UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Oncology (Injectable – Programmed Death Receptor-1) – Keytruda Qlex Utilization Management Medical Policy

- Keytruda Qlex™ (pembrolizumab and berahyaluronidase alfa-pmph subcutaneous injection – Merck)

REVIEW DATE: 09/24/2025; selected revision 10/08/2025 and 11/19/2025

OVERVIEW

Keytruda Qlex, a combination of pembrolizumab, programmed death receptor-1 (PD-1) blocking antibody, and berahyaluronidase alpha, an endoglycosidase, is indicated for the treatment of the following indications:[1]

- **Biliary tract cancer**, in combination with gemcitabine and cisplatin for the treatment of locally advanced unresectable or metastatic disease in adults.
- **Breast cancer, triple-negative**, in adults:
  - In combination with chemotherapy for the treatment of locally recurrent unresectable or metastatic disease in patients whose tumors express programmed death-ligand 1 (PD-L1) [combined positive score {CPS} ≥ 10] as determined by an FDA-approved test.
  - For the treatment of high-risk, early-stage disease in combination with chemotherapy as neoadjuvant treatment and then continued as a single agent as adjuvant treatment after surgery.
- **Cervical cancer**, in adults:
  - In combination with chemotherapy, with or without bevacizumab, for persistent, recurrent, or metastatic disease in patients whose tumor expresses PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.
  - As a single agent, for treatment of recurrent or metastatic disease with disease progression on or after chemotherapy in patients whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.
  - In combination with chemoradiotherapy in patients with locally advanced disease involving the lower third of the vagina, with or without extension to pelvic sidewall, or hydronephrosis/non-functioning kidney, or spread to adjacent pelvic organs (FIGO 2014 Stage III-IVA).
- **Cutaneous squamous cell carcinoma,** for treatment of adults with recurrent or metastatic disease, or locally advanced disease that is not curable by surgery or radiation.
- **Endometrial cancer**, in adults:
  - In combination with carboplatin and paclitaxel, followed by single agent therapy for adults with primary advanced or recurrent disease.
  - In combination with Lenvima® (lenvatinib capsules), for the treatment of advanced disease that is mismatch repair proficient (pMMR) as determined by an FDA-approved test or not microsatellite instability high (MSI-H), in patients who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.
  - As a single agent, for the treatment of advanced disease that is MSI-H or mismatch repair deficient (dMMR) as determined by an FDA-approved test, in patients who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.
- **Esophageal cancer**, treatment of adults with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) carcinoma (tumors with epicenter 1 to 5 centimeters above the

GEJ) that is not amenable to surgical resection or definitive chemoradiation in the following situations:
  - In combination with platinum- and fluoropyrimidine-based chemotherapy in patients whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.
  - As a single agent after one or more prior lines of systemic therapy for tumors of squamous cell histology that express PD-L1 (CPS ≥ 10) as determined by an FDA-approved test.
- **Gastric cancer**, in adults:
  - For the first-line treatment of locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (*HER2*)-positive gastric or GEJ adenocarcinoma whose tumors express PD-L1 (CPS ≥ 1), in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy in adults.
  - 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 GEJ adenocarcinoma whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.
- **Head and neck squamous cell carcinoma**, in adults:
  - As a single agent for the treatment of recurrent or metastatic disease with disease progression on or after platinum-containing chemotherapy.
  - In combination with platinum and fluorouracil for the first-line treatment of metastatic or unresectable, recurrent disease.
  - As a single agent, for the first line treatment of metastatic or unresectable, recurrent disease in patients whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.
  - As a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy with or without cisplatin and then as single agent, for resectable locally advanced disease in patients whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.
- **Hepatocellular carcinoma**, for treatment of adults with hepatocellular carcinoma secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1 containing regimen.
- **Melanoma**, in the following situations:
  - For the treatment of unresectable or metastatic disease in adults.
  - As adjuvant treatment of Stage IIB, IIC, or III melanoma following complete resection in patients ≥ 12 years of age.
- **Merkel cell carcinoma**, for treatment of recurrent locally advanced or metastatic disease in adult and pediatric patients ≥ 12 years of age.
- **Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancer**, for treatment of unresectable or metastatic MSI-H or dMMR solid tumors, as determined by an FDA-approved test, in adult and pediatric patients ≥ 12 years of age that have progressed following prior treatment and who have no satisfactory alternative treatment options.
- **MSI-H or dMMR colorectal cancer,** for the treatment of adults with unresectable or metastatic disease, as determined by an FDA-approved test.
- **Non-small cell lung cancer** (**NSCLC**), in adults:
  - As a single agent for the first-line treatment of tumors that express PD-L1 (tumor proportion score [TPS] ≥ 1%) as determined by an FDA-approved test, with no epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations and is stage III where patients are not candidates for surgical resection or definitive chemoradiation, or for metastatic disease.
  - As a single agent for the treatment of metastatic disease in patients whose tumors express PD-L1 (TPS ≥ 1%) as determined by an FDA-approved test and 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 Qlex.
    - In combination with pemetrexed and platinum-based chemotherapy, for the first-line treatment of metastatic nonsquamous NSCLC in patients with no *EGFR* or *ALK* genomic tumor aberrations.
    - In combination with carboplatin and either paclitaxel or paclitaxel protein-bound, for first-line treatment in metastatic squamous NSCLC.
    - In combination with platinum-containing chemotherapy, for the neoadjuvant treatment of resectable (tumors ≥ 4 cm or node positive) NSCLC and then continued as a single agent as adjuvant treatment after surgery.
    - As a single agent, as adjuvant treatment following resection and platinum-based chemotherapy for stage IB, II, or IIIA disease.
- **Pleural mesothelioma, malignant**, in combination with pemetrexed and platinum chemotherapy for the first-line treatment of adults with unresectable advanced or metastatic disease.
- **Renal cell carcinoma**, in adults:
    - In combination with Inlyta® (axitinib tablets) or Lenvima, for the first-line treatment of advanced disease in adults.
    - For adjuvant treatment of disease that is intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions.
- **Tumor mutational burden-high (TMB-H) cancer**, for treatment of unresectable or metastatic TMB-H (≥ 10 mutations/megabase) disease, as determined by an FDA-approved test, in adult and pediatric ≥ 12 years of age patients that have progressed following prior treatment and who have no satisfactory alternative treatment options.*
  Limitation of Use: The safety and effectiveness of Keytruda Qlex in pediatric patients ≥ 12 years of age with TMB-H central nervous system cancers have not been established.
- **Urothelial carcinoma**, in adults:
    - Treatment of locally advanced or metastatic disease in patients who are not eligible for platinum-containing chemotherapy as a single agent.
    - Treatment of locally advanced or metastatic disease in patients who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy as a single agent.
    - Treatment of Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer with carcinoma in situ with or without papillary tumors in patients who are ineligible for or have elected not to undergo cystectomy as a single agent.
    - In combination with Padcev® (enfortumab intravenous infusion), for the treatment of locally advanced or metastatic disease.

* This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Keytruda Qlex. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the criteria and dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Keytruda Qlex as well as the monitoring required for adverse events and long-term efficacy, approval requires Keytruda Qlex to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Keytruda Qlex is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. Biliary Tract Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
Note: Biliary tract cancer includes gallbladder cancer, intrahepatic cholangiocarcinoma, and extrahepatic cholangiocarcinoma. If the tumor is MSI-H or dMMR, see Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors criteria. If the tumor is mutational burden-high, see Tumor Mutational Burden-High (TMB-H) Cancer criteria.

A) Patient is ≥ 18 years of age; AND
B) Patient has locally advanced unresectable or metastatic disease; AND
C) The medication is used in combination with cisplatin and gemcitabine; AND
D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR
B) 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

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2. Breast Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
Note: If the tumor is MSI-H or dMMR, see Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors criteria. If the tumor is mutational burden-high, see Tumor Mutational Burden-High (TMB-H) Cancer criteria.

A) Patient is ≥ 18 years of age; AND
B) Patient has triple-negative breast cancer; AND
Note: Triple negative breast cancer is estrogen receptor-negative, progesterone receptor-negative, human epidermal growth factor receptor 2 (*HER2*)-negative.
C) Patient meets ONE of the following (i or ii):
  i. Patient meets ALL of the following (a, b, and c):
    a) Patient has locally recurrent unresectable or metastatic disease; AND
    b) The medication is used in combination with chemotherapy; AND
    c) Patient's tumor expression for programmed death-ligand 1 (PD-L1) has a combined positive score (CPS) ≥ 10; OR
  ii. The medication is used for neoadjuvant and/or adjuvant therapy; AND

D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR
B) 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

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3. Cervical Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
Note: If the tumor is MSI-H or dMMR, see Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors criteria. If the tumor is mutational burden-high, see Tumor Mutational Burden-High (TMB-H) Cancer criteria.
A) Patient is ≥ 18 years of age; AND
B) Patient meets ONE of the following (i or ii):
  i. Patient meets BOTH of the following (a and b):
    a) Patient has persistent, recurrent, or metastatic disease; AND
    b) Patient's tumor expression for programmed death-ligand 1 (PD-L1) has a combined positive score (CPS) ≥ 1; OR
  ii. Patient has FIGO 2014 stage III to IVA disease or FIGO 2018 stage III to IVA disease; AND
C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR
B) 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

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4. Cutaneous Squamous Cell Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has locally advanced, recurrent, or metastatic disease; AND
C) According to the prescriber, the disease is not curable by surgery or radiation; AND
D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR
B) 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

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5. Endometrial Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
Note: If the tumor is MSI-H or dMMR, see Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors criteria. If the tumor is mutational burden-high, see Tumor Mutational Burden-High (TMB-H) Cancer criteria.
A) Patient is ≥ 18 years of age; AND
B) Patient meets ONE of the following (i or ii):

i. Patients meets BOTH of the following (a and b):
  a) The medication is used for primary or adjuvant therapy; AND
  b) Patient meets ONE of the following [(1) or (2)]:
    (1) The medication is used in combination with carboplatin and paclitaxel; OR
    (2) The medication is used as a single agent for maintenance therapy; OR
ii. Patient meets BOTH of the following (a and b):
  a) Patient has recurrent disease; AND
  b) Patient meets ONE of the following [(1), (2), or (3)]:
    (1) The medication is used in combination with Lenvima (lenvatinib capsules); OR
    (2) The medication is used in combination with carboplatin and paclitaxel; OR
    (3) The medication is used as a single agent for maintenance therapy; AND

C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR
B) 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

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6. Esophageal Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
Note: If the tumor is MSI-H or dMMR, see Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors criteria. If the tumor is mutational burden-high, see Tumor Mutational Burden-High (TMB-H) Cancer criteria.
A) Patient is ≥ 18 years of age; AND
B) Patient has locally advanced or metastatic disease; AND
C) According to the prescriber, the patient is not a candidate for surgical resection or definitive chemoradiation; AND
D) Patient meets ONE of the following (i or ii):
i. Patient meets BOTH of the following (a and b):
  a) The tumor expression for programmed death-ligand 1 (PD-L1) has a combined positive score (CPS) ≥ 1; AND
  b) The medication is used in combination with chemotherapy; OR
  Note: Examples of chemotherapy include cisplatin plus fluorouracil or capecitabine; oxaliplatin plus fluorouracil or capecitabine; trastuzumab plus fluorouracil, cisplatin or oxaliplatin; and trastuzumab plus capecitabine, cisplatin or oxaliplatin.
ii. Patient meets BOTH of the following (a and b):
  a) The tumor expression for programmed death-ligand 1 (PD-L1) has a combined positive score (CPS) ≥ 10; AND
  b) The medication is used as subsequent line therapy; AND

E) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR
B) 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

7. Gastric Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
Note: If the tumor is MSI-H or dMMR, see Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors criteria. If the tumor is mutational burden-high, see Tumor Mutational Burden-High (TMB-H) Cancer criteria.
A) Patient is ≥ 18 years of age; AND
B) Patient has unresectable locally advanced unresectable, or metastatic disease; AND
C) Patient's tumor expression for programmed death-ligand 1 (PD-L1) has a combined positive score (CPS) ≥ 1; AND
D) The medication is used in combination with chemotherapy; AND
Note: Examples of chemotherapy include cisplatin or oxaliplatin, fluorouracil or capecitabine, and trastuzumab.
E) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR
B) 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

8. Head and Neck Squamous Cell Carcinoma. Approve for 1 year if the patients meets ALL of the following (A, B, C, and D):
Note: If the tumor is MSI-H or dMMR, see Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors criteria. If the tumor is mutational burden-high, see Tumor Mutational Burden-High (TMB-H) Cancer criteria.
A) Patient is ≥ 18 years of age; AND
B) Patient has recurrent, unresectable, or metastatic disease; AND
C) Patient meets ONE of the following (i or ii):
i. If the medication is used for first-line treatment, patient must meet ONE of the following (a or b):
a) The medication is used in combination with chemotherapy; OR
Note: Examples of chemotherapy are cisplatin, carboplatin, fluorouracil, and gemcitabine.
b) The tumors are PD-L1-positive (CPS ≥ 1); OR
ii. The medication is used for subsequent therapy; AND
D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR
B) 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

9. Hepatocellular Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C and D):
Note: If the tumor is MSI-H or dMMR, see Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors criteria. If the tumor is mutational burden-high, see Tumor Mutational Burden-High (TMB-H) Cancer criteria.
A) Patient is ≥ 18 years of age; AND
B) The disease is secondary to hepatitis B; AND

C) The medication is used as subsequent line therapy; AND
D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR
B) 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

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10. Melanoma. Approve for the duration noted below if the patient meets BOTH of the following (A and B):
Note: This includes cutaneous melanoma, brain metastases due to melanoma, and uveal melanoma.
A) Patient meets ONE of the following (i, ii, or iii):
  i. Approve for 1 year if the patient meets BOTH of the following (a and b):
    a) Patient is ≥ 18 years of age; AND
    b) Patient has unresectable or metastatic melanoma; OR
  ii. Approve for up to 1 year (total) if the patient meets BOTH of the following (a and b):
    a) Patient is ≥ 12 years of age; AND
    b) The medication will be used as adjuvant treatment; OR
  iii. Approve for 4 months if the patient meets BOTH of the following (a and b):
    a) Patient is ≥ 18 years of age; AND
    b) The medication will be used as neoadjuvant treatment; AND
B) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR
B) 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

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11. Merkel Cell Carcinoma. Approve for 1 year if the patient meets BOTH of the following (A, B and C):
A) Patient is ≥ 12 years of age; AND
B) Patient meets ONE of the following (i, ii, or iii):
  i. Patient has primary or recurrent locally advanced disease, if according to the prescriber curative surgery and curative radiation therapy are not feasible; OR
  ii. Patient has primary or recurrent regional disease, if according to the prescriber curative surgery and curative radiation therapy are not feasible; OR
  iii. Patient has metastatic (disseminated) disease; AND
C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, or B):
A) 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR
B) 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

12. Mesothelioma. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has ONE of the following (i, ii, iii, or iv):
  - **i.** Pleural mesothelioma; OR
  - **ii.** Peritoneal mesothelioma; OR
  - **iii.** Pericardial mesothelioma; OR
  - **iv.** Tunica vaginalis testis mesothelioma; AND
- **C)** The medication is used as first-line therapy; AND
- **D)** The medication is used in combination with pemetrexed and either cisplatin or carboplatin; AND
- **E)** The medication is prescribed by or in consultation with an oncologist.

Dosing: Approve ONE of the following dosing regimens (A or B):
- **A)** 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR
- **B)** 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa as administered subcutaneously not more frequently than once every 6 weeks.

13. Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors. Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.
Note**:** Examples of solid tumors with MSI-H or dMMR are adrenal gland, appendiceal neoplasms and cancers, biliary tract cancers, breast cancer, cervical cancer, chondrosarcoma, colon or rectal cancer, endometrial carcinoma, esophageal or esophagogastric cancers, Ewing sarcoma, gallbladder carcinoma, gastric cancer, head and neck squamous cell carcinoma, hepatocellular carcinoma, occult primary (cancer of unknown primary), osteosarcoma, ovarian/fallopian tube/primary peritoneal, pancreatic adenocarcinoma, penile cancer, neuroendocrine tumor, prostate cancer, small bowel adenocarcinoma, testicular cancer, vaginal cancer, vulvar cancer.

Dosing. Approve ONE of the following dosing regimens (A or B):
- **A)** 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR
- **B)** 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

14. Non-Small Cell Lung Cancer – Neoadjuvant and Adjuvant. Approve for the duration noted if the patient meets ALL of the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The tumor is negative for the following actionable biomarkers: epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R, anaplastic lymphoma kinase (ALK), RET, and ROS1; AND
- **C)** Patient has resectable or completely resected stage IB to III disease and meets one of the following (i or ii):
  - **i.** Approve for 4 months if the medication is used as neoadjuvant therapy in combination with platinum chemotherapy; OR
    Note: Examples of platinum chemotherapy include cisplatin plus pemetrexed and cisplatin plus gemcitabine.
  - **ii.** Approve for 1 year (total) if the patient meets ONE of the following (a or b):
    - **a)** Patient has received adjuvant chemotherapy; OR
    - **b)** Patient has received neoadjuvant treatment with the medication; AND

D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR
B) 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

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15. Non-Small Cell Lung Cancer – Recurrent, Advanced, or Metastatic Disease. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) The tumor is negative for the following actionable biomarkers: epidermal growth factor receptor *(EGFR)* exon 19 deletion or exon 21 L858R, anaplastic lymphoma kinase *(ALK)*, *RET*, and *ROS1*; AND
C) Patient meets ONE of the following (i, ii, iii, or iv):
- **i.** Patient meets BOTH of the following (a and b):
  - **a)** The medication is used as first-line therapy; AND
  - **b)** The tumor is positive for one of the following [(1), (2), or (3)]:
    - **(1)** *EGFR* exon 20 mutation; OR
    - **(2)** *ERBB2 (HER2)* mutation; OR
    - **(3)** *NRG1* gene fusion; OR
- **ii.** Patient meets BOTH of the following (a and b):
  - **a)** The medication is used as first-line or subsequent therapy; AND
  - **b)** The tumor is positive for one of the following [(1), (2), or (3)]:
    - **(1)** *BRAF* V600E mutation; OR
    - **(2)** *NTRK1/2/3* gene fusion; OR
    - **(3)** *MET* exon 14 skipping mutation; OR
- **iii.** The medication is used as subsequent therapy and meets ONE of the following (a or b):
  - **a)** The tumor is *EGFR* S768I, L861Q, and/or G719X mutation positive; OR
  - **b)** The medication is used as a single-agent and meets BOTH of the following [(1) and (2)]:
    - **(1)** The tumor is PD-L1 positive, with tumor proportion score (TPS) ≥ 1%; AND
    - **(2)** Patient has not progressed on prior therapy with a programmed death receptor-1 (PD-1)/PD-L1 inhibitor; OR

      Note: This includes previous therapy with either one of Keytruda (pembrolizumab intravenous infusion), Keytruda Qlex, Opdivo (nivolumab intravenous infusion), Opdivo Qvantig (nivolumab and hyaluronidase-nvhy subcutaneous injection), Libtayo (cemiplimab-rwlc intravenous infusion), Imfinzi (durvalumab intravenous infusion), or Tecentriq (atezolizumab intravenous infusion).
- **iv.** Patient meets BOTH of the following (a and b):
  - **a)** The medication is used as first-line or continuation maintenance therapy; AND
  - **b)** The tumor has no actionable mutations; AND

    Note: The tumor does NOT have the following mutations: *EGFR* exon 19 deletion, *EGFR* exon 21 L857R. *EGFR* S768I, *EGFR* L861Q, *EGFR* G719X, *EGFR* exon 20 insertion, , *ALK* rearrangement, *ROS1* rearrangement, *BRAF* V600E, *NTRK* 1/2/3 gene fusion, *METex14* skipping, *RET* rearrangement, *ERBB2* (HER2), and *NRG1* gene fusion.

D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR
B) 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

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16. Renal Cell Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patient meets ONE of the following (i or ii):
  i. Patient meets BOTH of the following (a and b):
    a) Patient has advanced disease; AND
    b) The medication is used in combination with Inlyta (axitinib tablets) or Lenvima (lenvatinib capsules); OR
  ii. The medication is used as adjuvant therapy; AND
C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR
B) 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

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17. Tumor Mutational Burden-High (TMB-H) Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
Note: Examples of solid tumors are adrenal cancer, ampullary adenocarcinoma, breast cancer, cervical cancer, cholangiocarcinoma (intrahepatic and extrahepatic), chondrosarcoma, chordoma, endometrial carcinoma, esophageal carcinoma, esophagogastric junction carcinoma, Ewing sarcoma, gall
er cancer, gastric cancer, head and neck cancer, neuroendocrine cancer, osteosarcoma, ovarian/fallopian tube/primary peritoneal carcinoma, pancreatic adenocarcinoma, penile cancer, primary occult, prostate cancer, salivary gland tumors, testicular cancer, thyroid cancer, uterine sarcoma, vaginal cancer, vulvar cancer.
A) Patient is ≥ 12 years of age; AND
B) Patient is not a surgical candidate or has unresectable or metastatic tumor mutational burden-high (≥ 10 mutations/megabase) solid tumor; AND
C) Patient has progressed on prior therapy; AND
D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR
B) 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

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18. Urothelial Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patient meets ONE of the following conditions (i, ii, iii, iv, or v):
  i. Patient has locally advanced or metastatic disease; OR
  ii. Patient has tried at least one platinum-based chemotherapy; OR

Note: Cisplatin and carboplatin are platinum-based chemotherapies.

iii. According to the prescriber, patient is not eligible for platinum-based chemotherapy; OR
Note: This is regardless of PD-L1 status. Cisplatin and carboplatin are platinum-based chemotherapies.

iv. The medication is used as adjuvant therapy; OR

v. Patient meets BOTH of the following (a and b):

a) Patient has high-risk, non-muscle invasive bladder cancer; AND

b) Patient is Bacillus Calmette-Guerin (BCG) unresponsive; AND

C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR

B) 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

Other Uses with Supportive Evidence

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19. Appendiceal Cancers. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
Note: If the tumor is MSI-H or dMMR, see Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors criteria.

A) Patient is ≥ 18 years of age; AND

B) Patient has recurrent, metastatic or progressive disease; AND

C) The disease is polymerase epsilon/delta (POLE/POLD1) mutation positive with ultra-hypermutated phenotype (tumor mutational burden > 50 mutations/megabase); AND

D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR

B) 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

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20. Gestational Trophoblastic Neoplasia. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient has multi-agent chemotherapy resistant disease; AND
Note: Examples of chemotherapy regimens contain etoposide, cisplatin/carboplatin, paclitaxel, bleomycin, ifosfamide, methotrexate.

C) The medication is used as a single-agent; AND

D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR

B) 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

21. Penile Cancer: Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
Note: If the tumor is MSI-H or dMMR, see Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors criteria. If the tumor is mutational burden-high, see Tumor Mutational Burden-High (TMB-H) Cancer criteria.
A) Patient is ≥ 18 years of age; AND
B) Patient has recurrent or metastatic disease; AND
C) Patient meets ONE of the following (i or ii):
i. The medication is used in combination with fluorouracil and either cisplatin or carboplatin; OR
ii. The medication is used as a single agent for maintenance therapy; AND
D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR
B) 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

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22. Thymic Carcinoma. Approve for 1 year if the patient meets BOTH of the following (A and B):
A) Patient is ≥ 18 years of age; AND
B) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR
B) 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

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23. Vaginal Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
Note: If the tumor is MSI-H or dMMR, see Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors criteria. If the tumor is mutational burden-high, see Tumor Mutational Burden-High (TMB-H) Cancer criteria.
A) Patient is ≥ 18 years of age; AND
B) Patient has recurrent or metastatic disease; AND
C) Patient has programmed death-ligand 1 (PD-L1) positive disease (combined positive score [CPS] ≥ 1); AND
D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR
B) 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

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24. Vulvar Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, and C):

Note: If the tumor is MSI-H or dMMR, see Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors criteria. If the tumor is mutational burden-high, see Tumor Mutational Burden-High (TMB-H) Cancer criteria.

A) Patient is ≥ 18 years of age; AND
B) Patient has advanced, recurrent, or metastatic disease; AND
C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):

A) 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 3 weeks; OR
B) 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously not more frequently than once every 6 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Keytruda Qlex is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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12. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 1.2026 – November 6, 2025). © 2025 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 7, 2025.
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17. The NCCN Gestational Trophoblastic Neoplasia Clinical Practice Guidelines in Oncology (version 1.2026 – November 10, 2025). © 2025 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 12, 2025.

18. The NCCN Penile Cancer Clinical Practice Guidelines in Oncology (version 1.2026 – November 12, 2025). © 2025 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 14, 2025.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/24/2025
Selected Revision	**Mesothelioma:** Removed the requirement that the patient has unresectable or advanced malignant pleural disease. Added that the patient has one of the following: pleural mesothelioma, peritoneal mesothelioma, pericardial mesothelioma, and tunica vaginalis testis mesothelioma as approval options. **Thymic Carcinoma:** Added as new condition of approval.	10/08/2025
Selected Revision	**Cervical Cancer:** The option that the patient has locally advanced FIGO 2014 stage III to IVA disease was modified to the patient has FIGO 2014 stage III to IVA disease or FIGO 2018 Stage III to IVA disease. **Endometrial Carcinoma:** The medication is used for primary or adjuvant therapy, in combination with carboplatin and paclitaxel, or as a single agent for maintenance therapy was added as an option for approval. Added the medication is used as a single agent for maintenance therapy as an approval option when the patient has recurrent disease. **Melanoma:** The approval duration was modified to approval up to 1 year (total) of treatment if the patient is ≥ 12 years of age and the medication will be used as adjuvant treatment. Added approve for 4 months of treatment if the patient is ≥ 18 years of age and the medication is used as neoadjuvant treatment as new option for approval. **Merkel Cell Carcinoma:** Removed the requirement that the patient has recurrent locally advanced or metastatic disease. Added requirement that the patients meets one of the following: patient has primary or recurrent locally advanced disease, if according to the prescriber curative surgery and curative radiation therapy are not feasible; or patient has primary or recurrent regional disease, if according to the prescriber curative surgery and curative radiation therapy are not feasible; or patient has metastatic (disseminated) disease. **Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors:** The note was modified to include appendiceal neoplasms and cancers and vaginal cancer. **Non-Small Cell Lung Cancer – Neoadjuvant and Adjuvant:** The tumor is negative for the following actionable biomarkers: epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R, anaplastic lymphoma kinase (ALK), RET, and ROS1 was added as a requirement of approval. The patient has resectable stage IB to III disease was modified to the patient has resectable or completely resected stage IB to III disease. **Non-Small Cell Lung Cancer – Recurrent, Advanced, or Metastatic Disease:** The tumor is negative for the following actionable biomarkers: epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R, anaplastic lymphoma kinase (ALK), RET, and ROS1 was added as a requirement of approval. The requirement that the patient meets one of the following: patient has squamous cell disease, and the medication is used in combination with chemotherapy; patient has no EGFR or ALK genomic tumor aberrations and the medication is used in combination with chemotherapy; or the tumor is PD-L1 positive, with tumor proportion score (TPS) ≥ 1%, as determined by an approved test was removed. Added the option of approval that the medication is used as first-line therapy and the tumor is positive for one of the following: EGFR exon 20 mutations, ERBB2 (HER2) mutations, or NRG1 gene fusion. The medication is used for first-line or subsequent therapy and the tumor is positive for one of the following: BRAF V600E mutation, NTRK1/2/3 gene fusion, MET exon 14 skipping mutation was added as an option for approval. Added the optional of approval that the medication is used as subsequent therapy and meets one of the following: tumor is EGFR S768I, L861Q, and/or G719X mutation positive or the medication is used as a single-agent and meets BOTH of the following: the tumor is PD-L1 positive, with tumor proportion score (TPS) ≥ 1% and the patient has not progressed on prior therapy with a programmed death receptor-1 (PD-1)/PD-L1 inhibitor; a Note was added listing previous therapy with either one of Keytruda (pembrolizumab intravenous infusion), Keytruda Qlex, Opdivo (nivolumab intravenous infusion), Opdivo Qvantig (nivolumab and hyaluronidase-nvhy subcutaneous injection), Libtayo (cemiplimab-rwlc intravenous infusion), Imfinzi (durvalumab intravenous infusion), or Tecentriq (atezolizumab	11/19/2025

	intravenous infusion). Added the option of approval that medication is used as first-line or continuation maintenance therapy and the tumor no actionable mutations; a Note was added listing the following actionable mutations: EFGR exon 19 deletion, EFGR exon 21 L858R, EFGR S768I, EGFR L861Q, EGFR G719X, EGFR exon 20 insertion, ALK rearrangement, ROS1 rearrangement, BRAF V600E, NTRK 1/2/3 gene fusion, METex14 skipping, RET rearrangement, ERBB2 (HER2), and NRG1 gene fusion. **Tumor Mutational Burden-High (TMB-H) Cancer:** The Note was modified to include vaginal cancer. **Urothelial Carcinoma:** Added patient has tried at least one platinum-based chemotherapy and the Note: cisplatin and carboplatin are platinum-based chemotherapy as new option for approval. Added according to the prescriber, patient is not eligible for platinum-based chemotherapy and the Note this is regardless of PD-L1 status. Cisplatin and carboplatin are platinum-based chemotherapy as an approval option. Added as an option for approval that the medication is used as adjuvant therapy." **Appendiceal Cancers:** Added as new condition of approval. **Gestational Trophoblastic Neoplasia:** Added as a new condition of approval. **Penile Cancer:** Added as a new condition of approval. **Vaginal Cancers:** Added as new condition of approval. **Vulvar Cancers:** Added as new condition of approval. **Breast Cancer, Cervical Cancer, Esophageal Cancer, Gastric Cancer, and Head and Neck Squamous Cell Carcinoma:** For all of these conditions of approval, the descriptor as determined by an approved test was removed from the approval option that the patient's tumor expression for programmed death-ligand 1 (PD-L1) has a combined positive score (CPS) ≥ 1.	