Pembrolizumab (Keytruda®)

Prior Authorization Drug Coverage Policy

Effective Date: 1/1/2021
Revision Date: n/a
Review Date: 10/6/2021
Lines of Business: Commercial
Policy type: Prior Authorization

This Drug Coverage Policy provides parameters for the coverage of pembrolizumab (Keytruda®). Consideration of medically necessary indications are based upon U.S. Food and Drug Administration (FDA) indications, recommended uses within the Centers of Medicare & Medicaid Services (CMS) five recognized compendia, including the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium (Category 1 or 2A recommendations), and peer-reviewed scientific literature eligible for coverage according to the CMS, Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 titled, "Off-Label Use of Anti-Cancer Drugs and Biologics." This policy evaluates whether the drug therapy is proven to be effective based on published evidence-based medicine.

Drug Description[1]

Binding of the programmed death ligand (PD-L), PD-L1 and PD-L2, to the programmed death receptor-1 (PD-1) receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-L1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

FDA Indications[1]

Pembrolizumab is FDA indicated for the following:

- Melanoma
  - Indicated for the treatment of patients with unresectable or metastatic melanoma.
  - Indicated for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.
- Non-Small Cell Lung Cancer (NSCLC)
  - Indicated in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations.

  - Indicated in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC.
  - Indicated as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS)≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is:
    - stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
    - metastatic.
  - Indicated as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab.
- Head and Neck Squamous Cell Cancer (HNSCC)
  - Indicated in combination with platinum and FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC.
  - Indicated as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test.
  - Indicated as a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.
- Classical Hodgkin Lymphoma (cHL)
  - Indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin Lymphoma (cHL)
  - Indicated for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy
- Primary Mediastinal Large B-Cell Lymphoma
  - 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.
    Limitations of Use: pembrolizumab is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.
- Urothelial Carcinoma
  - Indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.
  - Indicated 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.
    - Indicated 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.
- Microsatellite Instability-High Cancer or Mismatch Repair Deficient Colorectal Cancer
    - Indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
        - Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
        - Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.
- Microsatellite Instability-High or Mismatch Repair DeficientColorectal Cancer (CRC)
    - Indicated for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer
- Gastric Cancer
    - Indicated in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastaticHER2-positive gastric or gastroesophageal junction (GEJ)adenocarcinoma
    - Indicated as a single agent for the treatment of patients with recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS)≥1] as determined by an FDA-approved test, with disease progression on or after 2 or more prior lines of therapyi ncluding fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.
- Esophageal Cancer
    - Indicated for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:
        - in combination with platinum- and fluoropyrimidine-based chemotherapy, **OR**
        - as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test.
- Cervical Cancer
    - Indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

- Hepatocellular Carcinoma (HCC)
  - Indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.
- Merkel Cell Carcinoma (MCC)
  - Indicated for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC).
- Renal Cell Carcinoma (RCC)
  - Indicated in combination with axitinib, for the first-line treatment of adult patients with advanced RCC.
  - Indicated in combination with lenvatinib, for the first-line treatment of adult patients with advanced RCC.
- Endometrial Carcinoma
  - Indicated in combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapyi n any setting and are not candidates for curative surgery or radiation.
- Tumor Mutational Burden-High (TMB-H) Cancer
  - Indicated for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.
  - Limitations of Use: The safety and effectiveness of pembrolizumab in pediatric patients with TMB-H central nervous system cancers have not been established
- Cutaneous Squamous Cell Carcinoma (cSCC)
  - Indicated for the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma that is not curable by surgery or radiation.
- Triple-Negative Breast Cancer (TNBC)
  - Indicated for the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.
  - Indicated in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA approved test.

NCCN Compendium Supported Indications [2]

- Anal Carcinoma
- B-Cell Lymphomas- Diffuse Large B-Cell Lymphoma
- Bladder Cancer
- Bone Cancer
- Breast Cancer
- Central Nervous System Cancers
- Cervical Cancer

- Colon Cancer
- Cutaneous Melanoma
- Esophageal and Esophagogastric Junction Cancers
- Gastric Cancer
- Gestational Trophoblastic Neoplasia
- Head and Neck Cancers
- Hepatobiliary Cancers
- Hodgkin Lymphoma
- Kidney Cancer
- Malignant Pleural Mesothelioma
- Melanoma (Cutaneous)
- Melanoma (Uveal)
- Merkel Cell Carcinoma
- Neuroendocrine and Adrenal Tumors
- Non-Small Cell Lung Cancer
- Occult Primary
- Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer
- Pancreatic Adenocarcinoma
- Penile Cancer
- Primary Cutaneous Lymphoma
- Prostate Cancer
- Rectal Cancer
- Small Bowel Adenocarcinoma
- Small Cell Lung Cancer
- Soft Tissue Sarcoma
- Squamous Cell Skin Cancer
- T- Cell Lymphoma (extranodal NK/T-Cel lymphoma Nasal Type)
- Testicular Cancer
- Thymomas and Thymic Carcinoma
- Thyroid Carcinoma
- Uterine Neoplasms
- Vulvar Cancer

Coverage Determinations[1,2]

Pembrolizumab will require prior authorization. This agent is considered medically necessary for the following oncology indications if all criteria below are met:

Anal Carcinoma

- The member has a diagnosis of anal carcinoma with histology of squamous cell carcinoma **AND**

- Pembrolizumab is indicated as preferred second-line or subsequent therapy as a single-agent for metastatic disease (if not previously received).

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

B-Cell Lymphomas

- The member has a diagnosis of relapsed or refractory primary mediastinal large B-cell lymphoma (diffuse large b-cell lymphoma) **AND**
- Pembrolizumab will be used as a single agent

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Bone Cancer

- The member has a diagnosis of ONE of the following:
    - Osteosarcoma **OR**
    - Chondrosarcoma **OR**
    - Ewing Sarcoma **AND**
- Pembrolizumab will be used as single-agent therapy for unresectable or metastatic disease that has progressed following prior treatment and who have no satisfactory alternative treatment options for:
    - Patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) (preferred)
    - Tissue tumor mutation burden-high (TMB-H)tumors with 10 or more mutations per megabase (useful in certain circumstances)
- The member has a diagnosis of Chordoma **AND:**
    - Pembrolizumab will be used as single-agent therapy for unresectable or metastatic disease that has progressed following prior treatment and who have no satisfactory alternative treatment options for tissue mutation burden-high (TMB-H) tumors with 10 or more mutations per megabase (useful in certain circumstances)

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Breast Cancer

- The member has a diagnosis of high risk (Stage II-III) triple negative breast cancer and will be used as part of the following regimen:

  - Preoperative pembrolizumab in combination with carboplatin and paclitaxel **AND**
  - Followed by preoperative pembrolizumab in combination with cyclophosphamide and either doxorubicin or epirubicin **AND**
  - Followed by surgery, followed by adjuvant single agent pembrolizumab
- The member has a diagnosis of recurrent unresectable (local or regional) or stage IV (M1) disease that is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), or tumor mutational burden-high (TMB-H) tumors (≥10 muts/mb) that have progressed following prior treatment and has no satisfactory alternative treatment options (useful in certain circumstances) **AND**
  - Pembrolizumab will be used as a single agent
- The member has a diagnosis of PD-L1 positive, recurrent unresectable (local or regional) or stage IV (M1) triple negative breast cancer, **AND**
  - Pembrolizumab will be used in combination with either albumin-bound paclitaxel, paclitaxel, or gemcitabine with carboplatin as:
    - Preferred first-line therapy
    - Second and subsequent lines of therapy if PD-L1 inhibitor has not been previously used

Recommended dose:
High Risk Stage II-III Disease: Pembrolizumab 200mg IV every 21 days for 8 cycles (neoadjuvant), followed by Pembrolizumab 200mg IV every 21 days for 9 cycles (adjuvant)

Recurrent, unresectable or Stage IV Disease: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Central Nervous System Cancers
- The member has a diagnosis of melanoma or PD-L1 positive NSCLC with brain metastases, either limited or extensive.
  - IF limited brain metastases:
    - Pembrolizumab is given as a single agent as initial treatment in members who experience small asymptomatic brain metastases **OR**
    - Pembrolizumab is given as a single agent as treatment for recurrent brain metastases **OR**
    - Pembrolizumab is given as a single agent as treatment for relapsed disease with either stable systemic disease or reasonable systemic treatment options.
  - IF extensive brain metastases:
    - Pembrolizumab is given as single agent as initial treatment in members who experience small asymptomatic brain metastases **OR**
    - Pembrolizumab is given as a single agent as treatment for relapsed disease with either stable systemic disease or reasonable systemic treatment options.

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Cervical Cancer

- The member has a diagnosis of recurrent or metastatic cervical cancer **AND**
- Pembrolizumab single agent will be used a second line therapy **AND either:**
    - The member has PD-L1 tumor expression with combined positive score (CPS) ≥ 1 as determined by FDA-approved test **OR**
    - The member has MSI-H or dMMR disease.

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Colorectal Cancer

- The member has a diagnosis of adenocarcinoma colorectal cancer **AND**
- Pembrolizumab will be used as primary treatment as a single agent in patients (preferred for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] only):
    - As neoadjuvant therapy for resectable synchronous liver and/or lung metastases
    - For unresectable synchronous liver and/or lung metastases only
    - For unresectable metachronous metastases and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months
- Pembrolizumab therapy will be given as a single agent for patients dMMR/MSI-H tumors if no previous treatment with a checkpoint inhibitor:
    - As primary treatment for locally unresectable or medically inoperable disease
    - For unresectable synchronous liver and/or lung metastases that remain unresectable after primary systemic therapy
    - As primary treatment for synchronous abdominal/peritoneal metastases that are nonobstructing, or following local therapy for patients with existing or imminent obstruction
    - For synchronous unresectable metastases of other sites
    - As primary treatment for unresectable metachronous metastases in patients who have not received previous adjuvant FOLFOX or CapeOX within the past 12 months, who have received previous fluorouracil/leucovorin (5-FU/LV) or capecitabine therapy, or who have not received any previous chemotherapy
    - For unresectable metachronous metastases that remain unresectable after primary treatment and progressed on non-intensive therapy, except if received previous fluoropyrimidine, with improvement in functional status

- The member will receive pembrolizumab as subsequent therapy as a single agent for advanced or metastatic disease (preferred for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] only), if no previous treatment with a checkpoint inhibitor, following previous oxaliplatin- irinotecan- and/or fluoropyrimidine-based therapy

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Cutaneous Squamous Cell Carcinoma (cSCC)

- The member has a diagnosis of cSCC AND
- The member has recurrent or metastatic disease not curable by surgery or radiation **AND**
- Pembrolizumab will be used as monotherapy

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Esophageal and Esophagogastric Junction Cancers

- The member has a diagnosis of HER2 negative, unresectable, locally advanced, recurrent, or metastatic disease or is not a surgical candidate **AND**
- Pembrolizumab is being used as first-line therapy in combination with:
    - Oxaliplatin and fluorouracil or capecitabine (PD-L1 CPS ≥ 10) for adenocarcinoma or squamous cell carcinoma (if no prior tumor progression while on therapy with a checkpoint inhibitor)
    - Cisplatin and fluorouracil or capecitabine (PD-L1 CPS ≥ 10) for adenocarcinoma or squamous cell carcinoma (if no prior tumor progression while on therapy with a checkpoint inhibitor)
- The member has a diagnosis of unresectable locally advanced, recurrent, or metastatic esophageal disease or is not a surgical candidate with no prior tumor progression while on therapy with a checkpoint inhibitor as:
    - Preferred second-line therapy for esophageal squamous cell carcinoma (SCC) with PD-L1 expression by CPS of ≥10
    - Second-line or subsequent therapy as a single agent for microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors (useful in certain circumstances)
    - Second-line or subsequent therapy as a single agent for tumor mutational burden (TMB) high (≥ 10 mutations/megabase) tumors (useful in certain circumstances)
- The member has a diagnosis of HER2 positive adenocarcinoma, unresectable locally advanced, recurrent, or metastatic esophageal disease or is not a surgical candidate **AND**
- Pembrolizumab is being used as first-line therapy in combination with:

- Fluorouracil, cisplatin or oxaliplatin, and trastuzumab (if no prior tumor progression while on therapy with a checkpoint inhibitor)
- Capecitabine, cisplatin or oxaliplatin, and trastuzumab (if no prior tumor progression while on therapy with a checkpoint inhibitor)

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Gastric Cancer

- The member has a diagnosis of HER2 positive, recurrent, locally advanced, or metastatic gastric adenocarcinoma or is not a surgical candidate **AND**
- Pembrolizumab is being used as first-line therapy in combination with:
  - cisplatin, trastuzumab and fluorouracil or capecitabine
  - oxaliplatin, trastuzumab and fluorouracil or capecitabine
- The member has a diagnosis of HER2 positive, recurrent, locally advanced, or metastatic gastric adenocarcinoma **AND**
- The member is microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors or tumor mutational burden (TMB) high (≥ 10 mutations/megabase) **AND**
- Pembrolizumab is being used as second-line therapy as a single agent

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Gestational Trophoblastic Neoplasia

- The member has diagnosis of gestational trophoblastic neoplasia with pembrolizumab given as single-agent therapy for multiagent chemotherapy resistant for:
  - High-risk disease **OR**
  - Members with recurrent or progressive intermediate trophoblastic tumor (placental site trophoblastic tumor or epithelioid trophoblastic tumor) following treatment with a platinum/etoposide containing regimen.

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Head and Neck Cancers

- The member has a diagnosis, or recurrent or metastatic head and neck squamous cell carcinoma **AND**

    - Pembrolizumab will be used as first-line therapy **AND**
        - Pembrolizumab will be used in combination with a platinum chemotherapy agent and fluorouracil **OR**
        - Pembrolizumab will be used as a single agent for PD-L1 tumor expression with CPS ≥ 1% as determined by an FDA-approved test **OR**
        - Pembrolizumab will be used as a single agent if the member is tumor mutational burden high (TMB-H)
- The member has a diagnosis, or recurrent or metastatic head and neck squamous cell carcinoma (non-nasopharyngeal cancer) **AND**
    - Pembrolizumab will be used as subsequent therapy **AND**
        - As a single-agent if previously treated with disease progression on or after platinum therapy **OR**
        - As a single agent if the member is tumor mutational burden high (TMB-H)
- The member has a diagnosis, or recurrent or metastatic head and neck squamous cell carcinoma (non-nasopharyngeal cancer) **AND**
    - Pembrolizumab will be used as first-line or second-line therapy **AND**
    - Pembrolizumab will be used in combination with fluorouracil and either carboplatin or cisplatin **OR**
    - Pembrolizumab will be used as a single agent if microsatellite instability-high (MSI-H)

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Hepatobiliary Cancers

- The member has a diagnosis of hepatocellular carcinoma **AND**
- The member has previously been treatment with Nexavar® (sorafenib) **or**
- The member has a diagnosis of one of the following:
    - Gallbladder cancer **OR**
    - Intra-hepatic cholangiocarcinoma **OR**
    - Extra-hepatic cholangiocarcinoma **AND**
    - The member has unresectable or metastatic disease that is MSI-H or dMMR **AND**
    - Pembrolizumab is used as primary or subsequent single-agent therapy.

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Melanoma (Cutaneous)

- Pembrolizumab will be used as adjuvant treatment, as a single agent:

  - for resected stage III sentinel lymph node (SLN) positive disease during nodal basin ultrasound surveillance or after completion lymph node dissection (CLND)
  - for stage III disease with clinically positive node(s) following wide excision of primary tumor and therapeutic lymph node dissection (TLND)
  - for stage III disease with clinical satellite/in-transit metastases if no evidence of disease (NED) after complete excision to clear margins
  - for local satellite/in-transit recurrence if NED after complete excision to clear margins
  - following TLND and/or complete resection of nodal recurrence
  - following complete resection of distant metastatic disease
  - for resected stage III sentinel lymph node (SLN) positive disease during nodal basin ultrasound surveillance or after completion lymph node dissection (CLND)
  - for stage III disease with clinically positive node(s) following wide excision of primary tumor and therapeutic lymph node dissection (TLND)
  - for stage III disease with clinical satellite/in-transit metastases if no evidence of disease (NED) after complete excision to clear margins
  - for local satellite/in-transit recurrence if NED after complete excision to clear margins
  - following TLND and/or complete resection of nodal recurrence
  - following complete resection of distant metastatic disease
- Pembrolizumab will be used in metastatic or unresectable disease as a single agent:
  - First-line systemic therapy option for metastatic or unresectable disease
- Pembrolizumab will be used as a preferred second-line or subsequent systemic therapy option for metastatic or unresectable disease after progression or maximum clinical benefit from BRAF targeted therapy
  - as a single agent if anti-PD-1 immunotherapy was not previously used
  - in combination with low-dose ipilimumab for patients who progress on single-agent anti-PD-1 immunotherapy (if combination ipilimumab/anti-PD-1 immunotherapy not previously used)
  - may be considered as re-induction therapy as a single agent if prior anti-PD-1 immunotherapy resulted in disease control (complete response, partial response, or stable disease) and no residual toxicity, and disease progression/relapse occurred >3 months after treatment discontinuation
  - may be considered as re-induction therapy in combination with low-dose ipilimumab if prior combination ipilimumab/anti-PD-1 immunotherapy resulted in disease control (complete response, partial response, or stable disease) and no residual toxicity, and disease progression/relapse occurred >3 months after treatment discontinuation

<u>Recommended dose</u> :

- 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity in patients with unresectable or metastatic melanoma **OR**

- 200 mg IV every 21 days OR 400 mg IV every 42 days up to 12 months in adjuvant melanoma patients without disease recurrence or unacceptable toxicity.

Melanoma (Uveal)

- The member has a diagnosis of uveal melanoma **AND**
- The member has distant metastatic disease **AND**
- Pembrolizumab will be used as single agent therapy.

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Merkel Cell Carcinoma (MCC)

- The member has a diagnosis of recurrent locally advanced or metastatic Merkel cell carcinoma **AND**
- The member is at least 2 years old age **AND**
- Pembrolizumab will used as monotherapy.

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days OR 2mg/kg (up to 200mg) every 3 weeks for pediatric patients until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Malignant Pleural Mesothelioma

- The member has a diagnosis of malignant pleural mesothelioma **AND**
- Pembrolizumab will be administered as single agent therapy after subsequent systemic therapy.

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) or Tumor Mutational Burden High (TMB-H) tumors

- The member has a diagnosis of unresectable or metastatic MSI-H or dMMR or TMB-H cancer confirmed by polymerase chain reaction (PCR)-based assay genetic testing **AND**
- The member is at least 2 years of age **AND**
- Pediatric members must not have a diagnosis of MSI-H central nervous system cancer **AND**
- Pembrolizumab will be used as single agent for any one of the following (please refer to disease specific coverage determination sections for more details):
    - Bone cancer
    - Cervical cancer

- Colorectal cancer
- Gastric cancer
- Esophageal cancer
- Hepatobiliary cancer
- Ovarian cancer
- Occult primary
- Pancreatic cancer
- Penile cancer
- Testicular cancer
- Small bowel cancer
- Uterine cancer
- Vulvar squamous cell carcinoma
- Breast cancer
- Neuroendocrine cancer

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days OR 2mg/kg (up to 200mg) every 3 weeks for pediatric patients until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Neuroendocrine and Adrenal Tumors

- The member has a diagnosis of a Well Differentiated Neuroendocrine Tumor **AND**
  - Pembrolizumab will be used as treatment for locally advanced/metastatic disease with unfavorable biology (relative high Ki-67 [≥55%], rapid growth rate, negative SSR-based PET imaging) and tumor mutational burden high (≥10 muts/Mb) as determined by an FDA-approved test that has progressed following prior treatment and has no satisfactory alternative treatment options
- The member has a diagnosis of a Adrenal Gland Tumor **AND**
  - Pembrolizumab will be considered for the treatment of locoregional unresectable or metastatic adrenocortical carcinoma with or without mitotane
- The member has a diagnosis of a Poorly Differentiated/Large or Small Cell tumor **AND**
  - Pembrolizumab may be considered for the management of dMMR or MSI-H or TMB-H unresectable/metastatic adrenocortical tumors that have progressed following prior treatment and have no satisfactory alternative treatment options

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Non-Small Cell Lung Cancer (NSCLC)

- The member has a diagnosis of stage 3 NSCLC **AND**
  - Pembrolizumab monotherapy will be used as first line therapy in members who are not candidates for surgical resection or definitive chemoradiation with tumors

expressing PD-L1 (TPS) ≥ 1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations **OR**

- The member has a diagnosis of recurrent, advanced or metastatic NSCLC (excluding locoregional recurrence or symptomatic local disease with no evidence of disseminated disease) or mediastinal lymph node recurrence with prior radiation therapy **AND**
    - Pembrolizumab is being used as first line therapy either:
        - In combination with pemetrexed and either carboplatin or cisplatin for non-squamous cell histology for tumors that are EGFR or ALK negative **OR**
        - In combination with carboplatin and either paclitaxel or albumin bound paclitaxel for squamous cell histology **OR**
        - As single agent therapy for PD-L1 positive (preferred option for PD-L1 ≥ 50%; useful in certain circumstances if PD-L1 ≥ 1-49%) tumors that are EGFR, ALK, ROS1, BRAF negative **OR**
        - Used in members who are negative for genomic tumor aberrations (i.e. EGFR, ALK, ROS1 and BRAF) and have PD-L1 < 1% OR for BRAF V600E mutation positive tumors or NTRK gene fusion positive tumors **AND**
            - In combination with pemetrexed and either carboplatin or cisplatin for non-squamous cell histology **OR**
            - In combination with carboplatin and either paclitaxel or albumin bound paclitaxel for squamous cell histology **OR**
    - Pembrolizumab is being used as subsequent therapy **AND**
        - Used in patients who have genomic tumor aberration (i.e. EGFR, ALK, ROS1) positive disease and received prior targeted therapy OR for BRAF V600E mutation positive disease or NTRK gene fusion positive tumors OR for MET exon 14 skipping mutation positive tumors or RET rearrangement positive tumors **AND**
            - In combination with carboplatin AND either paclitaxel or albumin-bound paclitaxel for squamous cell histology **OR**
            - In combination with pemetrexed AND either carboplatin or cisplatin for non-squamous cell histology **OR**
        - Used in patients with tumors expressing PD-L1 (TPS ≥ 1%) as determined by an FDA-approved as single agent therapy **OR**
    - Used as continuation maintenance therapy in patients who have achieved tumor response or stable disease following initial therapy **AND**
        - Used in combination with pemetrexed following a first-line pembrolizumab/pemetrexed/carboplatin or cisplatin regimen for disease of non-squamous cell histology **OR**
        - Used as a single agent following a first-line pembrolizumab monotherapy regimen or pembrolizumab/(carboplatin or cisplatin)/(paclitaxel or nab-paclitaxel) regimen for disease of squamous cell histology **OR**
        - Used as a single agent following a first-line pembrolizumab monotherapy regimen for PD-L1 expression positive (≥ 1%) and genomic tumor aberration (i.e., EGFR, ALK, ROS1, BRAF) negative disease.

NCCN guidelines: if there is insufficient tissue to allow testing for all EGFR, ALK, ROS1, and BRAF, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, the member will be treated as though they do not have driver oncogenes.[2]

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Occult Primary

- The member has a diagnosis of occult primary adenocarcinoma or carcinoma not otherwise specified that is MSI-H/dMMR/TMB-H **AND**
    - Pembrolizumab is being used as a single agent for:
        - Axillary involvement in men if clinically indicated **OR**
        - Lung nodules or breast marker-negative pleural effusion **OR**
        - Resectable liver disease **OR**
        - Peritoneal mass or ascites with non-ovarian histology **OR**
        - Retroperitoneal mass of non-germ cell histology in selected patients **OR**
        - Unresectable liver disease or disseminated metastases.

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancers

- The member has a diagnosis of persistent or recurrent ovarian cancer, fallopian tube cancer, or primary peritoneal cancer that is MSI-H or dMMR or TMB-H **AND**
- Pembrolizumab monotherapy will be used for any of the following:
    - Member has progression on primary, maintenance, or recurrence therapy **OR**
    - Member has stable or persistent disease (if not on maintenance therapy) **OR**
    - Member has complete remission and relapse less than 6 months after completing chemotherapy **OR**
    - Member has radiographic and/or clinical relapse in patients with previous complete remission and relapse after 6 or more months after completing prior chemotherapy.

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Pancreatic Cancer

- The member has a diagnosis of pancreatic adenocarcinoma **AND**
- Pembrolizumab will be utilized as first-line therapy as a single agent for metastatic disease for patients with poor performance status who are MSI-H or dMMR **OR**
- Pembrolizumab will be utilized as second-line therapy as a single agent for MSI-H or dMMR locally advanced or metastatic disease and disease progression **OR**
- Pembrolizumab therapy will be used as a single agent for MSI-H or dMMR tumors for:
    - Local recurrence in the pancreatic operative bed after resection **OR**
    - The member has metastatic disease with or without local recurrence after resection if ≥ 6 months from completion of primary therapy **OR**
    - The member has metastatic disease with or without local recurrence after resection if less than 6 months from completion of primary therapy.

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Penile Cancer

- The member has a diagnosis of penile cancer **AND**
- Pembrolizumab will be given as a single agent as subsequent-line systemic therapy if disease is unresectable or metastatic, MSI-H or dMMR, and has progressed following prior treatment and no satisfactory alternative treatment options exist.

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Primary Cutaneous Lymphoma

- The member has a diagnosis of Mycosis Fungoides (MF)/Sezary Syndrome **AND**
- The member will receive pembrolizumab as primary treatment for:
    - Stage III MF
    - Stage IVA1 or IVA2 Sezary syndrome **OR**
- The member will receive pembrolizumab as subsequent treatment for:
    - relapsed or persistent stage III MF
    - relapsed or persistent stage IVA1 or IVA2 Sezary syndrome **OR**
- The member will receive pembrolizumab as single agent subsequent treatment for refractory disease to multiple previous therapies for:
    - stage IIB MF with limited tumor lesions
    - stage IIB MF with generalized tumor lesions
    - stage III MF
    - stage IVA1 or IVA2 Sezary syndrome
    - stage IVA2 non-Sezary or stage IVB visceral disease (solid organ)
    - large cell transformation (LCT) with limited cutaneous lesions

- LCT with generalized cutaneous or extracutaneous lesions

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Classical Hodgkin Lymphoma (cHL)

- Member must have a diagnosis of Classical Hodgkin Lymphoma **AND**
- The member has relapsed disease **AND**
- Pembrolizumab will be used as monotherapy **AND**
- The member is 2 years of age and older and has refractory or relapsed disease after 3 or more prior lines of therapy **OR**
- The member is ≥ 18 years of age **AND**
    - Pembrolizumab will be used second-line or subsequent systemic therapy (if not previously used) for relapsed or refractory disease as a single agent if not a candidate for transplant **OR**
    - Pembrolizumab will be used in the third line or subsequent setting for:
        - Disease that has relapsed or progressed after autologous hematopoietic stem cell transplant (HSCT) ± brentuximab vedotin **OR**
        - Patient is HSCT ineligible **OR**
        - Post-allogeneic transplant

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days OR 2mg/kg (up to 200mg) every 3 weeks for pediatric patients until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Renal Cell Carcinoma (RCC)

- The member has a diagnosis of advanced, relapsed or metastatic renal cell carcinoma with clear cell histology **AND**
    - Pembrolizumab will be used in combination with axitinib **OR**
    - Pembrolizumab will be used in combination with lenvatinib as:
        - preferred first-line therapy for favorable risk
        - preferred first-line therapy for poor/intermediate risk
        - subsequent therapy **OR**
- The member has a diagnosis of advanced, relapsed or metastatic renal cell carcinoma with non-clear cell histology
    - Pembrolizumab will be used as a single agent as subsequent therapy

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Refractory primary mediastinal large B-cell lymphoma (PMBCL)

- The member has a diagnosis of PMBCL **AND**
- The member is 2 years of age and older **AND**
- Pembrolizumab will be used as single agent **AND**
- The member has relapsed or refractory disease

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days OR 2mg/kg (up to 200mg) every 3 weeks for pediatric patients until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Small Bowel Adenocarcinoma

- The member has a diagnosis of advanced or metastatic small bowel adenocarcinoma **OR** ampullary cancer and pembrolizumab will be used as:
    - Initial therapy as a single agent (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] only), if no previous treatment with a checkpoint inhibitor
    - Subsequent therapy as a single agent (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] only), if no previous treatment with a checkpoint inhibitor and no prior oxaliplatin exposure in the adjuvant setting or contraindication to oxaliplatin

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Small Cell Lung Cancer

- The member has a diagnosis of metastatic small cell lung cancer (SCLC) **AND**
- Pembrolizumab single agent will be used as subsequent therapy for:
    - relapse following complete or partial response or stable disease with primary treatment (The use of immune checkpoint inhibitors is discouraged if there is progression on maintenance atezolizumab or durvalumab at time of relapse)
    - primary progressive disease

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Soft Tissue Sarcoma

- The member has a diagnosis of Soft Tissue Sarcoma - (Extremity/Body Wall, Head/Neck or Retroperitoneal/Intra-Abdominal) **AND**
    - Pembrolizumab is being utilized as single-agent therapy as subsequent lines of therapy for advanced/metastatic disease with disseminated metastases in:

        - Myxofibrosarcoma
        - undifferentiated pleomorphic sarcoma (UPS)
        - cutaneous angiosarcoma
        - undifferentiated sarcomas
- The member has a diagnosis of Soft Tissue Sarcoma – Angiosarcoma **AND**
    - Pembrolizumab is being used as single-agent therapy
- The member has a diagnosis of Alveolar Soft Part Sarcoma (APS) **AND**
    - Pembrolizumab is being used as preferred single-agent therapy

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

T-Cell Lymphomas – Extra-nodal NK/T-Cell Lymphoma nasal type

- The member has a diagnosis of T-cell lymphoma extranodal NK/T-cell lymphoma nasal type **AND**
- Pembrolizumab is being utilized for relapsed/refractory disease following additional therapy with an alternate combination chemotherapy regimen (asparaginase-based) not previously used, if a clinical trial is not available.

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Testicular Cancer

- The member has a diagnosis of testicular cancer, histology of non-seminoma or pure seminoma, **AND**
- Pembrolizumab therapy will be used as single-agent third-line therapy in patients with MSI-H/dMMR/TMB-H tumors.

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Thymomas and Thymic Carcinomas

- The member has a diagnosis of thymoma/thymic carcinoma **AND**
    - Consider pembrolizumab for postoperative treatment (for thymic carcinomas only) as a single agent for patients who cannot tolerate first-line combination regimens for thymic carcinoma after R1 or R2 resection **OR**
    - Consider pembrolizumab as first-line therapy (for thymic carcinomas only) as a single agent for patients who cannot tolerate first-line combination regimens for
        - unresectable locally advanced disease in combination with radiation therapy

    - potentially resectable locally advanced disease
    - potentially resectable solitary metastasis or ipsilateral pleural metastasis
    - consideration following surgery for solitary metastasis or ipsilateral pleural metastasis
    - extrathoracic metastatic disease
- Pembrolizumab will be utilized as a single agent as second-line therapy for (thymic carcinomas only) for:
    - unresectable disease following first-line chemotherapy for potentially resectable locally advanced disease, solitary metastasis, or ipsilateral pleural metastasis
    - extrathoracic metastatic disease

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Tumor Mutational Burden – High (TMB-H) Cancer

- The member has a diagnosis of unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test **AND**
- The member has progressed following prior treatment and has no satisfactory treatment options **AND**
- Pembrolizumab will be used as monotherapy

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Thyroid Carcinoma

- Pembrolizumab will be used for **Papillary, Follicular, or Hürthle Cell** carcinoma with tumor mutational burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) tumors in:
    - unresectable locoregional recurrent or persistent disease not amenable to radioactive iodine (RAI) therapy
    - distant metastatic disease not amenable to RAI therapy
- Pembrolizumab will be used for **Medullary Carcinoma** with tumor mutational burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) tumors in:
    - unresectable locoregional disease that is symptomatic or progressing by RECIST criteria
    - asymptomatic recurrent or persistent distant metastases if unresectable and progressing by RECIST criteria
    - recurrent or persistent distant metastases if symptomatic disease or progression
- Pembrolizumab will be used for **Anaplastic Carcinoma** with tumor mutational burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) tumors:
    - as aggressive first-line therapy for metastatic disease
    - as second-line therapy for metastatic disease

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Urothelial Carcinoma

- The member has a diagnosis of non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS), with or without papillary tumors **AND**
    - The member is diagnosed with Bacillus Calmette-Guerin (BCG)-unresponsive disease, **AND**
    - The member is considered high-risk, **AND**
    - The member is ineligible for or has elected not to undergo cystectomy.
- Pembrolizumab will be used as first-line systemic therapy as a single agent (preferred) in cisplatin ineligible patients whose tumors express PD-L1 or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression for:
    - cystectomy candidates with stage II (cT2, N0) disease if tumor is present following reassessment of tumor status 2-3 months after primary treatment with bladder preserving concurrent chemoradiotherapy
    - non-cystectomy candidates with stage II (cT2, N0) disease if tumor is present following reassessment of tumor status 2-3 months after primary treatment
    - stage IIIA (cT3, N0; cT4a, N0; cT1-T4a, N1) disease if tumor is present following reassessment of tumor status 2-3 months after primary treatment with bladder preserving concurrent chemoradiotherapy
    - for non-cystectomy candidates with stage IIIA (cT3, N0; cT4a, N0; cT1-4a, N1) disease if tumor is present upon reassessment of tumor status 2-3 months after primary treatment
    - stage IIIB (cT1-T4a, N2,3) disease as downstaging systemic therapy
    - stage IIIB (cT1-T4a, N2,3) disease following partial response or progression after primary treatment with concurrent chemoradiotherapy
    - stage IVA (cT4b, any N, M0; any T, any N, M1a) disease
    - stage IVA (cT4b, any N, M0) disease as consolidation therapy if no tumor present following reassessment of tumor status 2-3 months after primary treatment with concurrent chemoradiotherapy
    - stage IVA (cT4b, any N, M0) disease if tumor present following reassessment of tumor status 2-3 months after primary treatment with concurrent chemoradiotherapy
    - metastatic stage IVB (any T, any N, M1b) disease
    - muscle invasive local recurrence or persistent disease in a preserved bladder
    - metastatic or local recurrence post cystectomy

- Pembrolizumab will be used as second-line systemic therapy post-platinum or for those who received a therapy other than platinum or an immune checkpoint inhibitor in first-line, as a single agent (preferred) for:
    - cystectomy candidates with stage II (cT2, N0) disease if tumor is present following reassessment of tumor status 2-3 months after primary treatment with bladder preserving concurrent chemoradiotherapy
    - stage IIIA (cT3, N0; cT4a, N0; cT1-T4a, N1) disease if tumor is present following reassessment of tumor status 2-3 months after primary treatment with bladder preserving concurrent chemoradiotherapy
    - stage IIIB (cT1-T4a, N2,3) disease following partial response or progression after primary treatment with downstaging systemic therapy or concurrent chemoradiotherapy
    - stage IVA (cT4b, any N, M0) disease if tumor is present following reassessment of tumor status after primary treatment with first-line systemic therapy or concurrent chemoradiotherapy
    - stage IVA (any T, any N, M1a) disease if stable disease or progression following reassessment of tumor status after primary treatment with first-line systemic therapy
    - metastatic stage IVB (any T, any N, M1b) disease
    - muscle invasive local recurrence or persistent disease in a preserved bladder
    - metastatic or local recurrence post cystectomy
- The member has a diagnosis of advanced or metastatic urothelial carcinoma, **AND**
    - Pembrolizumab will be used as first-line systemic therapy (preferred) in cisplatin ineligible patients whose tumors express PD-L1 or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression
    - Pembrolizumab will be used second-line systemic therapy post-platinum or for patients who received a therapy other than platinum or an immune checkpoint inhibitor first-line (preferred)

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Uterine Neoplasms

- The member has a diagnosis of Endometrial Cancer with a histology of:
    - Carcinosarcoma **OR**
    - Clear cell carcinoma **OR**
    - Endometroid adenocarcinoma **OR**
    - Serous carcinoma **OR**
    - Undifferentiated/dedifferentiated carcinoma **AND**
        - Pembrolizumab therapy will be used in combination with lenvatinib for advanced or recurrent disease that is not MSI-H or dMMR and the

member is not a candidate for curative surgery or radiation and have progressed on prior systemic therapy **OR**
    - Pembrolizumab therapy will be used in members with recurrent, metastatic, or high-risk MSI-H, dMMR, or TMB-H tumors that have progressed following prior therapy **OR**
- The member has a diagnosis of Uterine Sarcoma with a histology of:
    - High-grade endometrial stromal sarcoma (ESS) **OR**
    - Undifferentiated uterine sarcoma (UUS) **OR**
    - Uterine leiomyosarcoma (uLMS) **AND**
        - Pembrolizumab therapy will be used in members with recurrent, metastatic, or high-risk MSI-H, dMMR, or TMB-H tumors that have progressed following prior therapy

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Vulvar Cancer

- The member has a diagnosis of vulvar cancer with squamous cell carcinoma histology **AND**
- Pembrolizumab therapy will be utilized as second-line therapy as a single agent for advanced, recurrent, or metastatic disease if:
    - The tumor is MSI-H or dMMR or TMB-H **OR**
    - The member has experienced disease progression on or after chemotherapy whose tumors expresses PD-L1 (CPS ≥1) as determined by an FDA-approved test.

Recommended dose: 200 mg IV every 21 days OR 400 mg IV every 42 days until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

All indications:

- Pembrolizumab will be approved for up to a 6-month duration, or as determined through clinical review.

Coverage Limitations

Treatment with Pembrolizumab is not considered medically necessary for members with the following concomitant conditions:

- Not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

- The safety and effectiveness of pembrolizumab in pediatric patients with MSI-H central nervous system cancers have not been established.
- The member has experienced disease progression while on or following PD-1/PD-L1 therapy.
- Indications not supported by NCCN category 2A or higher recommendations may not be considered medically necessary

Contraindications/Warnings/Precautions[1]

- There are no contraindications listed in the US manufacturer's labeling.
- Warnings/precautions:
    - Severe and Fatal Immune-Mediated Adverse Reactions to include:
        - Pneumonitis
        - Colitis
        - Hepatitis
    - Infusion-Related Reactions
    - Embryo-Fetal Toxicity

For specific recommendations on contraindications, warnings and precautions, patient monitoring, and on dose adjustments and discontinuation, please refer to the current prescribing information.

Billing

- Description: pembrolizumab, 1 mg
    - J9271

Disclaimer

Drug Coverage Policies are developed as needed, regularly reviewed, updated at least annually, and are subject to change. Other policies and coverage determination guidelines may apply. Federal and state regulatory requirements and member specific benefit plan documents, if applicable, must be reviewed prior to this Drug Coverage Policy. This Drug Coverage Policy is for informational purposes only and does not constitute medical advice or dictate how providers should practice medicine. This policy should not be reproduced, stored in a retrieval system, or altered from its original form without written permission from Oncology Analytics, Inc.

References

1. Keytruda [package insert]. Merck Sharp & Dohme Corp, Whitehouse Station, NJ. Available at: https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf
2. Pembrolizumab. NCCN Drugs & Biologics Compendium. Available at https://www.nccn.org/professionals/drug_compendium/content/

3. Migden MR, Rischin D, Schmults CD, et al. PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma. N Engl J Med. 2018 Jul 26;379(4):341-351. doi: 10.1056/NEJMoa1805131. Epub 2018 Jun 4.
4. Migden MR, Khushalani NI, Chang AL, et al. Primary analysis of Phase 2 results of cemiplimab, a human monoclonal anti-PD-1, in patients (pts) with locally advanced cutaneous squamous cell carcinoma (laCSCC). J Clin Oncol 37, 2019 (suppl; abstr 6015)