

POLICY Document for KEYTRUDA QLEX

The overall objective of this policy is to support the appropriate and cost-effective use of the medication, specific to use of preferred medication options, lower cost site of care and overall, clinically appropriate use. This document provides specific information to each of the three sections of the overall policy.

Section 1: Site of Care

- Policy information specific to site of care (outpatient, hospital outpatient, home infusion)

Section 2: Clinical Criteria

- Policy information specific to the clinical appropriateness for the medication

Section 1: Site of Care

Site of Care Criteria Checkpoint Inhibitors

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated.

Brand Name	Generic Name	Dosage Form
Opdivo Qvantig	nivolumab and hyaluronidase-nvhy	subcutaneous
Tecentriq Hybreza	atezolizumab and hyaluronidase-tqjs	subcutaneous
Keytruda Qlex	pembrolizumab and berahyaluronidase alfa-pmph	subcutaneous

Criteria For Approval For Administration In Outpatient Hospital Setting

This policy provides coverage for administration of a checkpoint inhibitor in an outpatient hospital setting for the initial 6 months approval and up to 45 days for renewal of therapy.

This policy provides coverage for administration of a checkpoint inhibitor in an outpatient hospital setting for a longer course of treatment when ANY of the following criteria are met:

The member has experienced an adverse reaction that did not respond to conventional interventions (e.g., acetaminophen, steroids, diphenhydramine, fluids, other pre-medications or slowing of injection rate) or a severe adverse event (anaphylaxis, anaphylactoid reactions, myocardial infarction, thromboembolism, or seizures) during or immediately after administration or has experienced severe toxicity requiring continuous monitoring (e.g. Grade 2-4 bullous dermatitis, transaminitis, pneumonitis, Stevens-Johnson syndrome, acute pancreatitis, primary adrenal insufficiency aseptic meningitis, encephalitis, transverse myelitis, myocarditis, pericarditis, arrhythmias, impaired ventricular function, conduction abnormalities).

The member is medically unstable (e.g., respiratory, cardiovascular, or renal conditions).

The member has significant behavioral issues and/or physical or cognitive impairment that would impact the safety of the drug administration AND the patient does not have access to a caregiver.

The member is receiving provider administered combination chemotherapy.

Alternative administration sites (pharmacy, physician office, ambulatory care, etc.) are greater than 30 miles from the member's home.

The member is less than 14 years of age.

For situations where administration of a checkpoint inhibitor does not meet the criteria for outpatient hospital administration, coverage for a checkpoint inhibitor is provided when administered in alternative sites such as; physician office, home infusion or ambulatory care.

Required Documentation

The following information is necessary to initiate the site of care prior authorization review (where applicable).

Medical records supporting the member has experienced an adverse reaction that did not respond to conventional interventions or a severe adverse event during or immediately after an administration or a severe toxicity requiring continuous monitoring.

Medical records supporting the member is medically unstable.

Medical records supporting the member has behavioral issues and/or physical or cognitive impairment and no access to a caregiver.

Medical records supporting the member is receiving provider administered combination therapy.

Records supporting alternative administration sites are greater than 30 miles from the member's home.

Medical records supporting the member is new to therapy.

Section 2: Clinical Criteria

Specialty Guideline Management

Keytruda Qlex

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Keytruda Qlex	pembrolizumab and berahyaluronidase alfa-pmph

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications¹

Melanoma

Keytruda Qlex is indicated for the treatment of adult patients with unresectable or metastatic melanoma.

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

Non-Small Cell Lung Cancer

Keytruda Qlex, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of adult patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.

Keytruda Qlex, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of adult patients with metastatic squamous NSCLC.

Keytruda Qlex, as a single agent, is indicated for the first-line treatment of adult 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.

Keytruda Qlex, as a single agent, is indicated for the treatment of adult patients with metastatic NSCLC whose tumors express PD-L1 (TPS $\geq 1\%$) as determined by an FDA approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Keytruda Qlex.

Keytruda Qlex, is indicated for the treatment of adult patients with resectable (tumors ≥ 4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

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

Malignant Pleural Mesothelioma

Keytruda Qlex, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic malignant pleural mesothelioma (MPM).

Head and Neck Squamous Cell Cancer

Keytruda Qlex, in combination with platinum and fluorouracil (FU), is indicated for the first-line treatment of adult patients with metastatic or with unresectable, recurrent head and neck squamous cell carcinoma (HNSCC).

Keytruda Qlex, as a single agent, is indicated for the first line treatment of adult 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.

Keytruda Qlex, as a single agent, is indicated for the treatment of adult patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

Urothelial Cancer

Keytruda Qlex, in combination with enfortumab vedotin, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer.

Keytruda Qlex, as a single agent, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma:

- who are not eligible for any platinum-containing chemotherapy, or
- who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Keytruda Qlex, as a single agent, is 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 Cancer

Keytruda Qlex is indicated for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer (CRC)

Keytruda Qlex is indicated for the treatment of adult patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by an FDA-approved test.

Gastric Cancer

- Keytruda Qlex, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.
- Keytruda Qlex, in combination with fluoropyrimidine- and platinum-containing chemotherapy is indicated for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.

Esophageal Cancer

Keytruda Qlex is indicated for the treatment of adult 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 for patients with tumors that express PD-L1 (CPS ≥ 1), 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

Keytruda Qlex, in combination with chemoradiotherapy (CRT), is indicated for the treatment of adult patients with locally advanced cervical cancer involving the lower third of the vagina, with or without extension to pelvic sidewall, or hydronephrosis/non-functioning kidney, or spread to adjacent pelvic organs (FIGO 2014 Stage III-IVA).

Keytruda Qlex, in combination with chemotherapy, with or without bevacizumab, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.

Keytruda Qlex, as a single agent, is indicated for the treatment of adult 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

Keytruda Qlex is indicated for the treatment of adult patients with hepatocellular carcinoma (HCC) secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1-containing regimen.

Biliary Tract Cancer

Keytruda Qlex, in combination with gemcitabine and cisplatin, is indicated for the treatment of adult patients with locally advanced unresectable or metastatic biliary tract cancer (BTC).

Merkel Cell Carcinoma

Keytruda Qlex is indicated for the treatment of adult and pediatric patients 12 years and older with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC).

Renal Cell Carcinoma

Keytruda Qlex, in combination with axitinib, is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).

Keytruda Qlex, in combination with lenvatinib, is indicated for the first-line treatment of adult patients with advanced RCC.

Keytruda Qlex is indicated for the adjuvant treatment of adult patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

Endometrial Carcinoma

Keytruda Qlex, in combination with carboplatin and paclitaxel, followed by Keytruda Qlex as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma.

Keytruda Qlex, in combination with lenvatinib, is indicated for the treatment of adult patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) or not MSI-H as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

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

Tumor Mutational Burden-High Cancer

Keytruda Qlex is indicated for the treatment of adult and pediatric patients 12 years and older 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 Keytruda Qlex in pediatric patients 12 years and older with TMB-H central nervous system cancers have not been established.

Cutaneous Squamous Cell Carcinoma

Keytruda Qlex is indicated for the treatment of adult patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced cSCC that is not curable by surgery or radiation.

Triple-Negative Breast Cancer

Keytruda Qlex is indicated for the treatment of adult patients with high-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

Keytruda Qlex, in combination with chemotherapy, is indicated for the treatment of adult patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥ 10) as determined by an FDA approved test.

All other indications are considered experimental/investigational and not medically necessary.

Documentation

Submission of the following information is necessary to initiate the prior authorization review:

Documentation of programmed death ligand 1 (PD-L1) tumor expression, where applicable.

Documentation of laboratory report confirming microsatellite instability-high (MSI-H) or mismatch repair (MMR) tumor status, where applicable.

Documentation of laboratory report confirming high tumor mutational burden (≥ 10 mutations/megabase [mut/Mb]), where applicable.

Documentation of laboratory report confirming that the cancer cells are negative for the following receptors, where applicable:

- human epidermal growth factor receptor 2 (HER-2)
- estrogen
- progesterone

Documentation of EGFR or ALK tumor aberration status, where applicable.

Exclusions

Coverage will not be provided for members with any of the following exclusions:

Pediatric members with TMB-H central nervous system cancers

Members who have experienced disease progression while on programmed death receptor-1 (PD-1) or PD-L1 inhibitor therapy

Coverage Criteria

Cutaneous Melanoma¹

Authorization of 6 months may be granted for treatment of cutaneous melanoma in any of the following settings:

- For unresectable or metastatic disease as a single agent.

- As adjuvant treatment following complete resection of stage IIB, IIC, or III disease as a single agent in members 12 years of age or older.

Non-small Cell Lung Cancer (NSCLC)¹

Authorization of 6 months may be granted:

- In combination with pemetrexed and platinum chemotherapy for first-line treatment of metastatic nonsquamous NSCLC when there are no EGFR or ALK genomic tumor aberrations (unless testing is not feasible due to insufficient tissue)
- In combination with carboplatin and either paclitaxel or paclitaxel protein-bound for first-line treatment of metastatic squamous NSCLC
- For NSCLC whose tumors express PD-L1 (TPS \geq 1 %) as a single agent and any of the following:
 - First-line treatment of metastatic or Stage III disease where patients are not candidates for surgical resection or definitive chemoradiation
 - Metastatic disease that has progressed on or after platinum-containing chemotherapy and FDA-approved targeted therapy, if tumor has EGFR or ALK genomic aberrations
- As neoadjuvant treatment when used in combination with platinum containing chemotherapy for resectable (tumors \geq 4 cm or node positive) NSCLC, and then continued as single agent adjuvant therapy after surgery
- As adjuvant treatment as a single agent following resection and platinum-based chemotherapy for Stage IB (T2a \geq 4 cm), II, or IIIA NSCLC

Head and Neck Cancer¹

Authorization of 6 months may be granted for treatment of head and neck squamous cell carcinoma (HNSCC) in any of the following regimens:

- In combination with platinum and fluorouracil for first-line treatment of metastatic or unresectable, recurrent disease
- As a single agent for any of the following:
 - First-line treatment of metastatic or unresectable, recurrent tumors expressing PD-L1 (CPS \geq 1)
 - Recurrent or metastatic disease with progression on or after platinum-containing chemotherapy

Urothelial Cancer¹

Authorization of 6 months may be granted as a single agent for treatment of urothelial cancer that is either of the following:

- Locally advanced or metastatic disease in members who are either:
 - Not eligible for any platinum containing chemotherapy or

- Have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

Bacillus Calmette Guerin (BCG) unresponsive, high risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors in members who will not undergo cystectomy

Authorization of 6 months may be granted in combination with enfortumab vedotin-ejfv for treatment of locally advanced or metastatic urothelial carcinoma.

Solid Tumors¹

Authorization of 6 months may be granted as a single agent for treatment of solid tumors in members 12 years of age or older with unresectable or metastatic disease that has progressed following prior treatment and who have no satisfactory alternative treatment options when either of the following criteria is met:

- The requested medication will be used for microsatellite instability-high or mismatch repair deficient solid tumors.
- The requested medication will be used for tumor mutational burden-high (≥ 10 mutations/megabase [mut/Mb]) solid tumors.

Colorectal Cancer¹

Authorization of 6 months may be granted as a single agent for the treatment of unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer.

Merkel Cell Carcinoma¹

Authorization of 6 months may be granted as a single agent for treatment of Merkel cell carcinoma in members 12 years of age or older with recurrent locally advanced or metastatic disease.

Gastric Cancer¹

Authorization of 6 months may be granted for first-line treatment of locally advanced unresectable or metastatic gastric or gastroesophageal (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥ 1) in any of the following regimens:

- In combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy for HER2 positive disease
- In combination with fluoropyrimidine- and platinum-containing chemotherapy for HER2-negative disease

Esophageal Cancer¹

Authorization of 6 months may be granted for treatment of locally advanced or metastatic esophageal or gastroesophageal (GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation in any of the following regimens:

- In combination with platinum and fluoropyrimidine-based chemotherapy in tumors expressing PD-L1 (CPS \geq 1)
- As a single agent in tumors expressing PD-L1 (CPS \geq 10) after at least one prior line of systemic therapy and squamous cell histology

Cervical Cancer¹

Authorization of 6 months may be granted for the treatment of cervical cancer in any of the following regimens:

- In combination with chemotherapy with or without bevacizumab for persistent, recurrent or metastatic tumors expressing PD-L1 (CPS \geq 1)
- As a single agent for recurrent or metastatic tumors expressing PD-L1 (CPS \geq 1) with disease progression on or after chemotherapy
- In combination with chemoradiotherapy (CRT) for FIGO 2014 stage III-IVA disease

Endometrial Carcinoma¹

Authorization of 6 months may be granted in any of the following regimens:

- In combination with lenvatinib for treatment of advanced endometrial carcinoma when both of the following criteria are met:
 - The disease is mismatch repair proficient (pMMR) or not MSI-H
 - The member has disease progression following prior systemic therapy and is not a candidate for curative surgery or radiation
- As a single agent for treatment of advanced endometrial carcinoma when both of the following criteria are met:
 - The disease is dMMR or MSI-H
 - The member has disease progression following prior systemic therapy and is not a candidate for curative surgery or radiation
- In combination with carboplatin and paclitaxel and continued as a single agent (for up to 20 cycles total) for primary advanced or recurrent endometrial carcinoma

Biliary Tract Cancers¹

Authorization of 6 months may be granted in combination with gemcitabine and cisplatin for locally advanced unresectable or metastatic biliary tract cancers.

Hepatocellular Carcinoma¹

Authorization of 6 months may be granted for treatment of hepatocellular carcinoma secondary to hepatitis B in members who have received prior systemic therapy other than a PD-1/PD-L1- containing regimen and will use the requested medication as a single agent.

Renal Cell Carcinoma¹

Authorization of 6 months may be granted for treatment of renal cell carcinoma in any of the following regimens:

- In combination with axitinib or lenvatinib for first-line treatment of advanced disease
- As a single agent for the adjuvant treatment of members with RCC at intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions.

Cutaneous Squamous Cell Carcinoma¹

Authorization of 6 months may be granted as a single agent for treatment of locally advanced, recurrent or metastatic cutaneous squamous cell carcinoma that is not curable by surgery or radiation.

Breast Cancer¹

- Authorization of 6 months may be granted for treatment of locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) when all of the following criteria are met:
 - The diagnosis of triple-negative breast cancer is confirmed by the cancer cells testing negative for ALL of the following receptors:
 - Human epidermal growth factor receptor 2 (HER-2)
 - Estrogen
 - Progesterone
 - Tumor must express PD-L1 (CPS \geq 10)
 - The requested medication will be used in combination with chemotherapy
- Authorization of 6 months may be granted for treatment of high-risk early-stage triple-negative breast cancer (TNBC) when all of the following criteria are met:
 - The diagnosis of triple-negative breast cancer is confirmed by the cancer cells testing negative for ALL of the following receptors:
 - Human epidermal growth factor receptor 2 (HER-2)
 - Estrogen
 - Progesterone
 - The requested medication will be used as neoadjuvant treatment in combination with chemotherapy and continued as single agent adjuvant treatment after surgery,

Malignant Pleural Mesothelioma¹

Authorization of 6 months may be granted for first-line treatment of unresectable advanced or metastatic malignant pleural mesothelioma when used in combination with pemetrexed and platinum chemotherapy.

Continuation of Therapy

Adjuvant Treatment of Melanoma, TNBC, RCC, or NSCLC

Authorization of 6 months may be granted (up to 12 months total) for continued treatment in members requesting reauthorization for adjuvant treatment of cutaneous melanoma, TNBC, RCC or NSCLC who have not experienced disease recurrence or unacceptable toxicity.

NSCLC, HNSCC, MSI-H or dMMR Cancers, Gastric Cancer, Esophageal Cancer, Cervical Cancer, HCC, MCC, RCC, Endometrial carcinoma, cSCC, TNBC, TMB-H Cancer, Biliary Tract Cancer, MPM

Authorization of 6 months may be granted (up to 24 months of continuous use) for continued treatment in members requesting reauthorization for NSCLC, HNSCC, MSI-H or dMMR cancers, gastric cancer, esophageal cancer, cervical cancer, HCC, MCC, RCC, endometrial carcinoma, cSCC, TNBC, TMB-H cancer, biliary tract cancer, and malignant pleural mesothelioma who have not experienced disease progression or unacceptable toxicity.

Urothelial Cancer

Authorization of 6 months may be granted (up to 24 months of continuous use) for continued treatment in members requesting reauthorization for urothelial carcinoma when both of the following criteria are met:

- Member has not experienced disease progression or unacceptable toxicity.
- For high-risk BCG-unresponsive non-muscle invasive bladder cancer only: disease is not persistent or recurrent.

Unresectable or Metastatic Cutaneous Melanoma

Authorization of 6 months may be granted for continued treatment in members requesting reauthorization for unresectable or metastatic cutaneous melanoma who have not experienced disease progression or an unacceptable toxicity.

REFERENCES

SECTION 1

1. Tecentriq Hybreza [package insert]. South San Francisco, CA: Genentech, Inc.; September 2024.
2. Opdivo Qvantig [package insert]. Princeton, NJ: Bristol-Myers Squibb Company.; December 2024.
3. Keytruda Qlex [package insert]. Rahway, NJ: Merck Sharp & Dohme LLC; September 2025.

SECTION 2

1. Keytruda Qlex [package insert]. Rahway, NJ: Merck Sharp & Dohme LLC; September 2025.