancer
PD-1	Programmed Death Receptor-1 (PD-1)
PMBCL	Primary Mediastinal Large B-Cell Lymphoma
pMMR	Mismatch Repair Proficient Cancer
RCC	Renal Cell Carcinoma
TMB-H	Tumor Mutational Burden-High Cancer
TNBC	Triple-Negative Breast Cancer
TPS	Tumor Proportion Score

Indications of Keytruda (pembrolizumab) that require Molecular Testing

Indication	Molecular Testing	Cut Point
Advanced Non-Small Cell Lung Cancer (NSCLC)		
First-line Monotherapy for Nonsquamous and Squamous Advanced NSCLC	PD-L1	TPS*≥1%
Second-line or Greater Monotherapy for Nonsquamous and Squamous mNSCLC	PD-L1	TPS*≥1%
Advanced Head and Neck Squamous Cell Carcinoma (HNSCC)		

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

First-line Monotherapy in Metastatic or Unresectable, Recurrent HNSCC	PD-L1	CPS** ≥1
Advanced Esophageal or GEJ Carcinoma		
Advanced Esophageal or GEJ Carcinoma	PD-L1	CPS** ≥10 Applies only to the 2nd line + monotherapy
Advanced Cervical Cancer		
First-line Combination Therapy for Advanced Cervical Cancer	PD-L1	CPS ≥1
Second-line Monotherapy for Advanced Cervical Cancer	PD-L1	CPS ≥1
Advanced Triple-Negative Breast Cancer (TNBC)		
Advanced Triple-Negative Breast Cancer	PD-L1	CPS ≥10
Advanced Gastric Cancer		
First -line Advanced Unresectable or Metastatic HER-2 Positive Gastric or Gastroesophageal Junction Cancer	PD-L1	CPS ≥1
Advanced MSI-H/dMMR Cancers		
Advanced MSI-H/dMMR Cancers	MSI-H*** or dMMR***	Presence
Advanced MSI-H/dMMR Colorectal Cancers	MSI-H*** or dMMR***	Presence
Advanced MSI-H/dMMR Endometrial Carcinoma (when used as a single agent)	MSI-H*** or dMMR***	Presence

* PD-L1 expression level in advanced NSCLC is determined by the Tumor Proportion Score (TPS), which is reported as a percentage on a scale of 0% to 100%. TPS is a scoring method that evaluates the percentage of viable tumor cells showing partial or complete membrane staining at any intensity.

** The Combined Positive Score (CPS) is used to assess PD-1L expression in metastatic or unresectable, recurrent HNSCC, advanced esophageal or GEJ carcinoma (2nd line + monotherapy), advanced cervical cancer, and advanced triple-negative breast cancer. This scoring method evaluates the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) relative to all viable tumor cells.

*** A deficient MMR (dMMR) system results in the persistence of DNA mismatches in microsatellites that may then be incorporated into the genetic code as mutations. A dMMR system can be hereditary or sporadic in nature. Tumors that have a dMMR system can develop MSI, which is the expansion or reduction in the length of repetitive sequences in tumor DNA compared with normal DNA. MSI/MMR can be identified by Immunohistochemistry (IHC, to detect the presence or absence of MMR protein expression; and Next Generation Sequencing (NGS, a gene sequencing technique used to identify genetic mutations or variants).

Definitions and Measures

- Adjuvant therapy: Treatment given after the primary treatment to increase the chances of a cure; may include chemotherapy, radiation, hormone or biological therapy.

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

- Anal cancer: Cancer originating in the tissues of the anus; the anus is the opening of the rectum (last part of the large intestine) to the outside of the body.
- BRAF: The oncogene which directions production of a protein in the regulating MAP kinase/ERKs signaling pathway, which affects cell division, differentiation, and secretion.
- Carcinoma in situ: A group of abnormal cells that stay in place where they were first formed, and have not spread, but may become cancerous. Also called stage 0 disease.
- Colon cancer: Cancer originating in the tissues of the colon (the longest part of the large intestine). Most colon cancers are adenocarcinomas that begin in cells that make and release mucus and other fluids.
- Colorectal cancer: Cancer originating in the colon (the longest part of the large intestine) or the rectum (the last several inches of the large intestine before the anus).
- Cystectomy: Surgery to remove all or part of the bladder. Also used to describe removal of a cyst.
- ECOG or Eastern Cooperative Oncology Group Performance Status: A scale and criteria used by doctors and researchers to assess how an individual's disease is progressing, assess how the disease affects the daily living abilities of the individual, and determine appropriate treatment and prognosis. This scale may also be referred to as the WHO (World Health Organization) or Zubrod score which is based on the following scale:
    - 0 = Fully active, able to carry on all pre-disease performance without restriction
    - 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
    - 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
    - 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
    - 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
    - 5 = Dead
- Immune checkpoint inhibitor: A type of drug that blocks certain proteins made by some types of immune system cells, such as T cells, and some cancer cells. When these proteins are blocked, the "brakes" on the immune system are released and T cells are able to kill cancer cells better. Examples of checkpoint proteins found on T cells or cancer cells include programmed death (PD)-1, PD-ligand 1 (PD-L1), and cytotoxic T-lymphocyte–associated antigen (CTLA)-4/B7-1/B7-2 (NCI, 2018).
- Karnofsky Performance Status: A scale and criteria used by doctors and researchers to assess an individual's prognosis, measure changes in their function and abilities, and determine their ability to tolerate therapies. The lower the score (from 0-100), the worse the likelihood of survival.
    - 100 = Normal, no complaints
    - 90 = Able to carry on normal activities
    - 80 = Normal activity with effort
    - 70 = Care for self. Unable to carry on normal activity or to do active work
    - 60 = Requires occasional assistance, but able to care for most of his needs

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

  - 50 = Requires considerable assistance and frequent medical care
  - 40 = Disabled. Requires special care and assistance
  - 30 = Severely disabled. Hospitalization indicated though death nonimminent
  - 20 = Very sick. Hospitalization necessary. Active supportive treatment necessary
  - 10 = Moribund
  - 0 = Dead
- Line of Therapy:
  - First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
  - Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
  - Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second- line therapy) are not effective or there is disease progression.
- Melanoma: A type of cancer that begins in the melanocytes. Melanoma is also referred to as malignant melanoma and cutaneous melanoma.
- Merkel cell carcinoma: A rare, aggressive skin cancer.
- Metastasis: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.
- Monoclonal antibody: A protein developed in the laboratory that can locate and bind to specific substances in the body and on the surface of cancer cells.
- Multiple myeloma: A type of cancer that begins in plasma cells (white blood cells that produce antibodies). Mutation: A permanent, transmissible change in genetic material.
- Neoadjuvant therapy: Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy.
- Non-small cell lung cancer: A group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of non-small cell lung cancer are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma.
- Non-Hodgkin Lymphoma (NHL): A group of malignant solid tumors or lymphoid tissues.
- Phase I trial: A study to test a new drug or treatment in a small group of participants for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.
- Programmed death (PD)-1: PD-1 proteins are found on T-cells and attach to PD ligands (PD-L1) found on normal (and cancer) cells (see immune checkpoint inhibitor above). Normally, this process keeps T-cells from attacking other cells in the body. Examples of FDA approved PD-1 inhibitors include Keytruda (pembrolizumab), Opdivo (nivolumab), and Libtayo (cemiplimab).
- Programmed death ligand (PD-L)-1: The ligands found on normal (and cancer) cells to which the PD-1 proteins attach (see immune checkpoint inhibitor above). Cancer cells can have large amounts of PD-L1

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

on their surface, which helps them to avoid immune attacks. Examples of FDA approved PD-L1 inhibitors include Bavencio (avelumab), Tecentriq (atezolizumab), and Imfinzi (durvalumab).

- Unresectable: Unable to be removed with surgery.
- Urothelial carcinoma: A type of bladder cancer which occurs in the urinary tract system. Urothelial carcinoma is also known as transitional cell carcinoma of the bladder.

Approved Indications

See "Background" section for all approved indications.

Other Uses

The FDA has withdrawn the subsequent therapy indications for nivolumab or pembrolizumab for patients with relapsed small cell lung cancer (SCLC), because phase 3 randomized trial data did not show an improvement in overall survival. However, the NCCN SCLC Panel still recommends these agents for certain patients. The panel decided that nivolumab or pembrolizumab are just as effective as, and sometimes better than, the other subsequent therapy options; nivolumab or pembrolizumab are also less toxic. In addition, many agents recommended as subsequent therapy options for patients with SCLC do not have an FDA indication in this setting but data show that they are effective. Patients with limited-stage SCLC who relapse and have not previously received immune checkpoint inhibitors may benefit from subsequent therapy with nivolumab or pembrolizumab. Per clinical judgment, the Hematology/Oncology subcommittee will continue to follow the FDA's guidance for SLCL.

Keytruda is currently being studied in clinical trials for a variety of other cancers not included in the background section of this Medical Policy. Keytruda is also currently being studied in ongoing clinical trials for other uses including, but not limited to other malignancies and solid tumors. However, for these off-label uses, currently there is insufficient published evidence to support the use of Keytruda for such conditions.

NCCN also provides a category 2A recommendation for use of Keytruda as palliative therapy for patients with esophageal and esophagogastric junction cancer who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease and Karnofsky performance score ≥60% or ECOG performance score of ≤2 and if no prior tumor progression while on therapy with a checkpoint inhibitor as preferred third-line or subsequent therapy as a single agent for esophageal and EGJ adenocarcinoma with PD-L1 expression levels by CPS of ≥1. At this time, there is lack of supporting data to support such use.

NCCN provides a category 2A recommendation for use of Keytruda as useful in certain circumstances in those with salivary gland tumors as single-agent systemic therapy for tumor mutational burden high (TMB-H) recurrent disease with distant metastases in patients with a performance status (PS) of 0-3, or unresectable locoregional recurrence or second primary with prior radiation therapy. The recommendation was based on an ongoing study (Marabelle 2020) that included three patients with TMB-H salivary gland cancer. Therefore, there is lack of supporting data to support such use at this time.

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

NCCN provides a category 2A recommendation for use of Keytruda in combination with ipilimumab in cutaneous melanoma as preferred second-line or subsequent therapy option for metastatic or unresectable disease after progression or maximum clinical benefit from BRAF targeted therapy. This recommendation was based on an open- label, phase 1b study (Carlino 2020), which resulted in treatment related adverse effects of 96.1% (35.9% with drug discontinuation), of which 47.1% were grade 3 and higher. Therefore, further data is warranted to support such use.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J9271	Injection, pembrolizumab, 1 mg [Keytruda]
ICD-10	**Description**
C00.0-C76.8	Malignant neoplasms
C15.3-C15.5	Malignant neoplasm of esophagus upper, middle, or lower third
C15.8-C15.9	Malignant neoplasm of overlapping sites of esophagus
C16.0	Malignant neoplasm of stomach
C17.0-C17.9	Malignant neoplasm of small intestine
C18.0-C18.9	Malignant neoplasm of colon
C19	Malignant neoplasm of colon and rectum
C20	Malignant neoplasm of rectum
C21.0-C21.8	Malignant neoplasm of anus, unspecified
C22.1	Intrahepatic bile duct carcinoma
C24.8	Malignant neoplasm: Overlapping lesion of biliary tract.
C24.9	Malignant neoplasm: Biliary tract, unspecified.
C34.00-C34.92	Malignant neoplasm of bronchus and lung
C37	Malignant neoplasm of thymus
C40.00-C41.9	Malignant neoplasm of bone and articular cartilage
C43.0-C43.8	Malignant melanoma of skin
C44.00-C44.99	Other and unspecified malignant neoplasm of skin
C45.0-C45.9	Mesothelioma
C46.0-C46.9	Kaposi's sarcoma
C47.0-C47.9	Malignant neoplasm of peripheral nerves and autonomic nervous system

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

C48.0-C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C49.0-C49.9	Malignant neoplasm of other connective and soft tissue
C4A.0-C4A.9	Merkel cell carcinoma
C50.011-C50.919	Malignant neoplasm of breast
C51.0-C57.9	Malignant neoplasms of female genital organs
C58	Malignant neoplasm of placenta
C60.0-C62.92	Malignant neoplasms of male genital organs
C63.7-C63.9	Malignant neoplasm of other specified, overlapping sites, unspecified male genital organs
C64.1- C68.0	Malignant neoplasm of kidney, renal pelvis, ureter, bladder, urethra
C69.30-C69.42	Malignant neoplasm of choroid, ciliary body
C69.60-C69.62	Malignant neoplasm of orbit
C71.0-C72.1	Malignant neoplasm of brain, cauda equina, spinal cord
C72.9	Malignant neoplasm of central nervous system, unspecified
C73	Malignant neoplasm of thyroid
C74.00-C74.02	Malignant neoplasm of cortex of adrenal gland
C74.90-C74.92	Malignant neoplasm of unspecified part of adrenal gland
C76.0-C76.8	Malignant neoplasm of other and ill-defined sites
C77.0-C79.9	Secondary malignant neoplasms
C7B.00-C7B.8	Secondary neuroendocrine tumors
C80.0-C80.1	Malignant neoplasm without specification of site
C81.10-C81.99	Hodgkin lymphoma (classical)
C84.00-C84.09	Mycosis fungoides
C84.10-C84.19	Sezary disease
C84.Z0-C84.Z9	Other mature T/NK-cell lymphomas
C84.90-C84.99	Mature T/NK-cell lymphomas, unspecified
C85.20-C85.29	Mediastinal (thymic) large B-cell lymphoma
C86.00	Extranodal NK/T-cell lymphoma, nasal type not having achieved remission
C86.60	Primary cutaneous CD30-positive T-cell proliferations not having achieved remission
C91.10-C91.12	Chronic lymphocytic leukemia of B-cell type
D09.0	Carcinoma in situ of bladder
D15.0	Benign neoplasm of thymus
D37.01	Neoplasm of uncertain behavior of lip
D37.02	Neoplasm of uncertain behavior of tongue
D37.05	Neoplasm of uncertain behavior of pharynx
D37.09	Neoplasm of uncertain behavior of other specified sites of the oral cavity
D37.1	Neoplasm of uncertain behavior of stomach
D37.8-D37.9	Neoplasm of uncertain behavior of other specified digestive organs
D38.0	Neoplasm of uncertain behavior of larynx

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

D38.4	Neoplasm of uncertain behavior of thymus
D38.5	Neoplasm of uncertain behavior of other respiratory organs
D38.6	Neoplasm of uncertain behavior of respiratory organ, unspecified
Z85.00-Z85.59	Personal history of malignant neoplasms
Z85.71	Personal history of Hodgkin lymphoma
Z85.810-Z85.9	Personal history of malignant neoplasms

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Pembrolizumab (Keytruda®) and Pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

Requests for Keytruda® (pembrolizumab) may be approved if the following criteria are met:

I. Individual has a diagnosis of **locoregional unresectable or metastatic Adrenocortical Carcinoma** (NCCN 2A);
AND
   A. Individual is using as single agent, or in combination with mitotane; **AND**
   B. Individual has a current ECOG performance status of 0-2; **AND**
   C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
   D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

II. Individual has a diagnosis of metastatic ampullary adenocarcinoma (NCCN 2A); **AND**
   A. Individual is using as a single agent; **AND**
   B. Individual has high tumor mutation burden (TMB) (greater than or equal to 10 mutations per megabase) or dMMR/MSI-H tumor; **AND**
   C. Individual is using as first-line therapy; **AND**
   D. Individual has not received treatment with another anti-PD-1, anti-PD-L1; **AND**
   E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant

OR

III. Individual has a diagnosis of **locally recurrent, unresectable, or metastatic Triple-Negative Breast Cancer** (TNBC); **AND**
   A. Individual is using in combination with paclitaxel/nab-paclitaxel, ***or*** in combination with gemcitabine and a platinum agent); **AND**
   B. Individual has a tumor with PD-L1 gene expression with Combined Positive Score (CPS) of greater than or equal to 10; **AND**
   C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**

D. Individual has a current Eastern Cooperative Group (ECOG) performance status of 0-2; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

IV. Individual has a diagnosis of high risk early-stage **Triple-Negative Breast Cancer** (TNBC) (Label, NCCN 2A);
AND
A. Individual is using in combination with chemotherapy in the neoadjuvant setting; **AND**
B. Individual will continue/is continuing Keytruda as single agent in the adjuvant setting after surgical intervention; **AND**
C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual has a current Eastern Cooperative Group (ECOG) performance status of 0-2; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant

OR

V. Individual has a diagnosis of locally advanced unresectable or metastatic Biliary Tract Cancer (BTC) (Label, NCCN 1, 2A); **AND**
A. Individual is using in combination with cisplatin and gemcitabine; **AND**
B. Individual has not received prior systemic therapy in the advanced or metastatic setting; **AND**
C. Individual has a current ECOG performance status of 0-2; **AND**
D. Individual has not received treatment with another anti-PD-1, anti-PD-L1, anti-PD-L2 agent, or with an agent directed to another stimulatory or coinhibitory T-cell receptor (e.g., CTLA-4 agent); **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

VI. Individual has a diagnosis of unresectable or resected gross residual (R2) disease or metastatic Biliary Tract Cancer (NCCN); **AND**
A. Using in one of the following ways:
1. Individual is using as primary treatment in combination with cisplatin and gemcitabine (NCCN 1); **OR**
2. Individual is using as primary treatment as monotherapy for MSI-H and/or dMMR disease (NCCN 2A); **OR**
3. Individual is using as subsequent treatment for progression on or after systemic treatment in combination with cisplatin and gemcitabine (NCCN 2A); **AND**
4. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent;

OR

VII. Individual has a diagnosis of **persistent, recurrent or metastatic Cervical Cancer** (Label, NCCN 2A); **AND**
A. Individual is using in combination with paclitaxel and a platinum agent, with or without

bevacizumab; **AND**

B. Individual has a tumor with PD-L1 gene expression with Combined Positive Score (CPS) of greater than or equal to 1 (CPS ≥ 1); **AND**
C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual has a current Eastern Cooperative Group (ECOG) performance status of 0-2; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

VIII. Individual has a diagnosis of **recurrent or metastatic Cervical Cancer**; **AND**
A. Individual is using as monotherapy; **AND**
B. Individual is using for one of the following:
1. Individual has a tumor with PD-L1 gene expression with Combined Positive Score (CPS) of greater than or equal to 1; **OR**
2. Individual has MSI-H or dMMR tumors;

AND

C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual has a current Eastern Cooperative Group (ECOG) performance status of 0-2; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

IX. Individual has a diagnosis of **FIGO 2014 Stage III-IVA cervical cancer** (Label, NCCN 1, 2A); **AND**
A. Individual is using in combination with chemoradiotherapy (Cisplatin or carboplatin (if cisplatin intolerant) plus external beam radiation therapy [EBRT] followed by brachytherapy (CRT)); **AND**
B. No prior definitive surgery, radiation, or systemic therapy for cervical cancer; **AND**
C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

X. Individual has a diagnosis of **Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma** (Keytruda QLEX does not share this indication) (NCCN 2A); **AND**
A. Individual is using as a single agent; **OR**
B. Individual is using in combination with ibrutinib; **AND**
C. Individual is using for histologic (Richter) transformation to diffuse large B-cell lymphoma; **AND**
D. One of the following:
1. Individual has del(17p)/TP53 mutation; **OR**
2. Individual has chemotherapy refractory; **OR**
3. Individual is unable to receive chemoimmunotherapy;

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

OR

XI. Individual has a diagnosis of **metastatic Anal Cancer** (NCCN 2A): **AND**
- A. Individual is using as second-line or subsequent therapy; **AND**
- B. Individual is using as monotherapy; **AND**
- C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; AND
- D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XII. Individual has a diagnosis of **Colorectal Cancer** (Label, NCCN 2A); **AND**
- A. Individual is using as monotherapy; **AND**
- B. Individual meets *one* of the following:
  1. Primary treatment as a single agent for unresectable metachronous metastases (deficient mismatch repair/high microsatellite instability [dMMR/MSIH] only) and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months;

     OR
  2. Subsequent therapy as a single agent (if nivolumab or pembrolizumab not previously given) for unresectable, locally advanced or metastatic disease (dMMR/MSIH only) following previous treatment with the following:
     a. Oxaliplatin-, irinotecan-, and/or fluoropyrimidine-based therapy;

        OR
     b. First line treatment as a single agent for unresectable, advanced, or metastatic disease (dMMR/MSIH only);

AND
- C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
- D. Individual has a current ECOG performance status of 0-2; **AND**
- E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XIII. Individual has a diagnosis of **locally advanced, regional, recurrent or metastatic Cutaneous Squamous Cell Carcinoma** (cSCC) (Label, NCCN 2A); **AND**
- A. Individual is using as monotherapy; **AND**
- B. Disease is not curable by surgery or radiation; **AND**
- C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
- D. Individual has a current ECOG performance status of 0-2; **AND**
- E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XIV. Individual has a diagnosis of **advanced Endometrial cancer** (Stage III-IV) (NCCN 1); **AND**
- A. One of the following:

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

1. Using in combination with carboplatin and paclitaxel; **OR**
2. Using as a single agent for maintenance therapy;

OR

XV. Individual has a diagnosis of **advanced Endometrial Cancer** (Label, NCCN 1, 2A); **AND**

A. Individual is using in one of the following ways:
1. Individual is using in combination with lenvatinib; **AND**
2. Individual is mismatch repair proficient (pMMR) or not microsatellite instability high (MSI-H); **AND**
3. One of the following:
a. Individual has disease progression after one or more prior lines of systemic therapy; **OR**
b. Individual has recurrent disease after prior platinum-based therapy in any setting, including neoadjuvant and adjuvant therapy;

OR

4. Individual is using as a single agent; **AND**
5. Individual is MSI-H or dMMR;
6. Individual is not a candidate for curative surgery or radiation; **AND**
7. Individual has disease progression after one or more prior lines of systemic therapy;

AND

B. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
C. Individual has a current ECOG performance status of 0-2; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XVI. Individual has a diagnosis of esophageal and esophagogastric junction cancers (NCCN)**; AND**

A. Individual is using for relieving dysphagia**; AND**
B. Individual is medically fit and planned for esophagectomy**; AND**
C. One of the following**:**
1. Individual has PD-L1 CPS ≥ 1 (NCCN 1); **AND**
2. Individual is using in combination with platinum- and fluoropyrimidine-based chemotherapy; **OR**
3. Individual has MSI-H or dMMR tumor (NCCN 2A); **AND**
4. Individual is using a single agent or in combination with platinum- and fluoropyrimidine-based chemotherapy;

OR

XVII. Individual has a diagnosis of Esophageal and Esophagogastric Junction Cancer or Gastric Cancer (NCCN 2A); **AND**

A. Individual has MSI-H or dMMR tumor; **AND**

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

B. Individual is using as monotherapy; **AND**
C. One of the following:
1. Individual is using as primary treatment; **OR**
2. Individual is using as perioperative immunotherapy for Esophageal and Esophagogastric junction cancer; **OR**
3. Individual is using as postoperative management for Gastric cancer following R0 resection in those who have received systemic therapy;

OR

XVIII. Individual has a diagnosis of **unresectable, recurrent locally advanced or metastatic squamous cell Esophageal Cancer** (Label, NCCN 1, 2A); **AND**
A. Individual is using as monotherapy; **AND**
B. Individual has a tumor with PD-L1 gene expression with CPS of greater than or equal to 10; **AND**
C. Individual has demonstrated disease progression after one or more prior lines of systemic therapy; **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual has a current ECOG performance status of 0-2; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XIX. Individual has a diagnosis of **unresectable, recurrent locally advanced, or metastatic Esophageal Cancer** (Label, NCCN 1, 2A); **AND**
A. Individual is using in combination with platinum and fluoropyrimidine-based chemotherapy; **AND**
B. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
C. Individual has a current ECOG performance status of 0-2; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XX. Individual has a diagnosis of unresectable locally advanced, recurrent, or metastatic Esophageal or Esophagogastric Junction cancer or Gastric Cancer (NCCN); **AND**
A. Individual has one of the following:
1. MSI-H or dMMR tumor (independent of PD-L1 status) (NCCN 2A); **AND**
a. Individual is using in combination with platinum- and a fluoropyrimidine-based chemotherapy (NCCN 1); **OR**
b. Individual is using as a single agent; **OR**
2. HER2 overexpression negative adenocarcinoma and PD-L1 CPS ≥ 1 for palliative therapy (NCCN 1, 2A); **AND**
a. Individual is using in combination with platinum- and a fluoropyrimidine-based chemotherapy; **AND**
b. Individual is using as first-line therapy; **OR**
3. HER2 overexpression positive adenocarcinoma and PD-L1 expression by CPS of ≥1 (NCCN 1); **AND**

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

a. Individual is using in combination with trastuzumab (or trastuzumab biosimilar), platinum- and fluoropyrimidine-based chemotherapy; **AND**
b. Individual is using as first-line therapy; **OR**

4. Squamous cell carcinoma for palliative therapy; **AND**
   a. Individual is using as a single agent for second-line therapy (NCCN 1); **AND**
   b. Individual has a PD-L1 expression by CPS of ≥ 10; **OR**
   c. Individual is using in combination with platinum- and a fluoropyrimidine-based chemotherapy for first-line therapy (NCCN 1); **AND**
   d. Individual has a PD-L1 expression by CPS of ≥ 1; **AND**

B. Individual has a current ECOG performance status of 0-2; **AND**
C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XVII. Individual has a diagnosis of **relapsed or refractory primary cutaneous anaplastic large cell lymphoma** (ALCL) (Keytruda QLEX does not share this indication) ; **AND**
A. Individual has multifocal lesions with ALCL or cutaneous ALCL with regional node (excludes systemic ALCL); **AND**
B. Individual is using as monotherapy; **AND**
C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XVIII. Individual has a diagnosis of **malignant chemotherapy-resistant gestational trophoblastic neoplasia**; **AND**
A. Individual has one of the following:
   1. High-risk disease; **OR**
   2. Recurrent or progressive intermediate trophoblastic tumor following treatment with a platinum-based regimen;

AND

B. Individual is using as monotherapy; **AND**
C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XIX. Individual has a diagnosis of **recurrent, unresectable, or metastatic Head and Neck Squamous Cell Carcinoma** (HNSCC) (Label, NCCN 1, 2A); **AND**
A. Individual is using as monotherapy; **AND**
   1. Individual meets *one* of the following:
      a. Individual is using as first-line treatment for tumor with PD-L1 gene expression with CPS of greater than or equal to 1; **OR**

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

b. Individual has demonstrated disease progression on or after platinum-containing chemotherapy; **OR**
c. Individual has a salivary gland tumor with either MSI-H, dMMR, TMB-H (≥ 10 mut/Mb), or PD-L1 positive recurrent disease; **OR**

2. Individual is using in combination; **AND**
3. Individual meets one of the following:
   a. Individual is using as first-line treatment in combination with platinum-containing chemotherapy and fluorouracil regardless of PD-L1 expression (NCCN 2A); **OR**
   b. Individual is using as first or subsequent-line in combination with platinum-containing chemotherapy and docetaxel; **AND**

B. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
C. Individual has a current ECOG performance status of 0-2; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XX. Individual has a diagnosis of **resectable, locally advanced (Stage III-IVA) HNSCC (Label);** **AND**
A. Individual has a tumor with PD-L1 gene expression with CPS of greater than or equal to 1; **AND**
B. Individual is using pembrolizumab in one of the following ways**;**
   1. As a single agent for neoadjuvant therapy; **OR**
   2. As adjuvant treatment in combination with radiotherapy with or without cisplatin**; OR**
   3. As a single agent, following adjuvant therapy;

OR

XXI. Individual has a diagnosis of **recurrent, unresectable, or metastatic cancer of the nasopharynx** (NCCN 2A); **AND**
A. Individual has squamous cell carcinoma with mixed subtypes; **AND**
B. Individual is using as first-line systemic therapy or subsequent-line (if not previously used**); AND**
C. Individual is using in combination with cisplatin and gemcitabine**; AND**
D. Individual is determined to not be amenable to definitive surgery or radiation therapy**; AND**
E. Individual has a current ECOG performance status of 0-2**; AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXII. Individual has a diagnosis of **Hepatocellular Carcinoma** (HCC) (Label, NCCN 2A); **AND**
A. Individual is using as first-line systemic therapy as a single agent (may or may not have microsatellite instability high (MSI-H) tumors); **AND**
   1. Individual has one of the following:
      a. Individual has liver-confined, unresectable disease and is deemed ineligible for transplant; **OR**

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

b. Individual has extrahepatic/metastatic disease and are deemed ineligible for resection, transplant, or locoregional therapy; **OR**

B. Individual has demonstrated disease progression or intolerance on or after treatment with an approved first-line agent;

AND

C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**

D. Individual has a current ECOG performance status of 0-2; **AND**

E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXIII. Individual has a diagnosis of **relapsed or refractory Hodgkin Lymphoma** except for those with lymphocyte- predominant Hodgkin lymphoma (Keytruda QLEX does not share this indication) (Label, NCCN 2A);

OR

XXIV. Individual has a diagnosis of **Kaposi Sarcoma** (NCCN 2A); **AND**

A. Individual is using as subsequent therapy for relapsed/refractory advanced cutaneous, oral, visceral, or nodal disease that has progressed on or not responded to previous first-line systemic therapies; **AND**

B. Individual is using as monotherapy;

C. Individual has current ECOG performance status of 0-2; **AND**

D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**

E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXV. Individual has a diagnosis of **Melanoma (cutaneous and uveal)** (Label, NCCN 2A); **AND**

A. Individual has *unresectable or metastatic melanoma*; **AND**

B. Individual is using as monotherapy; **AND**

C. Individual meets one of the following:

1. Individual is using as first-line therapy in untreated disease; **AND**
2. Individual has current ECOG performance status of 0-2; **AND**
3. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
4. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

5. Individual is using as second-line or subsequent therapy for disease progression while receiving or since completing most recent therapy and/or intolerance to previous therapy;
6. Individual has current ECOG performance status of 0-2;

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

OR

XXVI. Individual has a diagnosis of **Melanoma (cutaneous)** (Label, NCCN 1, 2A); **AND**

A. Individual has *resected, stage IIB, IIC or high-risk stage III disease*; **AND**
B. Individual is using as monotherapy; **AND**
C. Individual is using as adjuvant therapy for up to 12 months; **AND**
D. Individual has a current ECOG performance status of 0-2; **AND**
E. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXVII. Individual has a diagnosis of **Melanoma (cutaneous)** (NCCN 2A); **AND**

A. Individual has metastatic or unresectable disease that has progressed following treatment with anti-PD-1/PD-L1-based therapy, including after anti-PD-1/PD-L1-based therapy that was used in combination with an anti-CTLA-4 for ≥2 doses; **AND**
B. Individual is using in combination with lenvatinib**; AND**
C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXVIII. Individual has a diagnosis of **Melanoma (cutaneous)** (NCCN 2A); **AND**

A. Individual has metastatic or unresectable disease**; AND**
B. Individual Is using Keytruda (pembrolizumab) in combination with low-dose Yervoy (ipilimumab) for a total of four doses, followed by pembrolizumab every 3 weeks as monotherapy for 2 years; **AND**
C. The combination is used as second-line or subsequent therapy for progression following anti-PD-1 therapy in advanced melanoma; **AND**
D. Individual has not previously used a combination of Yervoy (ipilimumab) and anti-PD-1; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXIX. Individual has a diagnosis of **metastatic or unresectable Melanoma (cutaneous)** (NCCN 2A); **AND**

A. Individual is BRAF V600E mutation positive**; AND**
B. Individual is using in combination with trametinib and dabrafenib**; AND**
C. Individual is using as second-line or subsequent therapy following disease progression or intolerance if BRAF/MEK and/or PD(L)-1 inhibitor was not previously used;

OR

XXX. Individual has a diagnosis of **metastatic Melanoma with brain metastases** (NCCN 2A); **AND**

A. Individual has one of the following:
   1. Individual has a primary diagnosis of BRAF non-specific melanoma; **OR**
   2. Individual is PD-L1 positive**; AND**

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

B. Individual is using as single agent for brain metastases; **AND**
C. Individual has a current ECOG performance status of 0-2; **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXI. Individual has a diagnosis of **Merkel Cell Carcinoma** (MCC) (Label, NCCN 2A); **AND**
A. Individual is using as monotherapy; **AND**
B. Individual has presence of metastatic or advanced locoregional MCC determined to be not amenable to definitive surgery or radiation therapy; **AND**
C. Individual has a current ECOG performance status of 0-2; **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXII. Individual has a diagnosis of **Adrenal Gland Tumor** (NCCN 2A); **AND**
A. Individual has locoregional unresectable or metastatic adrenocortical carcinoma; **AND**
B. Individual is using in combination with or without mitotane; **AND**
C. Individual has a current ECOG performance status of 0-2; **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant.

OR

XXXIII. Individual has a diagnosis of **Malignant Pleural or Peritoneal Mesothelioma** (Label, NCCN 1, 2A); **AND**
A. Individual has an unresectable advanced or metastatic disease; **AND**
B. Individual is using in combination with pemetrexed and platinum chemotherapy; **AND**
C. Individual is using as first-line treatment; **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant; **AND**
F. Individual has a current ECOG performance status of 0-2;

OR

XXXIV. Individual has a diagnosis of **Primary Mediastinal Large B-Cell Lymphoma** (Keytruda QLEX does not share this indication) (Label, NCCN 2A); **AND**
A. Individual is using in one of the following ways:
1. Individual is using as monotherapy;
AND
2. Individual is using to treat refractory disease or subsequent therapy for disease relapse after receiving two or more prior lines of therapy;

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

OR

3. Individual is 18 years and younger and using in combination with brentuximab vedotin after a partial response to second-line therapy (Pediatric Aggressive Mature B-Cell Lymphomas NCCN Guideline);

AND

B. Individual has a current ECOG performance status of 0-2; **AND**
C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXV. Individual has a diagnosis of **resectable Stage II, IIIA, or IIIB (N2) Non-Small Cell Lung Cancer (NSCLC)** (Label, NCCN 1, 2A); **AND**

A. Individual is using in one of the following ways:
1. Individual is using in combination with platinum-containing chemotherapy as neoadjuvant therapy; **OR**
2. Individual is using as a single agent for post-surgical adjuvant treatment for resectable (tumors≥ 4 cm or node positive) NSCLC; **AND**

B. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXVI. Individual has a diagnosis of **Stage IB (T2a ≥ 4cm), II, or IIIA (T2a ≥ 4cm), or IIIB (T3-4, N2) Non-Small Cell Lung Cancer** (NSCLC) (Label, NCCN 2A);

A. Individual is using as adjuvant treatment; **AND**
B. Individual is using following resection and prior platinum-based chemotherapy; **AND**
C. Individual is using as monotherapy; **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual has a current ECOG performance status of 0-2; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXVII. Individual has a diagnosis of ***advanced, recurrent, or metastatic*** **Non-Small Cell Lung Cancer** (NSCLC) (Label, NCCN 2A); **AND**

A. Individual is using for the first-line treatment; **AND**
B. Individual's disease is stage III or IV NSCLC; **AND**
C. Individual is using as monotherapy; **AND**
D. Tumor expresses PD-L1 gene on at least 1% or greater of tumor cells; **AND**
E. Individual does not have presence of actionable molecular markers*; **AND**
F. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent and has not undergone previous systemic therapy for metastatic disease; **AND**
G. Individual has a current ECOG performance status of 0-2; **AND**

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

H. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXVIII. Individual has a diagnosis of ***advanced, recurrent, or metastatic nonsquamous* NSCLC** (Label, NCCN 2A); **AND**

A. Individual is using for first-line treatment; **AND**
B. Disease is stage IIIb or IV NSCLC; **AND**
C. Individual is using in combination with pemetrexed and a platinum agent; **AND**
D. Individual does not have presence of actionable molecular markers*; **AND**
E. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent and has not undergone previous systemic therapy for metastatic disease; **AND**
F. Individual has a current ECOG performance status of 0-2; **AND**
G. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXIX. Individual has a diagnosis of **advanced, recurrent, or metastatic *squamous* NSCLC** (Label, NCCN 2A); **AND**

A. Individual is using for first line treatment; **AND**
B. Disease is stage IV NSCLC; **AND**
C. In one of the following ways:
   1. Individual is using in combination with carboplatin plus paclitaxel or nab-paclitaxel; **OR**
   2. Individual is using as monotherapy when PD-L1 ≥ 50% and there are contraindications to combination chemotherapy (NCCN 1); **AND**
D. Individual does not have presence of actionable molecular markers*; **AND**
E. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent and has not undergone previous systemic therapy for metastatic disease; **AND**
F. Individual has a current ECOG performance status of 0-2; **AND**
G. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XL. Individual has a diagnosis of **advanced, recurrent or metastatic *nonsquamous* NSCLC** (NCCN 1, 2A); **AND**

A. Using in one of the following ways:
   1. Individual is using in combination with pemetrexed as continuation maintenance therapy, if given first-line as part of pembrolizumab/pemetrexed and platinum-based regimen**; OR**
   2. Individual is using as monotherapy when PD-L1 ≥ 50% as continuous maintenance therapy, if given first-line as pembrolizumab monotherapy (NCCN 1); **AND**
B. Individual has tumor response or stable disease following initial cytotoxic therapy; **AND**
C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual has a current ECOG performance status of 0-2; **AND**

E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XLI. Individual has a diagnosis of **advanced, recurrent, or metastatic *squamous* cell NSCLC** (NCCN 2A); **AND**

A. Individual is using as monotherapy as *continuation maintenance therapy*, if given first-line as part of pembrolizumab/carboplatin/paclitaxel (or nab-paclitaxel) regimen or as pembrolizumab monotherapy; **AND**
B. Individual has tumor response or stable disease following initial cytotoxic therapy; **AND**
C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual has a current ECOG performance status of 0-2; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XLII. Individual has a diagnosis of **advanced, recurrent, metastatic NSCLC** (NCCN 1, 2A); **AND**

A. Individual is using as monotherapy in second or subsequent line of therapy; **AND**
B. Individual has tumor with PD-L1 gene expression level greater than or equal to 1% with disease progression on or after platinum-containing chemotherapy; **AND**
C. If individual has anaplastic lymphoma kinase (ALK) or epidermal growth factor receptor (EGFR) genomic tumor aberrations present, they must have disease progression on U.S. Food and Drug Administration (FDA) approved therapy for the aberrations prior to receiving pembrolizumab (Keytruda); **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent ; **AND**
E. Individual has a current ECOG performance status of 0-2; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XLIII. Individual has a diagnosis of **metastatic NSCLC with brain metastases** (NCCN 2A); **AND**

A. Individual has a primary diagnosis of non-small cell lung cancer; **AND**
B. Individual is using as single agent for brain metastases; **AND**
C. Individual has tumor with PD-L1 gene expression level greater than or equal to 1%; **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual has a current ECOG performance status of 0-2; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XLIV. Individual has diagnosis of **recurrent or refractory hypermutant tumor pediatric diffuse high-grade glioma** (NCCN 2A); **AND**

A. Individual is using as a single agent; **AND**
B. Individual has not received treatment with another PD-1 or anti-PD-L1 agent; **AND**
C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XLV. Individual has a diagnosis of penile cancer (NCCN 2A); **AND**
A. Individual is using as first-line therapy for local recurrence in the inguinal region or metastatic disease; **AND**
B. Individual is using in one of the following ways:
1. Individual is using Keytruda in combination with fluorouracil and platinum-based chemotherapy; **OR**
2. Individual is using Keytruda as maintenance therapy following efficacy of platinum-based chemotherapy; **AND**
C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XLVI. Individual has diagnosis of **relapsed or refractory Mycosis fungoides/Sezary syndrome** (NCCN 2A); **AND**
A. Individual is using for one of the following:
1. Individual is using as primary treatment for systemic therapy in stage III Mycosis fungoides (MF) or Stage IV Sezary Syndrome; **OR**
2. Individual is using as subsequent therapy for refractory disease to multiple previous therapies for Stage IIB MF with limited tumor or generalized tumor lesions, Stage III MF, Stage IV Sezary Syndrome, Stage IVA2 non-Sezary or stage IVB visceral disease; **AND**
B. Individual has not received treatment with another PD-1 or anti-PD-L1 agent; **AND**
C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XLVII. Individual has diagnosis of **advanced Renal Cell Carcinoma** (RCC) (Label, NCCN 1); **AND**
A. Using in one of the following ways:
1. Individual is using as first-line therapy; **AND**
2. Individual is using in combination with axitinib or lenvatinib; **AND**
3. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
4. Individual has a current Karnofsky performance status of ≥ 70%; **AND**
5. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

6. Individual is using as subsequent therapy; **AND**
7. Individual is using in combination with axitinib or lenvatinib; **AND**
8. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring

treatment with a systemic immunosuppressant;

OR

XLVIII. Individual has diagnosis of **Renal Cell Carcinoma** (RCC) (Label, NCCN 2A); **AND**

A. Individual is using as adjuvant treatment in those with intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions; **AND**

B. Individual has not received treatment with another PD-1 or anti-PD-L1 agent; **AND**

C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XLIX. Individual has a diagnosis of **Renal Cell Carcinoma** (RCC) (NCCN 2A); **AND**

A. Individual has RCC with non-clear cell histology; **AND**

B. Individual is using as single-agent therapy for relapse or stage IV disease as systemic therapy; **AND**

C. Individual has not received treatment with another PD-1 or anti-PD-L1 agent; **AND**

D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

L. Individual has a diagnosis of **Ovarian cancer** (NCCN 2A); **AND**

A. Individual is using for platinum-resistant persistent disease; **OR**

B. Individual is using for recurrence in combination with oral cyclophosphamide and bevacizumab (or bevacizumab biosimilars); **AND**

C. Individual has not received treatment with another PD-1 or anti-PD-L1 agent**; AND**

D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

LI. Individual has a diagnosis of **alveolar soft part sarcoma** (ASPS); **AND**

A. Individual is using in combination with axitinib (Inlyta); **AND**

B. Individual has not received treatment with another anti PD-1 or anti PD-L1 agent; **AND**

C. Individual has a current ECOG performance status of 0-1; **AND**

D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

LII. Individual has a diagnosis of **unresectable, recurrent, advanced, or metastatic Soft Tissue Sarcoma** (NCCN 2A); **AND**

A. Individual is using as monotherapy for first line or subsequent therapy; **AND**

B. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**

C. Individual has a current ECOG performance status of 0-2; **AND**

D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

OR

LIII. Individual has a diagnosis of **unresectable or metastatic solid tumors; AND**
- A. Individual is using as monotherapy; **AND**
- B. One of the following:
  1. Individual has high tumor mutation burden (TMB) (greater than or equal to 10 mutations per megabase); **OR**
  2. Individual has a dMMR/MSI-H tumor**; AND**
- C. Individual has disease progression following prior treatment with no other satisfactory alternative treatment options; **AND**
- D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
- E. Individual has a current ECOG performance status of 0-2; **AND**
- F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

LIV. Individual has a diagnosis of **relapsed or refractory primary cutaneous anaplastic large cell lymphoma (ALCL)** (Keytruda QLEX does not share this indication) (NCCN 2A); **AND**
- A. Disease is either ALCL with multifocal lesions or cutaneous ALCL (excluding systemic ALCL); **AND**
- B. Individual is using as a single agent; **AND**
- C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; AND
- D. Individual has a current ECOG performance status of 0-2**; AND**
- E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

LV. Individual has a diagnosis of **relapsed or refractory extranodal NK-T-cell lymphoma** (Keytruda QLEX does not share this indication); **AND**
- A. Individual is using following treatment with asparaginase-based regimen; **AND**
- B. Individual is using as monotherapy; **AND**
- C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
- D. Individual has a current ECOG performance status of 0-2; **AND**
- E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

LVI. Individual has a diagnosis of **unresectable or metastatic Thymic Carcinoma** (NCCN 2A); **AND**
- A. Individual is using as monotherapy; **AND**
- B. Individual has disease progression following chemotherapy, or intolerance to first-line combination regimens; **AND**
- C. Individual does not have thymomas; **AND**
- D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
- E. Individual has a current ECOG performance status of 0-2; **AND**

F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

LVII. Individual has a diagnosis of **metastatic thyroid cancer** (NCCN 2A); **AND**

A. Individual is using in combination with lenvatinib; **AND**
B. Individual is using as first-line or second-line therapy; **AND**
C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual has a current ECOG performance status of 0-2; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

LVIII. Individual has a diagnosis of **locally advanced or metastatic Urothelial Cancer** (Label); **AND**

A. Individual is using in combination with enfortumab vedotin (Padcev); **AND**
B. Individual has a current ECOG performance status of 0-2; **AND**
C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

LIX. Individual has diagnosis of **muscle invasive bladder cancer (MIBC)** (Label); **AND**

A. Individual is ineligible for cisplatin-containing chemotherapy; **AND**
B. Individual is using in in combination with enfortumab vedotin**; AND**
C. Individual is using as as neoadjuvant treatment and then continued after cystectomy as adjuvant treatment;

OR

LX. Individual has a diagnosis of **locally advanced or metastatic Urothelial Carcinoma** (Label, NCCN 1, 2A); **AND**

A. Individual is using as monotherapy; **AND**
B. Individual meets *one* of the following:
   1. Individual is not eligible for any platinum-containing chemotherapy; **OR**
   2. Individual is using as subsequent therapy; **OR**
   3. Individual has disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy;

AND

C. Individual has not received treatment with another anti PD-1 or anti-PD-L1 agent; **AND**
D. Individual has a current ECOG performance status of 0-2; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

LXI. Individual has a diagnosis of **high-risk non-muscle invasive (T1, high grade Ta, and/or carcinoma in situ [CIS]) Urothelial Carcinoma of the Bladder with or without papillary tumors** (Label, NCT02625961); **AND**

A. Individual has Bacillus Calmette-Guerin (BCG)- unresponsive disease defined as one of the following:
   1. Persistent disease despite adequate BCG therapy (adequate defined as administration of at least 5 doses of an initial induction course *plus either* at least 2 doses of maintenance therapy or at least 2 doses of a second induction course); **OR**
   2. Disease recurrence after an initial tumor-free state following adequate BCG therapy (adequate defined as administration of at least 5 doses of an initial induction course *plus either* at least 2 doses of maintenance therapy or at least 2 doses of a second induction course); **OR**
   3. T1 disease (i.e., tumor has spread to the connective tissue, but not the muscle) following a single induction course of BCG; **AND**

B. Individual is ineligible for cystectomy; **AND**

C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**

D. Individual has a current ECOG performance status of 0-2; **AND**

E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

LXII. Individual has a diagnosis of **metastatic squamous cell vaginal cancer**; **AND**

A. Individual is using in pembrolizumab in combination with paclitaxel and platinum-containing chemotherapy with or without bevacizumab (or bevacizumab biosimilars); **AND**

B. Individual has a PD-L1 positive tumor; **AND**

C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**

D. Individual has a current ECOG performance status of 0-2; **AND**

E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

LXIII. Individual has a diagnosis of **advanced, recurrent, or metastatic vulvar cancer**;

A. Individual is using as a single agent; **AND**
   1. Individual has a tumor with PD-L1 gene expression with Combined Positive Score (CPS) of greater than or equal to 1 (CPS ≥ 1); **AND**
   2. Individual has disease progression on or after chemotherapy;

OR

B. Individual is using in combination with paclitaxel and a platinum-containing agent with or without bevacizumab (or bevacizumab biosimilars); **AND**
   1. Individual is using as first-line therapy or second-line or beyond, if not previously used;

OR

C. Individual is using in combination with bevacizumab (or bevacizumab biosimilars) for

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

maintenance therapy; **AND**

D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant.

***Note:** Actionable molecular markers include EGFR, ALK, ROS1, BRAF, NTRK, MET and RET mutations. The NCCN panel recommends testing prior to initiating therapy to help guide appropriate treatment. If there is insufficient tissue to allow testing for all of these markers, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes (NCCN 1, 2A).

B. Criteria For Continuation of Therapy

i. MMM considers continuation of Keytruda (pembrolizumab) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of unacceptable toxicity or disease progression, or the maximum duration of therapy has not been exceeded. The following information should be supplied for reauthorization:

   A. A current oncology note documenting the patient's response to treatment showing no progression of disease
   B. Current imaging studies and other objective measures, as appropriate, showing no progression of disease when compared with previous results

ii. Keytruda (pembrolizumab) will be approved for:

   A. A total of 24 months in cases where Keytruda is used for unresectable, locally advanced, or metastatic cancers.
   B. A total of 12 months if Keytruda is used as adjuvant treatment of adult patients with melanoma, NSCLC, or RCC.
   C. A total of 12 months if Keytruda is used in pediatric patients (12 years and older) for adjuvant treatment of melanoma.
   D. For resectable NSCLC
      1. In the neoadjuvant phase (before surgery), Keytruda in combination with chemotherapy will be approved for a total of 12 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity.
      2. After surgery Keytruda as a single agent will be approved for 39 weeks or until disease recurrence or unacceptable toxicity.
   E. In adult patients with high-risk early-stage TNBC
      1. When used as neoadjuvant treatment (in combination with chemotherapy), Keytruda (pembrolizumab) will be approved for 24 weeks (8 doses of 200 mg every 3 weeks or 4 doses of 400 mg every 6 weeks) or until disease progression.
      2. When used as adjuvant after surgery, Keytruda (as a single agent), will be approved will be approved for up to 27 weeks (9 doses of 200 mg every 3 weeks or 5 doses of 400 mg every 6 weeks) or until disease recurrence or unacceptable toxicity.

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

C. Authorization Duration

i. Initial Approval Duration: Up to 6 months
ii. Reauthorization Approval Duration: Up to 6 months

D. **Conditions Not Covered**

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. Keytruda (pembrolizumab) may not be approved when the above criteria (Section A: Criteria for Initial Approval) are not met and for all other indications

Limits or Restrictions

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Indication (see abbreviation list in the "Background" section)	Limit	Duration
Monotherapy		
Adult patients with unresectable or metastatic melanoma	200 mg every 3 weeks or 400 mg every 6 weeks	Until disease progression or unacceptable toxicity
Adjuvant treatment of adult patients with melanoma, NSCLC, or RCC	200 mg every 3 weeks or 400 mg every 6 weeks	Until disease recurrence, unacceptable toxicity, or up to 12 months
Adult patients with NSCLC, HNSCC, cHL, PMBCL, locally advanced or metastatic	200 mg every 3 weeks or 400 mg every 6 weeks	Until disease progression, unacceptable toxicity, or up to 24 months

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

Indication (see abbreviation list in the "Background" section)	Limit	Duration
Urothelial Carcinoma, MSI- H or dMMR Cancer, MSI-H or dMMR CRC, MSI-H or dMMR Endometrial Carcinoma, Esophageal Cancer, Cervical Cancer, HCC, MCC, TMB-H Cancer, or cSCC		
Adult patients with high-risk BCG- unresponsive NMIBC	200 mg every 3 weeks or 400 mg every 6 weeks	Until persistent or recurrent high-risk NMIBC, disease progression, unacceptable toxicity, or up to 24 months
Pediatric patients with cHL, PMBCL, MSI-H or dMMR Cancer, MCC, or TMB-H Cancer	2 mg/kg every 3 weeks (up to a maximum of 200 mg)	Until disease progression, unacceptable toxicity, or up to 24 months
Pediatric patients (12 years and older) for adjuvant treatment of melanoma	2 mg/kg every 3 weeks (up to a maximum of 200 mg)	Until disease recurrence, unacceptable toxicity, or up to 12 months
Combination Therapy		
Adult patients with resectable NSCLC	200 mg every 3 weeks or 400 mg every 6 weeks	Neoadjuvant treatment in combination with chemotherapy for 12 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with Keytruda as a single agent after surgery for 39 weeks or until disease recurrence or unacceptable toxicity
Adult patients with NSCLC, Gastric Cancer (HER-2 negative or positive), HNSCC, or Esophageal Cancer or Biliary Tract Cancer	200 mg every 3 weeks or 400 mg every 6 weeks	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with locally advanced or metastatic urothelial carcinoma	200 mg every 3 weeks or 400 mg every 6 weeks	Until disease progression, unacceptable toxicity, or up to 24 months

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

Indication (see abbreviation list in the "Background" section)	Limit	Duration
Adult patients with Cervical Cancer	200 mg every 3 weeks or 400 mg every 6 weeks	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with RCC	200 mg every 3 weeks or 400 mg every 6 weeks	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with Endometrial Carcinoma	200 mg every 3 weeks or 400 mg every 6 weeks	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with high-risk early-stage TNBC	200 mg every 3 weeks or 400 mg every 6 weeks	Neoadjuvant treatment in combination with chemotherapy for 24 weeks (8 doses of 200 mg every 3 weeks or 4 doses of 400 mg every 6 weeks) or until disease progression or unacceptable toxicity, followed by adjuvant treatment with Keytruda as a single agent for up to 27 weeks (9 doses of 200 mg every 3 weeks or 5 doses of 400 mg every 6 weeks) or until disease recurrence or unacceptable toxicity.
Adult patients with locally recurrent unresectable or metastatic TNBC	200 mg every 3 weeks or 400 mg every 6 weeks	Until disease progression, unacceptable toxicity, or up to 24 months
Exceptions		
N/A		

Keytruda is administered as a 30-minute intravenous infusion. Refer to the full prescribing information for Keytruda for the agents administered in combination with Keytruda for recommended dosing information as appropriate. Refer to full prescribing information for Keytruda for dosage modifications and preparation and administration instructions.

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

Keytruda QLEX recommended dosage and duration of treatment:

Indication	Recommended Dosage of KEYTRUDA QLEX	Duration/Timing of Treatment
Monotherapy		
Adult patients with unresectable or metastatic melanoma	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks	Until disease progression or unacceptable toxicity
Adjuvant treatment of adult patients with melanoma, NSCLC, or RCC	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks	Until disease recurrence, unacceptable toxicity, or up to 12 months
Adult patients with NSCLC, HNSCC, locally advanced or metastatic Urothelial Carcinoma, MSI-H or dMMR Cancer, MSI-H or dMMR CRC, MSI-H or dMMR or Endometrial Carcinoma, Esophageal, Cancer, Cervical Cancer, HCC, MCC, TMB-H Cancer, or cSCC	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks	Until disease progression, or unacceptable toxicity, or up to 24 months
Adult patients with high-risk BCG unresponsive NMIBC	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks	Until persistent or recurrent high-risk NMIBC, disease progression, unacceptable toxicity, or up to 24 months
Pediatric patients* (12 years and older who weigh greater than 40 kg) with MSI-H or dMMR Cancer, MCC, or TMB-H Cancer	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks	Until disease progression, or unacceptable toxicity, or up to 24 months
Pediatric patients* (12 years and older who weigh greater than 40 kg) for adjuvant treatment of melanoma	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks	Until disease recurrence, unacceptable toxicity, or up to 12 months
Combination Therapy		
Adult patients with resectable NSCLC	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer KEYTRUDA QLEX prior to	Neoadjuvant treatment in combination with chemotherapy for 12 weeks or until disease progression that precludes definitive surgery or

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

	chemotherapy when given on the same day	unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA QLEX as a single agent after surgery for 39 weeks or until disease recurrence or unacceptable toxicity
Adult patients with NSCLC, MPM, HNSCC, HER2-negative Gastric Cancer, Esophageal Cancer, or BTC	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer KEYTRUDA QLEX prior to chemotherapy when given on the same day	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with locally advanced or metastatic urothelial cancer	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer KEYTRUDA QLEX prior to chemotherapy when given on the same day	Until disease progression, unacceptable toxicity, or up to 24 months
Indication	Recommended Dosage of KEYTRUDA QLEX	Duration/Timing of Treatment
Adult patients with locally advanced HNSCC	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer KEYTRUDA QLEX prior to cisplatin when given on the same day.	Neoadjuvant: • Administer KEYTRUDA QLEX for 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity. Adjuvant: • Administer KEYTRUDA QLEX in combination with RT with or without cisplatin. • Continue KEYTRUDA QLEX as a single agent. Continue KEYTRUDA QLEX until disease recurrence or unacceptable toxicity or up to one year
Adult patients with MIBC	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer KEYTRUDA QLEX after enfortumab vedotin when given on the same day.	Neoadjuvant: • Administer KEYTRUDA QLEX 395 mg/4,800 units every 3 weeks for 3 doses in combination with enfortumab vedotin or until disease progression that precludes curative-intent cystectomy or unacceptable toxicity. Adjuvant: • Administer KEYTRUDA QLEX 395 mg/4,800 units every 3

Policy Name	**Policy Number**	**Scope**
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

		weeks for 14 doses or 790 mg/9,600 units every 6 weeks for 7 doses in combination with enfortumab vedotin or until disease recurrence or unacceptable toxicity
Adult patients with HER2-positive Gastric Cancer	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer KEYTRUDA QLEX prior to trastuzumab and chemotherapy when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with Cervical Cancer	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer KEYTRUDA QLEX prior to chemoradiotherapy or prior to chemotherapy with or without bevacizumab when given on the same day.	Until disease progression, unacceptable toxicity, or for KEYTRUDA QLEX, up to 24 months
Adult patients with RCC	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer KEYTRUDA QLEX in combination with axitinib 5 mg orally twice daily‡ or Administer KEYTRUDA QLEX in combination with lenvatinib 20 mg orally once daily.	Until disease progression, unacceptable toxicity, or for KEYTRUDA QLEX, up to 24 months
Adult patients with Endometrial Carcinoma	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer KEYTRUDA QLEX prior to carboplatin and paclitaxel when given on the same day or Administer KEYTRUDA QLEX in combination with lenvatinib 20 mg orally once daily.	Until disease progression, unacceptable toxicity, or for KEYTRUDA QLEX, up to 24 months
Adult patients with high-risk early-stage TNBC	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer	Neoadjuvant treatment in combination with chemotherapy for 24 weeks (8 doses of 395 mg/4,800

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

	KEYTRUDA QLEX prior to chemotherapy when given on the same day.	units every 3 weeks or 4 doses of 790 mg/9,600 units every 6 weeks) or until disease progression or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA QLEX as a single agent for up to 27 weeks (9 doses of 395 mg/4,800 units every 3 weeks or 5 doses of 790 mg/9,600 units every 6 weeks) or until disease recurrence or unacceptable toxicity§
Adult patients with locally recurrent unresectable or metastatic TNBC	395 mg/4,800 units every 3 weeks or 790 mg/9,600 units every 6 weeks Administer KEYTRUDA QLEX prior to chemotherapy when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months

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    d. Biliary Tract Cancers. V1.2023. Revised January 24,2024.
    e. Bladder Cancer V2.2023. Revised February 9, 2023.

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

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h. Central Nervous System Cancers V1.2023. Revised March 24, 2023.
i. Cervical Cancer. V1.2024. Revised January 24, 2024.
j. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. V2.2023. Revised January 25, 2023.
k. Colon Cancer V1.2023. Revised March 29, 2023.
l. Cutaneous Melanoma V2.2023. Revised March 10, 2023.
m. Esophageal and Esophagogastric Junction Cancers. V2.2023. Revised March 10, 2023.
n. Gastric Cancer V2.2023. Revised January 24, 2024.
o. Gestational Trophoblastic Neoplasia V1.2023. Revised December 20, 2022.
p. Head and Neck Cancer V1.2023. Revised December 20, 2022.
q. Hepatobiliary Cancers V1.2023. Revised March 10, 2023.
r. Hodgkin Lymphoma V2.2023. Revised November 8, 2022.
s. Kaposi Sarcoma. V1.2023. Revised December 20, 2022.
t. Kidney Cancer V2.2024. Revised January 24, 2024.
u. Malignant Pleural Mesothelioma V2.2021. Revised February 16, 2021.
v. Merkel Cell Carcinoma V1.2023. Revised April 10, 2023.
w. Neuroendocrine and Adrenal Tumors V2.2022. Revised December 21, 2022.
x. Non-Small Cell Lung Cancer. V3.2023. Revised April 13, 2023.
y. Occult Primary. V3.2023. Revised December 21, 2022.
z. Ovarian Cancer V1.2023. Revised December 22, 2022.
aa. Pancreatic Adenocarcinoma V2.2022. December 6, 2022.
bb. Pediatric Aggressive Mature B-Cell Lymphomas. V1.2023. Revised April 4, 2023.
cc. Pediatric Central Nervous System Cancers. V2.2023. Revised October 31, 2022.
dd. Pediatric Hodgkin Lymphoma. V2.2023. March 9, 2023.
ee. Penile Cancer V1.2023. Revised December 1, 2022.
ff. Primary Cutaneous Lymphomas. V1.2023. Revised January 5, 2023.
gg. Prostate Cancer. V1.2023. Revised September 16, 2022.
hh. Rectal Cancer V1.2023. Revised March 29, 2023.
ii. Small Bowel Adenocarcinoma V1.2023. Revised January 9, 2023.
jj. Small Cell Lung Cancer. V3.2023. Revised December 21, 2022.
kk. Soft Tissue Sarcoma. V1.2023. Revised March 13, 2023.
ll. Squamous Cell Skin Cancer. V1.2023. Revised March 10, 2023. mm.T-Cell Lymphomas V1.2023. Revised January 5, 2023.
nn. Testicular cancer V1.2023. Revised January 26, 2023.
oo. Thyroid Carcinoma. V1.2023. Revised March 24, 2023.
pp. Thymomas and Thymic Carcinomas V1.2023. Revised December 15, 2022.
qq. Uterine Neoplasms V1.2024. Revised January 24, 2024.
rr. Uveal Melanoma V2.2023. Revised December 22, 2022.
ss. Vulvar Cancer (Squamous Cell Carcinoma) V1.2023. Revised December 22, 2022.

Policy Name	Policy Number	Scope
pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Select Review 12/1/2025	Addition of Keytruda Qlex as SubQ dosage form alternative for Keytruda only for solid tumor indications/ recommendations (Labe/NCCN). Addition of clinical criteria for neoadjuvant treatment in MIBC. Addition of Keytruda QLEX recommended dosage to quantity limit section.	12/3/2025	12/11/2025
Annual Review 10/2/2025	Add FDA indication for use in Malignant Pleural mesothelioma in combination for first-line treatment of unresectable advanced or metastatic disease. Coding Reviewed: Added ICD-10-CM C45.0. Add NCCN	10/7/2025	10/17/2025

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pembrolizumab (Keytruda®) and pembrolizumab and berahyaluronidase alfa-pmph (KEYTRUDA QLEX™)	MP-RX-FP-49-23	☒ MMM MA ☒ MMM Multihealth

	recommendations: use as first-line in metastatic ampullary adenocarcinoma if MSI-H/dMMR or TMB-H (≥ 10 mut/Mb); Add use in unresectable or resected gross residual disease or metastatic biliary tract cancer. Clarify use in MSI-H or dMMR tumors for recurrent or metastatic cervical cancer. Add use in CLL/SLL with ibrutinib or as a single agent. Add use in advanced or metastatic NSCLC include small bowel cancer as a single agent in those with dMMR, MSI-H, or POLE/POLD1 mutation with ultra-hypermutated phenotype (e.g. TMB >50 mut/Mb).Update criteria for use esophageal and esophagogastric junction cancers for relieving dysphagia and for mutation specific disease. Update criteria for mutation specific head and neck squamous cell carcinoma. Clarify use in Kaposi sarcoma. Clarify disease state use in cutaneous melanoma. Clarify use in squamous and nonsquamous NSCLC . Clarify disease states in Thymic cancer for use in metastatic only. Clarify disease state in thyroid disease for use in metastatic only. Add use in metastatic squamous cell vaginal cancer. Add combination uses for vulvar cancer. Wording and formatting updates. Added references. Coding Reviewed: Removed ICD-10-CM C86.6. Removed D09.10-D09.19 from range D09.0-D09.19 and updated description. Removed C80.2 from range C80.0-C80.2. Added ICD-10-CM C86.00, C86.60. Removed the following codes from range C00.0-C76.8: C22.2, C22.4-C22.7, C26.1-C26.9, C38.0-C39.9, C49.A0-C49.A9, C63.00-C63.2, C68.1-C69.22, C69.50-C69.52, C69.80-C70.9, C72.20- C72.59, C74.10-C74.12, C75.0-C75.9 and updated descriptions for resulting codes/ranges. Add FDA indication for use in resectable HNSCC as neoadjuvant, adjuvant,		

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	and continued single agent therapy for PD-L1 expressing tumors.		
Annual Review 10/16/2024	Update section XVI: Recurrent locally advanced unresectable, or metastatic Gastric or Gastroesophageal Junction Adenocarcinoma, to specify criteria for use without trastuzumab or biosimilar in patients with HER2 negative status.	3/20/2025	4/2/2025
Select Review 05/09/2024	Update statement for criteria for initial approval: Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met all approval criteria.	4/18/2024	6/28/2024
Select Review	• Add criteria for use in FDA approved use in advanced or metastatic biliary tract cancer in combination with carboplatin and paclitaxel. • Update endometrial cancer to clarify NCCN use as a single agent in maintenance therapy for stage III-IV disease. • Consolidate criteria for use in unresectable or metastatic solid tumors in RN XLIII and XLIV. • Add criteria for use in in combination with gemcitabine and cisplatin, for the treatment of patients with locally advanced unresectable or metastatic biliary tract cancer. • Update Gastric cancer indications (removed second line use indication with fluoropyridine and a platinum-containing regimen in metastatic gastric or gastroesophageal junction adenocarcinoma; added indication for use with trastuzumab plus platinum and fluoropyrimidine-based chemotherapy as first line treatment in locally advanced	3/25/2024	6/28/2024

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	unresectable or metastatic HER2 positive gastric or gastroesophageal junction adenocarcinoma). • Add the recommendation of the FDA of requiring PD-L1 gene expression with CPS of greater than or equal to 1 when using as first line treatment in patients with locally advanced unresectable or metastatic Gastric or Gastroesophageal Junction Adenocarcinoma. • Add the new indication of use in combination with chemoradiotherapy, for the treatment of patients with FIGO 2014 Stage III-IVA cervical cancer. • Coding Reviewed: Added ICD-10-CM C24.0-C24.9, C67-67.9, C22.1, C24.8, C24.9		
Policy Inception	Elevance Health's Medical Policy adoption.	N/A	11/30/2023