PREMERA HMO

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MEDICAL POLICY – 5.01.591

Immune Checkpoint Inhibitors

Effective Date:	**Feb. 5, 2027***	RELATED POLICIES/GUIDELINES:	
Last Revised:	Oct. 13, 2026	5.01.543	General Medical Necessity Criteria for Companion Diagnostics Related to Drug Approval
Replaces:	N/A	5.01.589	BRAF and MEK Inhibitors
*View current version here.		11.01.523	Site of Service: Infusion Drugs and Biologic Agents

The Site of Service Medical Necessity criteria within this policy DO NOT apply to Alaska fully-insured members; refer to the infusion and injection drug Medical Necessity criteria only.

Site of Service *and* the infusion and injection drug Medical Necessity criteria apply to all other plan members.

Please contact Customer Service for more information.

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Chemotherapy, often called chemo, is cancer treatment that uses drugs. Radiation and surgery treat one area of cancer. But chemo usually travels through the bloodstream to treat the whole body. Treating the whole body is called a systemic treatment. Immunotherapy is a new type of cancer treatment that helps the body's immune cells fight cancer more effectively. Cancer cells sometimes "hide" from the body's cells that are designed to search for cells that don't belong, like cancer cells or bacteria. Immune checkpoint inhibitors are drugs that block the way that cancer cells do this and so help the immune cells find them so they can be stopped. It is one of the ways we can make the environment less friendly to cancer and slow its growth.

Current immunotherapy drugs are complex molecules that must be given through a vein (intravenous). In the future, some may be given by a shot (injection) the individual could inject

without help. This policy gives information about immunotherapy drugs and the criteria for when they may be medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Site of Service (SOS) Medical Necessity criteria applies ONLY to medical benefit reviews. SOS Medical Necessity criteria does NOT apply to Alaska fully-insured members; refer to the infusion and injection drug Medical Necessity criteria only. Please contact Customer Service for more information.

We will review specific intravenous (IV) and injectable drugs for medical necessity for all ages.

For those aged 13 and older, we also will review the site of service for medical necessity. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician's office, or at home. Click **here** to be directed to the site of service review criteria.

Drugs subject to site of service review addressed in this policy are:

- Keytruda (pembrolizumab) IV
- Keytruda Qlex (pembrolizumab and berahyaluronidase alfa-pmph) SC
- Imfinzi (durvalumab) IV
- Jemperli (dostarlimab-gxly) IV
- Opdivo (nivolumab) IV
- Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) SC

- Tecentriq (atezolizumab) IV
- Tecentriq Hybreza (atezolizumab-hyaluronidase-tqjs) SC

Note: Keytruda, Keytruda Qlex, Imfinzi, Jemperli, Opdivo, Opdivo Qvantig, Tecentriq, and Tecentriq Hybreza are subject to review for site of service administration except when it is used concurrently with other infusion or injection medications for cancer treatment.

Click on the links below to be directed to the related medical necessity criteria:

Bavencio (avelumab)

Imfinzi (durvalumab)

Imjudo (tremelimumab-actl)

Jemperli (dostarlimab-gxly)

Keytruda (pembrolizumab)

Keytruda Qlex (pembrolizumab and berahyaluronidase alfa-pmph)

Libtayo (cemiplimab)

Loqtorzi (toripalimab-tpzi)

Opdivo (nivolumab)

Opdivo Qvantig (nivolumab and hyaluronidase-nvhy)

Opdualag (nivolumab and relatlimab-rmbw)

Penpulimab-kcqx

Tecentriq (atezolizumab)

Tecentriq Hybreza (atezolizumab and hyaluronidase-tqjs)

Tevimbra (tislelizumab-jsgr)

Unloxcyt (cosibelimab-ipdl)

Yervoy (ipilimumab)

Zynyz (retifanlimab-dlwr)

Site of Service Administration	Medical Necessity
Medically necessary sites of service • **Physician's office** • **Infusion center** • **Home infusion**	**IV infusion and injection therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site:** • These are the preferred **medically necessary** sites of service for specified drugs.

Site of Service Administration	Medical Necessity
Hospital-based outpatient setting • **Outpatient hospital IV infusion department** • **Hospital-based outpatient clinical level of care**	**IV infusion and injection therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site.** **This site is considered medically necessary for the first 90 days for the following:** • The initial course of infusion or injection of a pharmacologic or biologic agent **OR** • Re-initiation of an agent after 6 months or longer following discontinuation of therapy* * This does not include when standard dosing between infusions or injections is 6 months or longer. **This site is considered medically necessary when there is no outpatient infusion center within 50 miles of the individual's home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions or injections of this drug.** **This site is considered medically necessary only when the individual has a clinical condition which puts him or her at increased risk of complications for infusions or injections, including any 1 of the following:** • Known cardiac condition (e.g., symptomatic cardiac arrhythmia) or pulmonary condition (e.g., significant respiratory disease, serious obstructive airway disease, %FVC less than or equal to 40%) that may increase the risk of an adverse reaction • Unstable renal function which decreases the ability to respond to fluids • Difficult or unstable vascular access • Acute mental status changes or cognitive conditions that impact the safety of infusion or injection therapy

Site of Service Administration	Medical Necessity
	• A known history of severe adverse drug reactions and/or anaphylaxis to prior treatment with a related or similar drug **This site is considered medically necessary when the individual has cytokine release syndrome (CRS), and all the following are met:** • CRS is grade 3 or 4 as evidenced by ALL the following: ○ Temperature at least 38 °C ○ Hypotension that requires 1 or more vasopressors ○ Hypoxia that requires oxygen through a high-flow nasal cannula, face mask, non-rebreather mask, or Venturi mask OR positive pressure (continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, or mechanical ventilation) **AND** • The individual will be admitted into an inpatient setting as soon as possible
Hospital-based outpatient setting • **Outpatient hospital IV infusion department** • **Hospital-based outpatient clinical level of care**	**These sites are considered not medically necessary for infusion and injectable therapy services of various medical and biologic agents when the site-of-service criteria in this policy are not met.**

Drug	Medical Necessity
CTLA-4 Inhibitor • **Imjudo (tremelimumab-actl) IV**	**Imjudo (tremelimumab-actl) may be considered medically necessary when all the following are met:** • The individual is aged 18 years or older **AND** • Meets 1 of the following: ○ Has unresectable hepatocellular carcinoma (uHCC) and Imjudo (tremelimumab-actl) will be used in combination with Imfinzi (durvalumab) ○ Has metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR)

Drug	Medical Necessity
	mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations and Imjudo (tremelimumab-actl) will be used in combination with Imfinzi (durvalumab) and platinum-based chemotherapy
CTLA-4 Inhibitor • **Yervoy (ipilimumab) IV**	**Yervoy (ipilimumab) may be considered medically necessary for:** • Melanoma ○ Treatment of unresectable or metastatic melanoma in individuals aged 12 years and older ○ Adjuvant treatment of individuals with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy ○ As a single agent treatment for brain metastases if active against primary tumor (melanoma) in individuals with recurrent disease • Treatment of individuals with intermediate or poor-risk, previously untreated advanced renal cell carcinoma (RCC) when used in combination with Opdivo (nivolumab) • Treatment of adult and pediatric individuals aged 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) unresectable or metastatic colorectal cancer when used in combination with Opdivo (nivolumab) • Hepatocellular Carcinoma (HCC) ○ First-line treatment of unresectable or metastatic HCC when used in combination with Opdivo (nivolumab) ○ Unresectable or metastatic HCC who have been previously treated with sorafenib, in combination with Opdivo (nivolumab) • Non-Small Cell Lung Cancer (NSCLC) ○ Metastatic NSCLC expressing PD-L1 (at least 1%) as determined by an FDA-approved test, with no EGFR or ALK/ROS1 genomic tumor aberrations, as first-line treatment in combination with Opdivo (nivolumab) ○ Metastatic or recurrent NSCLC, with no EGFR or ALK/ROS1 genomic tumor aberrations, as first-line treatment in combination with Opdivo (nivolumab) and 2 cycles of

Drug	Medical Necessity
	platinum-doublet (e.g., carboplatin and pemetrexed, cisplatin and pemetrexed, carboplatin and paclitaxel) chemotherapy • Unresectable malignant pleural mesothelioma as first-line treatment in combination with Opdivo (nivolumab) • First-line treatment of adult individuals with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC) whose tumors express PD-L1 (at least 1) when used in combination with Opdivo (nivolumab)
PD-1 inhibitor • **Jemperli (dostarlimab-gxly) IV**	**Jemperli (dostarlimab-gxly) is subject to review for site of service administration except when it is used concurrently with other infusion or injection medications for cancer treatment.** **Jemperli (dostarlimab-gxly) may be considered medically necessary for the treatment of adult individuals with primary advanced or recurrent endometrial cancer when all the following are met:** • The individual is aged 18 years or older **AND** • Has been diagnosed with primary advanced or recurrent endometrial cancer **AND** • Jemperli (dostarlimab-gxly) will be used in combination with carboplatin and paclitaxel **Jemperli (dostarlimab-gxly) may be considered medically necessary for the treatment of adult individuals with recurrent or advanced endometrial cancer when all the following are met:** • The individual is aged 18 years or older **AND** • Has been diagnosed with recurrent or advanced endometrial cancer that is mismatch repair deficient (dMMR)* **AND** • Has progressed on or following prior treatment with a platinum- (e.g., cisplatin, carboplatin, oxaliplatin) containing regimen

Drug	Medical Necessity
	AND • Is not a candidate for curative surgery or radiation **Jemperli (dostarlimab-gxly) may be considered medically necessary for the treatment of adult individuals with recurrent or advanced solid tumors when all the following are met:** • The individual is aged 18 years or older **AND** • Has been diagnosed with recurrent or advanced solid tumors that are mismatch repair deficient (dMMR)* **AND** • Has progressed on or following prior treatment **AND** • Has no satisfactory alternative treatment options * FDA-approved testing confirming the presence of a specific genetic feature known as mismatch repair deficient (dMMR) is required before coverage determination for Jemperli can be established.
PD-1 inhibitor • **Keytruda (pembrolizumab) IV**	**Keytruda (pembrolizumab) is subject to review for site of service administration except when it is used concurrently with other infusion or injection medications for cancer treatment.** **Keytruda (pembrolizumab) may be considered medically necessary for treatment of any of the following:** • Melanoma ○ Unresectable or metastatic melanoma ○ Adjuvant treatment of adult and pediatric (aged 12 years and older) individuals with Stage IIB, IIC, or III melanoma following complete resection ○ Adjuvant treatment of individuals with melanoma with involvement of lymph node(s) following complete resection • Non-Small Cell Lung Cancer (NSCLC): ○ First-line as a single agent in individuals with metastatic NSCLC with PD-L1 protein overexpression [Tumor Proportion Score (TPS) is at least 1%], with no EGFR or ALK/ROS1 genomic tumor mutations

Drug	Medical Necessity
	○ First-line treatment of metastatic non-squamous NSCLC when used in combination with pemetrexed and platinum chemotherapy (e.g., cisplatin, carboplatin, oxaliplatin) in individuals with no EGFR or ALK/ROS1 genomic tumor aberrations or while awaiting the results of such confirmed genomic testing ○ First-line treatment of metastatic squamous NSCLC in combination with carboplatin and either paclitaxel or Abraxane (paclitaxel protein-bound) ○ Metastatic NSCLC with PD-L1 expression with disease progression on or after platinum-containing chemotherapy treatment ○ Metastatic NSCLC with EGFR or ALK/ROS1 genomic mutations who have disease progression on US Food and Drug Administration (FDA) -approved therapy for these mutations (i.e., anti-EGFR or anti-ALK/ROS1 agents) ○ Metastatic NSCLC when used as a single agent for the first-line treatment of individuals expressing PD-L1 [Tumor Proportion Score (TPS) is at least 1%], and no EGFR or ALK/ROS1 genomic tumor mutations ○ Stage III NSCLC where individuals are not candidates for surgical resection or definitive chemoradiation when used as a single agent for the first-line treatment of individuals expressing PD-L1 [Tumor Proportion Score (TPS) is at least 1%], and no EGFR or ALK/ROS1 genomic tumor mutations ○ Resectable (tumors at least 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 ○ Stage IB (T2a at least 4 cm), II, or IIIA NSCLC when used as a single agent, as adjuvant treatment following resection and platinum-based chemotherapy in adult individuals • Unresectable advanced or metastatic malignant pleural mesothelioma (MPM) as first-line treatment in adult individuals when used in combination with pemetrexed and platinum chemotherapy • Head and Neck Squamous Cell Cancer (HNSCC)

Drug	Medical Necessity
	○ Resectable locally advanced HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) is at least 1] as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy with or without cisplatin and then as a single agent ○ Metastatic or unresectable, recurrent HNSCC when used in combination with platinum and fluorouracil for first-line treatment ○ Recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy ○ Metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) is at least 1] as a single agent for the first line treatment • Classical Hodgkin Lymphoma (cHL) ○ Adult individuals with relapsed or refractory cHL ○ Pediatric individuals with refractory cHL, or cHL that has relapsed after 2 or more prior lines of therapy • Adult and pediatric individuals with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy • Urothelial Cancer ○ Treatment of locally advanced or metastatic urothelial carcinoma ▪ In individuals who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) is at least 10] ▪ In individuals who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status ▪ In individuals who have disease progression during or following platinum-containing therapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy ○ When used in combination with Padcev (enfortumab vedotin-ejfv) in adults individuals with locally advanced or metastatic urothelial carcinoma • Treatment of adult individuals with muscle invasive bladder cancer (MIBC) when used in combination with enfortumab

Drug	Medical Necessity
	vedotin, as neoadjuvant treatment and then continued after cystectomy as adjuvant treatment • Treatment of individuals 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 (MSI-H) or Mismatch Repair Deficient (dMMR): ○ Unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options ○ Unresectable or metastatic MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan ○ First-line treatment of MSI-H or dMMR unresectable or metastatic colorectal cancer • Gastric Cancer ○ 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 at least 1) when used in combination with trastuzumab, fluoropyrimidine- and platinum (e.g., cisplatin, carboplatin, oxaliplatin) containing chemotherapy ○ 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 at least 1) when used in combination with fluoropyrimidine- and platinum- (e.g., cisplatin, carboplatin, oxaliplatin) containing chemotherapy • Locally advanced or metastatic esophageal or gastroesophageal (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:

Drug	Medical Necessity
	○ In combination with platinum (e.g., cisplatin, carboplatin, oxaliplatin) and fluoropyrimidine (e.g., 5-fluorouracil, capecitabine) containing chemotherapy ○ As a single agent after one or more prior lines of systemic therapy with tumors of squamous cell histology that express PD-L1 (CPS is at least 10) • Cervical Cancer ○ Recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS at least 1) ○ In combination with chemotherapy, with or without bevacizumab, for the treatment of individuals with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS at least 1) ○ In combination with chemoradiotherapy (CRT), for the treatment of individuals with FIGO 2014 Stage III-IVA cervical cancer • Hepatocellular Carcinoma (HCC) ○ HCC previously treated with Nexavar (sorafenib) ○ HCC secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1-containing regimen • Adult and pediatric individuals with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC) • Renal Cell Carcinoma (RCC) ○ First-line treatment of individuals with advanced RCC in combination with Inlyta (axitinib) ○ First-line treatment of individuals with advanced RCC in combination with Lenvima (lenvatinib) ○ Adjuvant treatment of individuals with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions ○ In combination with belzutifan, for the adjuvant treatment of adult individuals with RCC with a clear cell component (ccRCC) at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions

Drug	Medical Necessity
	• Endometrial Carcinoma ○ In combination with lenvatinib, for the treatment of individuals with advanced endometrial carcinoma 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 individuals with advanced endometrial carcinoma that is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation ○ Adults with primary advanced or recurrent endometrial carcinoma in combination with carboplatin and paclitaxel followed by Keytruda (pembrolizumab) as a single agent • Adult and pediatric individuals with unresectable or metastatic tumor mutational burden-high (TMB-H) [at least 10 mutations/megabase (mut/Mb)] solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options • Recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced cSCC that is not curable by surgery or radiation • Triple-Negative Breast Cancer (TNBC) ○ In combination with chemotherapy for the treatment of individuals with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS at least 10) ○ In combination with sacituzumab govitecan-hziy, for the first line treatment of adult individuals with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 (CPS at least 10) ○ High-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery • In combination with paclitaxel, with or without bevacizumab, for the treatment of adult individuals with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal

Drug	Medical Necessity
	carcinoma whose tumors express PD-L1 (CPS at least 1), and who have received one or two prior systemic treatment regimens • Locally advanced unresectable or metastatic biliary tract cancer (BTC) in combination with gemcitabine and cisplatin **Note:** FDA-approved testing confirming presence of PD-L1, EGFR, or ALK/ROS1 proteins or TMB-H is required before coverage determination for Keytruda can be established.
PD-1 inhibitor • **Keytruda Qlex (pembrolizumab and berahyaluronidase alfa-pmph) SC**	**Keytruda Qlex (pembrolizumab and berahyaluronidase alfa-pmph) is subject to review for site of service administration except when it is used concurrently with other infusion or injection medications for cancer treatment.** **Keytruda Qlex (pembrolizumab and berahyaluronidase alfa-pmph) may be considered medically necessary when the following criteria are met:** • The individual must receive Keytruda (pembrolizumab) IV o **Exception**: This may be granted when there is inadequate peripheral venous access **AND** • Has been diagnosed and meets 1 of the following: o Melanoma ▪ Adults with unresectable or metastatic melanoma ▪ Adjuvant treatment of adult and pediatric (aged 12 years and older) individuals with Stage IIB, IIC, or III melanoma following complete resection ▪ Adjuvant treatment of adults with melanoma with involvement of lymph node(s) following complete resection o Non-Small Cell Lung Cancer (NSCLC) ▪ First-line as a single agent in adults with metastatic NSCLC with PD-L1 protein overexpression [Tumor Proportion Score (TPS) at least 1%], with no EGFR or ALK/ROS1 genomic tumor mutations ▪ First-line treatment of metastatic non-squamous NSCLC when used in combination with pemetrexed and

Drug	Medical Necessity
	platinum chemotherapy (e.g., cisplatin, carboplatin, oxaliplatin) in adults with no EGFR or ALK/ROS1 genomic tumor aberrations or while awaiting the results of such confirmed genomic testing ▪ First-line treatment of adults with metastatic squamous NSCLC in combination with carboplatin and either paclitaxel or Abraxane (paclitaxel protein-bound) ▪ Adults with metastatic NSCLC with PD-L1 expression and disease progression on or after platinum-containing chemotherapy treatment ▪ Adults with metastatic NSCLC with EGFR or ALK/ROS1 genomic mutations who have disease progression on US Food and Drug Administration (FDA) approved therapy for these mutations (i.e., anti-EGFR or anti-ALK/ROS1 agents) ▪ Adults with metastatic NSCLC when used as a single agent for the first-line treatment of individuals expressing PD-L1 [Tumor Proportion Score (TPS) at least 1%], with no EGFR or ALK/ROS1 genomic tumor mutations ▪ Adults with stage III NSCLC where individuals are not candidates for surgical resection or definitive chemoradiation when used as a single agent for the first-line treatment of individuals expressing PD-L1 [Tumor Proportion Score (TPS) at least 1%], with no EGFR or ALK/ROS1 genomic tumor mutations ▪ Adults with resectable (tumors at least 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 ▪ Stage IB (T2a at least 4 cm), II, or IIIA NSCLC when used in combination with platinum-containing chemotherapy as neoadjuvant treatment, then continued as a single agent as adjuvant treatment following resection ○ Unresectable advanced or metastatic malignant pleural mesothelioma (MPM) as first-line treatment in adults when

Drug	Medical Necessity
	used in combination with pemetrexed and platinum chemotherapy ○ Head and Neck Squamous Cell Cancer (HNSCC) ▪ Adult individuals with resectable locally advanced HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) is at least 1] as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy with or without cisplatin and then as a single agent ▪ Adults with metastatic or unresectable, recurrent HNSCC when used in combination with platinum and fluorouracil for first-line treatment ▪ Adults with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy ▪ Adults with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) at least 1] as a single agent for the first line treatment ○ Urothelial Cancer ▪ Treatment of locally advanced or metastatic urothelial carcinoma: ▫ In individuals who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) at least 10] ▫ In individuals who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status ▫ In individuals who have disease progression during or following platinum-containing therapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy ▪ When used in combination with Padcev (enfortumab vedotin-ejfv) in adults individuals with locally advanced or metastatic urothelial cancer ○ Treatment of adult individuals with muscle invasive bladder cancer (MIBC) when used in combination with enfortumab

Drug	Medical Necessity
	vedotin, as neoadjuvant treatment and then continued after cystectomy as adjuvant treatment ○ Treatment of adults 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 (MSI-H) or Mismatch Repair Deficient (dMMR) Cancer ▪ Adult and pediatric (aged 12 years and older) individuals with unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options ▪ Adult individuals with unresectable or metastatic MSI-H or dMMR colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan ▪ First-line treatment of adults with MSI-H or mismatch repair deficient (dMMR) unresectable or metastatic colorectal cancer ○ Gastric Cancer ▪ 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 at least 1) when used in combination with trastuzumab, fluoropyrimidine- and platinum (e.g., cisplatin, carboplatin, oxaliplatin) containing chemotherapy ▪ 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 at least 1) when used in combination with fluoropyrimidine- and platinum-(e.g., cisplatin, carboplatin, oxaliplatin) containing chemotherapy

Drug	Medical Necessity
	○ Adults with locally advanced or metastatic esophageal or 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 (e.g., cisplatin, carboplatin, oxaliplatin) and fluoropyrimidine (e.g., 5-fluorouracil, capecitabine) containing chemotherapy ▪ As a single agent after one or more prior lines of systemic therapy with tumors of squamous cell histology that express PD-L1 (CPS at least 10) ○ Cervical Cancer ▪ Adults with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS at least 1) ▪ In combination with chemotherapy, with or without bevacizumab, for the treatment of adult individuals with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS at least 1) ▪ In combination with chemoradiotherapy (CRT), for the treatment of adult individuals with FIGO 2014 Stage III-IVA cervical cancer ○ Hepatocellular Carcinoma (HCC) ▪ Adults with HCC previously treated with Nexavar (sorafenib) ▪ Adults with HCC secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1-containing regimen ○ Adult and pediatric (aged 12 years and older) individuals with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC) ○ Renal Cell Carcinoma (RCC) ▪ First-line treatment of adult individuals with advanced RCC in combination with Inlyta (axitinib) ▪ First-line treatment of adult individuals with advanced RCC in combination with Lenvima (lenvatinib) ▪ Adjuvant treatment of adult individuals with RCC at intermediate-high or high risk of recurrence following

Drug	Medical Necessity
	nephrectomy, or following nephrectomy and resection of metastatic lesions ▪ In combination with belzutifan, for the adjuvant treatment of adult individuals with RCC with a clear cell component (ccRCC) at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions o Endometrial Carcinoma ▪ In combination with lenvatinib, for the treatment of adult individuals with advanced endometrial carcinoma 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 adult individuals with advanced endometrial carcinoma that is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation ▪ Adults with primary advanced or recurrent endometrial carcinoma in combination with carboplatin and paclitaxel followed by Keytruda Qlex (pembrolizumab and berahyaluronidase alfa-pmph) as a single agent o Adult and pediatric (aged 12 years and older) individuals with unresectable or metastatic tumor mutational burden-high (TMB-H) [at least 10 mutations/megabase (mut/Mb)] solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options o Adults with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced cSCC that is not curable by surgery or radiation o Triple-Negative Breast Cancer (TNBC) ▪ In combination with chemotherapy for the treatment of adult individuals with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS at least 10)

Drug	Medical Necessity
	▪ In combination with sacituzumab govitecan-hziy, for the first line treatment of adult individuals with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 (CPS at least 10) ▪ Adults 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 ○ In combination with paclitaxel, with or without bevacizumab, for the treatment of adult individuals with platinum resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinoma whose tumors express PD-L1 (CPS at least 1), and who have received one or two prior systemic treatment regimens ○ Adults with locally advanced unresectable or metastatic biliary tract cancer (BTC) in combination with gemcitabine and cisplatin **Note:** FDA-approved testing confirming presence of PD-L1, EGFR, or ALK/ROS1 proteins or TMB-H is required before coverage determination for Keytruda Qlex can be established. **Note:** Keytruda Qlex is FDA-approved for the identical indications as Keytruda except Keytruda Qlex is NOT approved for the following: (1) Classical Hodgkin lymphoma (cHL); (2) Primary mediastinal large B-cell lymphoma (PMBCL).
PD-1 inhibitor • **Libtayo (cemiplimab) IV**	**Libtayo (cemiplimab) may be considered medically necessary for the treatment of individuals with:** • Cutaneous Squamous Cell Carcinoma (CSCC) ○ Metastatic CSCC or locally advanced CSCC who are not candidates for curative surgery or curative radiation ○ CSCC at high risk of recurrence after surgery and radiation when used as adjuvant treatment for adult individuals, and the high risk of recurrence is documented by at least one of the following features: ▪ Extracapsular extension (ECE) with at least 1 node greater than or equal to 20 mm

Drug	Medical Necessity
	▪ Greater than or equal to 3 involved lymph nodes regardless of ECE ▪ Skin or subcutaneous metastases greater than 2 cm from the primary lesion but not beyond the regional nodal basin ▪ Invasion of the skeleton or base of the skull (T4 Lesion) ▪ Perineural invasion ▪ Locally recurrent tumor with at least 1 one of the following additional adverse features: multiple ipsilateral nodes, at least T3 (at least 4 cm diameter or bone erosion or invasion greater than 6 mm), or poorly differentiated histology and recurrent lesion greater than or equal to 20 mm diameter • Locally advanced or metastatic basal cell carcinoma previously treated with a hedgehog pathway inhibitor (e.g., Erivedge [vismodegib], Odomzo [sonidegib]) or for whom a hedgehog pathway inhibitor is not appropriate • Non-Small Cell Lung Cancer (NSCLC) ○ Locally advanced, where individuals are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) at least 50%] with no EGFR, ALK or ROS1 aberrations when Libtayo is used as a single agent for first-line treatment ○ Locally advanced, where individuals are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC with no EGFR, ALK or ROS1 aberrations when Libtayo is used in combination with platinum (e.g., cisplatin, carboplatin, oxaliplatin) based chemotherapy for first-line treatment
PD-1 inhibitor • **Loqtorzi (toripalimab-tpzi) IV**	**Loqtorzi (toripalimab-tpzi) may be considered medically necessary for the treatment of any of the following:** • Adults with metastatic or with recurrent locally advanced nasopharyngeal carcinoma (NPC) in combination with cisplatin and gemcitabine

Drug	Medical Necessity
	• Adults with recurrent unresectable or metastatic NPC with disease progression on or after a platinum-containing chemotherapy
PD-1 inhibitor • **Opdivo (nivolumab) IV**	**Opdivo (nivolumab) is subject to review for site of service administration except when it is used concurrently with other infusion or injection medications for cancer treatment.** **Opdivo (nivolumab) may be considered medically necessary for treatment of any of the following:** • Melanoma o Adjuvant treatment of completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma in individuals aged 12 years and older o Unresectable or metastatic melanoma, in combination with Yervoy (ipilimumab) o Melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting • Non-Small Cell Lung Cancer (NSCLC) o Resectable (tumors at least 4 cm or node positive) NSCLC in the neoadjuvant setting, in combination with platinum-doublet chemotherapy (e.g., cisplatin and gemcitabine, cisplatin and pemetrexed, carboplatin and paclitaxel) o Resectable (tumors at least 4 cm or node positive) NSCLC with no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements, and Opdivo is used in the neoadjuvant setting in combination with platinum-doublet chemotherapy (e.g., cisplatin and gemcitabine, cisplatin and pemetrexed, carboplatin and paclitaxel), followed by single-agent nivolumab as adjuvant treatment after surgery o Metastatic NSCLC expressing PD-L1 (at least 1%) as determined by an FDA-approved test, with no EGFR or ALK/ROS1 genomic tumor aberrations, as first-line treatment in combination with Yervoy (ipilimumab) o Metastatic or recurrent NSCLC, with no EGFR or ALK/ROS1 genomic tumor aberrations, as first-line treatment in

Drug	Medical Necessity
	combination with Yervoy (ipilimumab) and 2 cycles of platinum-doublet (e.g., carboplatin and pemetrexed, cisplatin and pemetrexed, carboplatin and paclitaxel) chemotherapy ○ Metastatic NSCLC and progression on or after platinum-based chemotherapy. Individuals with EGFR or ALK/ROS1 genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Opdivo (nivolumab) • Unresectable malignant pleural mesothelioma as first-line treatment in combination with Yervoy (ipilimumab) • Renal Cell Carcinoma (RCC) ○ Individuals with advanced RCC who have received prior anti-angiogenic therapy ○ First-line treatment of individuals with advanced RCC in combination with Cabometyx (cabozantinib) ○ Intermediate or poor-risk, previously untreated advanced RCC, in combination with Yervoy (ipilimumab) • Classical Hodgkin lymphoma (cHL) ○ Individuals with cHL that has relapsed or progressed after: autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, **OR** 3 or more lines of systemic therapy that includes autologous HSCT ○ First-line treatment in adults with stage I or II classical Hodgkin lymphoma with one or more high-risk features (e.g., mediastinal adenopathy greater than 1/3 maximum transverse chest diameter, involvement of greater than 3 lymph node regions on one side of the diaphragm, age greater than 50 years, erythrocyte sedimentation rate [ESR] of 50, or ESR greater than 30 with one of the following: intermittent fever of greater than 38 °C, drenching night sweats, or greater than 10% unintentional weight loss over 6 months) in combination with doxorubicin, vinblastine, and dacarbazine ○ First-line treatment in individuals aged 12 years or older with stages IIb through IV classical Hodgkin lymphoma in combination with doxorubicin, vinblastine, and dacarbazine

Drug	Medical Necessity
	• Recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy • Urothelial Carcinoma ○ First-line treatment in adults with unresectable or metastatic urothelial carcinoma with use in combination with cisplatin and gemcitabine ○ Adjuvant treatment of individuals with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC ○ Locally advanced or metastatic urothelial carcinoma in individuals with: ▪ Disease progression during or following platinum-containing chemotherapy ▪ Disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy • Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Cancer ○ MSI-H or dMMR metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent ○ Treatment of adult and pediatric individuals aged 12 years and older with MSI-H or dMMR unresectable or metastatic colorectal cancer when used in combination with Yervoy (ipilimumab) • Hepatocellular Carcinoma (HCC) ○ First-line treatment of unresectable or metastatic HCC when used in combination with Yervoy (ipilimumab) ○ Individuals with unresectable or metastatic HCC who have been previously treated with sorafenib when used in combination with Yervoy (ipilimumab) • Adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in adult individuals who have received neoadjuvant chemoradiotherapy (CRT)

Drug	Medical Necessity
	• Advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma whose tumors express PD-L1 (at least 1) when used in combination with fluoropyrimidine (e.g., 5-fluorouracil, capecitabine) and platinum (e.g., cisplatin, carboplatin, oxaliplatin) containing chemotherapy • Esophageal Squamous Cell Carcinoma (ESCC) ○ First-line treatment of adult individuals with unresectable advanced or metastatic ESCC when used in combination with fluoropyrimidine (e.g., 5-fluorouracil, capecitabine) and platinum (e.g., cisplatin, carboplatin, oxaliplatin) containing chemotherapy whose tumors express PD-L1 (at least 1) ○ First-line treatment of adult individuals with unresectable advanced or metastatic ESCC when used in combination in combination with Yervoy (ipilimumab) whose tumors express PD-L1 (at least 1) ○ Unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy
PD-1 inhibitor • **Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) SC**	**Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) is subject to review for site of service administration except when it is used concurrently with other infusion or injection medications for cancer treatment.** **Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) may be considered medically necessary when the following criteria are met:** • The individual must receive Opdivo (nivolumab) IV ○ **Exception**: This may be granted when there is inadequate peripheral venous access **AND** • Has been diagnosed and meets 1 of the following: ○ Melanoma ▪ Adjuvant treatment of completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma in individuals aged 12 years and older ▪ Unresectable or metastatic melanoma

Drug	Medical Necessity
	▪ Unresectable or metastatic melanoma following combination treatment with intravenous Opdivo (nivolumab) and Yervoy (ipilimumab) ▪ Melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting ○ Non-Small Cell Lung Cancer ▪ Resectable (tumors at least 4 cm or node positive) NSCLC in the neoadjuvant setting, in combination with platinum-doublet chemotherapy (e.g., cisplatin and gemcitabine, cisplatin and pemetrexed, carboplatin and paclitaxel) ▪ Resectable (tumors at least 4 cm or node positive) NSCLC with no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements, and Opdivo Qvantig is used in the neoadjuvant setting in combination with platinum-doublet chemotherapy (e.g., cisplatin and gemcitabine, cisplatin and pemetrexed, carboplatin and paclitaxel), followed by single-agent Opdivo Qvantig as adjuvant treatment after surgery ▪ Metastatic NSCLC and progression on or after platinum-based chemotherapy. Individuals with EGFR or ALK/ROS1 genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Opdivo Qvantig ○ Renal Cell Carcinoma (RCC) ▪ Individuals with advanced RCC who have received prior anti-angiogenic therapy ▪ First-line treatment of individuals with advanced RCC in combination with Cabometyx (cabozantinib) ▪ Intermediate or poor-risk, previously untreated advanced RCC, following combination treatment with intravenous Opdivo (nivolumab) and Yervoy (ipilimumab) ○ Classical Hodgkin lymphoma (cHL)

Drug	Medical Necessity
	▪ Individuals with cHL that has relapsed or progressed after: autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, **OR** 3 or more lines of systemic therapy that includes autologous HSCT ▪ First-line treatment in adults with stage I or II classical Hodgkin lymphoma with one or more high-risk features (e.g., mediastinal adenopathy greater than 1/3 maximum transverse chest diameter, involvement of greater than 3 lymph node regions on one side of the diaphragm, age greater than 50 years, erythrocyte sedimentation rate [ESR] of 50, or ESR greater than 30 with one of the following: intermittent fever of greater than 38 °C, drenching night sweats, or greater than 10% unintentional weight loss over 6 months) in combination with doxorubicin, vinblastine, and dacarbazine ▪ First-line treatment in adults with stages IIb through IV classical Hodgkin lymphoma in combination with doxorubicin, vinblastine, and dacarbazine ○ Recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy ○ Urothelial Carcinoma ▪ First-line treatment in adults with unresectable or metastatic urothelial carcinoma with use in combination with cisplatin and gemcitabine ▪ Adjuvant treatment of individuals with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC ▪ Locally advanced or metastatic urothelial carcinoma in individuals with: ▫ Disease progression during or following platinum-containing chemotherapy ▫ Disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

Drug	Medical Necessity
	○ Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or as a single agent following combination treatment with intravenous Opdivo (nivolumab) and Yervoy (ipilimumab) ○ Hepatocellular Carcinoma (HCC) ▪ Unresectable or metastatic HCC, as a first-line treatment following combination treatment with intravenous Opdivo (nivolumab) and Yervoy (ipilimumab) ▪ Unresectable or metastatic HCC, who have been previously treated with sorafenib and following combination treatment with intravenous Opdivo (nivolumab) and Yervoy (ipilimumab) ○ Adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in adult individuals who have received neoadjuvant chemoradiotherapy (CRT) ○ Esophageal Squamous Cell Carcinoma (ESCC) ▪ First-line treatment of adult individuals with unresectable advanced or metastatic ESCC whose tumors express PD-L1 (at least 1) when used in combination with fluoropyrimidine (e.g., 5-fluorouracil, capecitabine) and platinum (e.g., cisplatin, carboplatin, oxaliplatin) containing chemotherapy ▪ Unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy ○ Advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma whose tumors express PD-L1 (at least 1) when used in combination with fluoropyrimidine (e.g., 5-fluorouracil, capecitabine) and platinum (e.g., cisplatin, carboplatin, oxaliplatin) containing chemotherapy
PD-1 inhibitor • **Tevimbra (tislelizumab-jsgr)**	**Tevimbra (tislelizumab-jsgr) may be considered medically necessary for:** • Esophageal Squamous Cell Carcinoma (ESCC)

Drug	Medical Necessity
	○ The first-line treatment of adults with unresectable or metastatic ESCC whose tumors express PD-L1 (at least 1) when used in combination with platinum-containing chemotherapy ○ Adults with unresectable or metastatic ESCC after prior systemic chemotherapy that did not include a PD-L1 inhibitor • First-line treatment of adults with unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 (at least 1) when used in combination with platinum (e.g., cisplatin, carboplatin, oxaliplatin) and fluoropyrimidine (e.g., 5-fluorouracil, capecitabine) based chemotherapy • First line treatment of adult individuals with HER2 positive (IHC 3+ or IHC 2+/ISH+) unresectable locally advanced or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma when used in combination with zanidatamab-hrii and fluoropyrimidine-and platinum containing chemotherapy
PD-1 inhibitor and LAG-3 inhibitor • **Opdualag (nivolumab and relatlimab-rmbw)**	**Opdualag (nivolumab and relatlimab-rmbw) may be considered medically necessary for:** • Adult and pediatric individuals aged 12 years and older with unresectable or metastatic melanoma.
PD-L1 inhibitor • **Bavencio (avelumab) IV**	**Bavencio (avelumab) may be considered medically necessary for the treatment of:** • Adults and pediatric individuals aged 12 years and older with metastatic Merkel Cell Carcinoma (MCC) • Maintenance treatment of individuals with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy • Individuals with locally advanced or metastatic urothelial carcinoma (UC) who: ○ Have disease progression during or following platinum-containing chemotherapy ○ Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

Drug	Medical Necessity
	• First-line treatment, in combination with Inlyta (axitinib) of individuals with advanced renal cell carcinoma (RCC)
PD-L1 inhibitor • **Imfinzi (durvalumab) IV**	**Imfinzi (durvalumab) is subject to review for site of service administration except when it is used concurrently with other infusion or injection medications for cancer treatment.** **Imfinzi (durvalumab) may be considered medically necessary when all the following are met:** • The individual is aged 18 years or older **AND** • Meets 1 of the following: ○ Non-Small Cell Lung Cancer (NSCLC) ▪ Has resectable (tumors at least 4 cm and/or node positive) NSCLC and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements and Imfinzi (durvalumab) will be used in combination with platinum-containing chemotherapy as neoadjuvant treatment followed by Imfinzi (durvalumab) as a single agent ▪ Has unresectable, stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy ▪ Has metastatic NSCLC with no sensitizing EGFR mutations or ALK genomic tumor aberrations and Imfinzi (durvalumab) will be used in combination with Imjudo (tremelimumab-actl) and platinum-based chemotherapy ○ Has limited-stage small cell lung cancer (LS-SCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy (cCRT) and Imfinzi (durvalumab) is used as a single agent ○ Requires first-line treatment of extensive-stage small cell lung cancer (ES-SCLC) and Imfinzi (durvalumab) will be used in combination with etoposide and either carboplatin or cisplatin

Drug	Medical Necessity
	○ Has locally advanced or metastatic biliary tract cancer (BTC) and Imfinzi (durvalumab) will be used in combination with gemcitabine and cisplatin ○ Has unresectable hepatocellular carcinoma (uHCC) and Imfinzi (durvalumab) will be used in combination with Imjudo (tremelimumab-actl) ○ Has primary advanced or recurrent endometrial cancer that is mismatch repair deficient (dMMR) and Imfinzi (durvalumab) will be used in combination with carboplatin and paclitaxel followed by Imfinzi (durvalumab) as a single agent ○ Used in combination with Bacillus Calmette-Guérin (BCG) for the treatment of adult individuals with BCG-naive, high-risk non-muscle-invasive bladder cancer (NMIBC) ○ Has muscle invasive bladder cancer (MIBC) and is used in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by single agent Imfinzi (durvalumab) as adjuvant treatment following radical cystectomy ○ Treatment of adult individuals with resectable gastric or gastroesophageal junction adenocarcinoma (GC/GEJC) and used in combination with fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) chemotherapy as neoadjuvant and adjuvant treatment, followed by single agent durvalumab
PD-1 inhibitor **Penpulimab-kcqx IV**	**Penpulimab-kcqx may be considered medically necessary for:** • The first-line treatment of adults with recurrent or metastatic non-keratinizing nasopharyngeal carcinoma (NPC) when used in combination with either cisplatin or carboplatin and gemcitabine • Treatment of adults with metastatic non-keratinizing NPC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy when used as a single agent
PD-L1 inhibitor • **Tecentriq (atezolizumab) IV**	**Tecentriq (atezolizumab) is subject to review for site of service administration except when it is used concurrently with other infusion or injection medications for cancer treatment.**

Drug	Medical Necessity
	Tecentriq (atezolizumab) may be considered medically necessary for: • Non-Small Cell Lung Cancer ○ The first-line treatment of adult individuals with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained at least 50% of tumor cells [TC at least 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering at least 10% of the tumor area [IC at least 10%]), with no EGFR or ALK genomic tumor aberrations ○ The first-line treatment of adult individuals with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations when used in combination with bevacizumab, paclitaxel, and carboplatin ○ The first-line treatment of adult individuals with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations in combination with paclitaxel protein-bound and carboplatin ○ As adjuvant treatment following resection and platinum-based chemotherapy for adult individuals with Stage II and IIIA NSCLC whose tumors have PD-L1 expression on at least 1% of tumor cells ○ The treatment of adult individuals with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Individuals with EGFR or ALK/ROS1 genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations (i.e., anti-EGFR or anti-ALK/ROS1 agents) prior to receiving Tecentriq. • Extensive-Stage Small Cell Lung Cancer (ES-SCLC) ○ The first-line treatment of adult individuals with ES-SCLC when used in combination with carboplatin and etoposide ○ The maintenance treatment of adult individuals with ES-SCLC, when used in combination with Zepzelca (lurbinectedin), whose disease has not progressed after first-line induction therapy with Tecentriq (atezolizumab) or Tecentriq Hybreza (atezolizumab and hyaluronidase-tqjs), carboplatin and etoposide

Drug	Medical Necessity
	• The treatment of adult individuals with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy when used in combination with bevacizumab • The treatment of individuals with BRAF V600 mutation-positive unresectable or metastatic melanoma when used in combination with Cotellic (cobimetinib) and Zelboraf (vemurafenib) • The treatment of unresectable or metastatic alveolar soft part sarcoma (ASPS) in individuals aged 2 and older when used as a single agent • Adjuvant treatment of adult individuals with muscle invasive bladder cancer (MIBC) after cystectomy who have circulating tumor DNA molecular residual disease (ctDNA MRD)
PD-L1 inhibitor • **Tecentriq Hybreza (atezolizumab and hyaluronidase-tqjs) SC**	**Tecentriq Hybreza (atezolizumab and hyaluronidase-tqjs) is subject to review for site of service administration except when it is used concurrently with other infusion or injection medications for cancer treatment.** **Tecentriq Hybreza (atezolizumab and hyaluronidase-tqjs) may be considered medically necessary when the following criteria are met:** • The individual must receive Tecentriq (atezolizumab) IV ○ **Exception**: This may be granted when there is inadequate peripheral venous access **AND** • Has been diagnosed and meets 1 of the following: ○ Non-Small Cell Lung Cancer (NSCLC) ▪ The first-line treatment of adult individuals with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained at least 50% of tumor cells [TC at least 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering at least 10% of the tumor area [IC at least 10%]), with no EGFR or ALK genomic tumor aberrations ▪ The first-line treatment of adult individuals with metastatic non-squamous NSCLC with no EGFR or ALK

Drug	Medical Necessity
	genomic tumor aberrations when used in combination with bevacizumab, paclitaxel, and carboplatin ▪ The first-line treatment of adult individuals with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations in combination with paclitaxel protein-bound and carboplatin ▪ As adjuvant treatment following resection and platinum-based chemotherapy for adult individuals with Stage II and IIIA NSCLC whose tumors have PD-L1 expression on at least 1% of tumor cells ▪ The treatment of adult individuals with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. An individual with EGFR or ALK/ROS1 genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations (i.e., anti-EGFR or anti-ALK/ROS1 agents) prior to receiving Tecentriq Hybreza. o Extensive-Stage Small Cell Lung Cancer (ES-SCLC) ▪ The first-line treatment of adult individuals with ES-SCLC when used in combination with carboplatin and etoposide ▪ The maintenance treatment of adult individuals with ES-SCLC, when used in combination with Zepzelca (lurbinectedin), whose disease has not progressed after first-line induction therapy with Tecentriq Hybreza (atezolizumab and hyaluronidase-tqjs) or Tecentriq (atezolizumab), carboplatin and etoposide o The treatment of adult individuals with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy when used in combination with bevacizumab o The treatment of adult individuals with BRAF V600 mutation-positive unresectable or metastatic melanoma when used in combination with Cotellic (cobimetinib) and Zelboraf (vemurafenib)

Drug	Medical Necessity
	○ The treatment of individuals aged 12 years and older who weigh at least 40 kg diagnosed with unresectable or metastatic alveolar soft part sarcoma (ASPS) when used as a single agent ○ Adjuvant treatment of adult individuals with muscle invasive bladder cancer (MIBC) after cystectomy who have circulating tumor DNA molecular residual disease (ctDNA MRD)
PD-L1 inhibitor • **Unloxcyt (cosibelimab-ipdl) IV**	**Unloxcyt (cosibelimab-ipdl) may be considered medically necessary for the treatment of metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC) when all the following are met:** • The individual is aged 18 years or older **AND** • Is not a candidate for curative surgery or curative radiation **AND** • Has not received prior treatment with an anti-PD-1/PD-L1 blocking antibody or other immune checkpoint inhibitor **AND** • Unloxcyt (cosibelimab-ipdl) is prescribed as monotherapy for the treatment of mCSCC or laCSCC **AND** • The dose is limited to 1,200 mg administered every 3 weeks
PD-L1 inhibitor • **Zynyz (retifanlimab-dlwr) IV**	**Zynyz (retifanlimab-dlwr) may be considered medically necessary for:** • The treatment of adult individuals with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC) who may have received surgery or radiation, but have not received a prior systemic therapy • First-line treatment of adults with inoperable locally recurrent or metastatic squamous cell carcinoma of the anal canal (SCAC) when used in combination with carboplatin and paclitaxel • Treatment of adults with locally recurrent or metastatic SCAC with disease progression on or intolerance to platinum-based chemotherapy when used as a single agent

Drug	Investigational
As listed	**The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.** **All other uses of Bavencio, Imfinzi, Imjudo, Jemperli, Keytruda, Keytruda Qlex, Libtayo, Loqtorzi, Opdivo, Opdivo Qvantig, Opdualag, Tecentriq, Tecentriq Hybreza, Tevimbra, Unloxcyt, Yervoy, and Zynyz not listed in this policy are considered investigational.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**All drugs listed in policy may be approved up to 6 months.**
Re-authorization criteria	**All drugs listed in the policy may be approved up to 12 months as long as the drug-specific coverage criteria are met, and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.**

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis, relevant history, physical evaluation and medication history

Coding

Code	Description
HCPCS	
C9399	Unclassified drugs or biologicals (use to report: penpulimab-kcqx)
J3263	Injection, toripalimab-tpzi (Loqtorzi), 1 mg
J9022	Injection, atezolizumab (Tecentriq), 10 mg

Code	Description
J9023	Injection, avelumab (Bavencio), 10 mg
J9024	Injection, atezolizumab, 5 mg and hyaluronidase-tqjs (Tecentriq Hybreza)
J9119	Injection, cemiplimab-rwlc (Libtayo), 1 mg
J9173	Injection, durvalumab (Imfinzi), 10 mg
J9228	Injection, ipilimumab (Yervoy), 1 mg
J9271	Injection, pembrolizumab (Keytruda), 1 mg
J9272	Injection, dostarlimab-gxly (Jemperli), 10 mg
J9275	Injection, cosibelimab-ipdl (Unloxcyt), 2 mg
J9277	Injection, pembrolizumab, 1 mg and berahyaluronidase alfa-pmph (Keytruda Qlex) (new code effective 04/01/26)
J9289	Injection, nivolumab, 2 mg and hyaluronidase-nvhy (Opdivo Qvantig)
J9298	Injection, nivolumab and relatlimab-rmbw (Opdualag), 3 mg/1 mg
J9299	Injection, nivolumab (Opdivo), 1 mg
J9329	Injection, tislelizumab-jsgr (Tevimbra), 1mg
J9345	Injection, retifanlimab-dlwr (Zynyz), 1 mg
J9347	Injection, tremelimumab-actl (Imjudo), 1 mg
J9999	Not otherwise classified, antineoplastic drugs (use to report: penpulimab-kcqx)

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Programmed Cell Death Protein 1 (PD-1)

Programmed cell death protein 1, also known as PD-1 and CD279 (cluster of differentiation 279), is a protein on the surface of cells that has a role in regulating the immune system's response to the cells of the human body by down-regulating the immune system and promoting self-tolerance by suppressing T-cell inflammatory activity. This prevents autoimmune diseases, but it can also prevent the immune system from killing cancer cells. PD-1 is an immune checkpoint

and guards against autoimmunity through two mechanisms. First, it promotes apoptosis (programmed cell death) of antigen-specific T-cells in lymph nodes. Second, it reduces apoptosis in regulatory T-cells (anti-inflammatory, suppressive T-cells).

Programmed Death-Ligand 1 (PD-L1)

Programmed death-ligand 1 (PD-L1) also known as cluster of differentiation 274 (CD274) or B7 homolog 1 (B7-H1) is a protein that in humans is encoded by the CD274 gene. PD-L1 is a 40kDa type 1 transmembrane protein that has been speculated to play a major role in suppressing the immune system during particular events such as pregnancy, tissue allografts, autoimmune disease and other disease states such as hepatitis. Normally the immune system reacts to foreign antigens that are associated with exogenous or endogenous danger signals, which triggers a proliferation of antigen-specific CD8+ T-cells and/or CD4+ helper cells. The binding of PD-L1 to PD-1 or B7.1 transmits an inhibitory signal that reduces the proliferation of antigen-specific T-cells in lymph nodes, while simultaneously reducing apoptosis in regulatory T-cells (anti-inflammatory, suppressive T-cells) further mediated by a lower regulation of the gene Bcl-2.

PD-1 and PD-L1 Inhibitors

PD-1 inhibitors, a new class of drugs that block PD-1, activate the immune system to attack tumors and are used to treat certain types of cancer. Similarly, PD-L1 inhibitors block PD-L1, preventing it from binding to PD-1. These drugs product effects similar to PD-1 inhibitors, improving the ability of CD4+ and CD8+ cells to target and eliminate cancer cells.

Benefit Application

The drugs in this policy are managed through the medical benefit.

Evidence Review

Description

Imjudo (tremelimumab-actl)

Imjudo (tremelimumab-actl) is a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blocking human IgG2 monoclonal antibody. CTLA-4 is a negative regulator of T-cell activity. Tremelimumab-actl is a monoclonal antibody that binds to CTLA-4 and blocks the interaction with its ligands CD80 and CD86, releasing CTLA-4-mediated inhibition of T-cell activation. In synergistic mouse tumor models, blocking CTLA-4 activity resulted in decreased tumor growth and increased proliferation of T cells in tumors.

Imfinzi (durvalumab)

Imfinzi (durvalumab) is a human immunoglobulin G1 kappa monoclonal antibody which blocks programmed cell death ligand 1 (PD-L1) binding to PD-1 and CD80 (B7.1); PD-L1 blockade leads to increased T-cell activation, allowing T-cells to kill tumor cells. PD-L1 is an immune check point protein expressed on tumor cells and tumor infiltrating cells and down regulates anti-tumor t-cell function by binding to PD-1 and B7.1; blocking PD-1 and B7.1 interactions restores antitumor t-cell function.

Jemperli (dostarlimab-gxly)

Jemperli (dostarlimab-gxly) is a programmed death receptor-1 (PD-1)–blocking IgG_4 humanized 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.

Keytruda (pembrolizumab)

Keytruda (pembrolizumab) is a programmed death receptor-1 (PD-1)-blocking antibody which is expressed on antigen-stimulated T-cells and induces downstream signaling that inhibits T-cell proliferation, cytokine release, and cytotoxicity. Melanoma and many other tumors express PD-1 ligand (PD-L1) on the cell surface, resulting in suppression of cytotoxic T-cell activity, allowing the tumor to proliferate unchecked.

Opdivo (nivolumab)

Opdivo (nivolumab) is a human monoclonal antibody to programmed death receptor-1 (PD-1), which is expressed on antigen-stimulated T-cells and induces downstream signaling that inhibits T-cell proliferation, cytokine release, and cytotoxicity. Melanoma and many other tumors express PD-1 ligand (PD-L1) on the cell surface, resulting in suppression of cytotoxic T-cell activity.

Opdualag (nivolumab and relatlimab-rmbw)

Opdualag is a combination of nivolumab, a PD-1 blocking antibody, and relatlimab, a lymphocyte activation gene-3 (LAG-3) blocking antibody. LAG-3 blockade enhances the anti-tumor activity of PD-1 blockage. The combination of nivolumab and relatlimab causes a bigger increase in T-cell activation than the activity of either antibody alone.

Tecentriq (atezolizumab)

Tecentriq (atezolizumab) is a monoclonal antibody that binds to PD-L1 and blocks its interactions with both PD-1 and B7.1 receptors. This releases the PD-L1/PD-1 mediated inhibition of the immune response, including activation of the anti-tumor immune response without inducing antibody dependent cellular cytotoxicity. In syngeneic mouse tumor models, blocking PD-L1 activity resulted in decreased tumor growth. PD-L1 may be expressed on tumor cells and/or tumor-infiltrating immune cells and can contribute to the inhibition of the anti-tumor immune response in the tumor microenvironment. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T-cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production.

Tevimbra (tislelizumab-jsgr)

Binding of the PD-1 ligands PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Tevimbra (tislelizumab-jsgr) binds to PD-1 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. Tislelizumab-jsgr decreased tumor growth in xenograft models and a human PD-1 transgenic mouse model.

Unloxcyt (cosibelimab-ipdl)

Unloxcyt (cosibelimab-ipdl) is a human programmed death ligand-1 (PD-L1) blocking antibody. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation, and cytokine production. Cosibelimab-ipdl binds PD-L1 and blocks the interaction between PD-L1 and its receptors PD-1 and B7.1. This interaction releases the inhibitory effects of PD-L1 on the anti-tumor immune response. Cosibelimab-ipdl has also been shown to induce antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro.

Yervoy (ipilimumab)

Yervoy (ipilimumab) is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody. CTLA-4 is a negative regulator of T-cell activity. Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor immune response.

Zynyz (retifanlimab-dlwr)

Zynyz (retifanlimab-dlwr) is a programmed death receptor (PD-1) blocking antibody. PDL1 and PDL2 are ligands of the PD-1 receptor found on the T cell. By binding on the PD-1 receptors, PDL1 and PDL2 inhibits T-cell proliferation and cytokine production. Retifanlimab-dlwr binds to the PD-1 receptor and blocks the binding pf PDL1 and PDL2, which blocks the T-cell activities, including the anti-tumor immune response.

Safety and Efficacy

Bavencio (avelumab)

Bavencio (avelumab) is the first FDA approved pharmacotherapy for Merkel cell carcinoma. avelumab offers a significant increase in ORR and median DOR in individuals with histologically confirmed stage IV Merkel cell carcinoma refractory to chemotherapy. Efficacy was demonstrated irrespective of PD-L1 status, eliminating the need for expensive genetic testing prior to therapy administration.

The evidence supporting avelumab's efficacy was demonstrated in the JAVELIN Merkel 200 trial. The multi-center, open-label, non-randomized trial included 88 individuals with stage IV Merkel cell carcinoma. The efficacy results yielded an ORR of 33.0% (95% CI, 23.3-34.8) with a complete response rate of 11.4% (95% CI, 6.6-19.8) and a partial response rate of 21.6% (95% CI, 13.5-31.7). At the time of the data cutoff the median duration of response had not been reached and response duration had ranged from 2.8 months to 23.3+ months.

Imfinzi (durvalumab)

The efficacy of durvalumab and FLOT as neoadjuvant and adjuvant treatment, followed by IMFINZI as a single agent was evaluated in MATTERHORN (NCT04592913), a randomized, double-blind, placebo-controlled, multicenter trial conducted in 948 individuals with previously untreated and resectable, Stage II to Stage IVA, GC/GEJC. Eligible individuals had no prior exposure to immune-mediated therapy and a WHO/ECOG performance status of 0 or 1. Individuals with active or prior documented autoimmune or inflammatory disorders, or use of immunosuppressive medication within 14 days of the first dose of durvalumab were ineligible. Individuals were randomized (1:1) to receive either durvalumab and FLOT or placebo and FLOT. The major efficacy outcome measure was event-free survival (EFS) by blinded independent central review assessment. Additional efficacy outcome measures were overall survival (OS) and pathological complete response (pCR) rate by blinded central pathology review. The trial was not designed to isolate the effect of durvalumab in each phase (neoadjuvant or adjuvant) of treatment. Median EFS was not reached (NR) (95% CI: 40.7, not estimable [NE]) in the durvalumab + FLOT arm and was 32.8 months (95% CI: 27.9, NE) in the placebo + FLOT arm (hazard ratio [HR] 0.71 [95% CI: 0.58, 0.86]; p-value <0.001). Median OS was NR in both arms (HR 0.78 [95% CI: 0.63, 0.96]; p-value 0.021). The pCR rate was 19.2% (95% CI: 15.7, 23.0) and 7.2% (95% CI: 5.0, 9.9) in the respective arms (p-value <0.001).

Jemperli (dostarlimab-gxly)

The efficacy of dostarlimab was evaluated in the GARNET study (NCT02715284), a multicenter, multicohort, open-label study conducted in individuals with advanced solid tumors. The efficacy population consisted of a cohort of 71 individuals with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer who had progressed on or after treatment with a platinum-containing regimen. Individuals with prior treatment with PD-1/PD-L1–blocking antibodies or other immune checkpoint inhibitor therapy and individuals with autoimmune disease that required systemic therapy with immunosuppressant agents within 2 years were excluded from the study.

Individuals that received dostarlimab 500 mg intravenously every 3 weeks for 4 doses followed by 1,000 mg intravenously every 6 weeks. Treatment continued until disease progression or unacceptable toxicity. The major efficacy outcome measures were Overall Response Rate (ORR) and Duration of Response (DOR) as assessed by blinded independent central review (BICR) according to the Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1. The confirmed ORR with dostarlimab was 42.3% (95% CI: 30.6%-54.6%) and the DOR median in months was not reached yet at the time of FDA approval.

The most common adverse reactions with dostarlimab are fatigue (48%), nausea (30%), diarrhea (26%), anemia (24%), and constipation (20%). There are warnings and precautions regarding immune-mediated adverse reactions, infusion-related reactions, embryo-fetal toxicity, and complications of allogeneic HSCT.

Keytruda (pembrolizumab)

Keytruda (pembrolizumab) is approved for multiple indications based on the following clinical evidence.

Unresectable or Metastatic Melanoma

Study KEYNOTE-006 was a randomized, open-label, active-controlled trial evaluating 834 individuals with unresectable or metastatic melanoma and no prior ipilimumab treatment who received either pembrolizumab or ipilumumab. Evaluating pembrolizumab 10 m/kg every 3 weeks or every 2 weeks, pembrolizumab demonstrated significant improvement in the primary endpoints, OS (33%, p=0.004 and 30%, p<0.001) and PFS (57%, p<0.001 and 56%, p<0.001), relative to ipilimumab (OS 40% and PFS 68%). Study KEYNOTE-002 was a randomized, blinded,

active-controlled trial evaluating 540 individuals with unresectable or metastatic melanoma *with* prior ipilumumab treatment. The study showed statistically significant improvement in PFS for individuals randomized to both dosing regimens of pembrolizumab compared to chemotherapy (72% and 70% vs 87%, p<0.001 for all).

Metastatic NSCLC

Study KEYNOTE-024 was a randomized, open-label, active-controlled trial in 305 individuals with metastatic NSCLC and had not received prior systemic treatment for metastatic NSCLC who received either pembrolizumab or chemotherapy. The study showed statistically significant improvement in PFS for individuals randomized to pembrolizumab compared with chemotherapy (47% vs 77%, p<0.001). Study KEYNOTE-021 was a randomized, open-label, multi-cohort study evaluating 123 individuals with metastatic NSCLC who received either pembrolizumab in combination with pemetrexed and carboplatin or just pemetrexed and carboplatin. The study showed that there were significant improvements in ORR in the pembrolizumab combination arm (55%) versus the control arm (29%), p=0.0032. Study KEYNOTE-010 evaluated 1033 individuals with metastatic NSCLC that had progressed following platinum-containing chemotherapy who received either pembrolizumab or docetaxel. The study demonstrated significant improvements in OS in pembrolizumab compared to docetaxel (p<0.001 for all).

Recurrent or Metastatic Head and Neck Cancer

Study KEYNOTE-012 was a non-randomized, open-label study that evaluated 174 individuals with recurrent or metastatic HNSCC who had disease progression on or after platinum-containing chemotherapy who received pembrolizumab. The ORR was 16% (95% CI 11 to 22), with a complete response rate of 5%. Duration of response had not been reached.

Classical Hodgkin Lymphoma

Study KEYNOTE-087 was a non-randomized, open-label study that evaluated 210 individuals with relapsed or refractory cHL who received pembrolizumab. The ORR was 69% (95% CI 62 to 75%) and the duration of response was a median of 11.1 months.

Advanced or Metastatic Urothelial Carcinoma

Study KEYNOTE-052 was an open-label, single-arm trial that evaluated 370 individuals with locally advanced or metastatic urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy. The ORR was 29% (95% CI 24 to 34) and the duration of response was not reached. Study KEYNOTE-045 was a randomized, active-controlled trial that evaluated 542 individuals with disease progression on or after platinum-containing chemotherapy who received pembrolizumab or chemotherapy. The study demonstrated significant improvements in OS and ORR for pembrolizumab compared to chemotherapy (57% vs 66%, p=0.004 and 21% vs 11%, p=0.002), but there was no statistically significant difference with respect to PFS.

Microsatellite Instability-High Cancer

The efficacy of pembrolizumab was evaluated in individuals with MSI-H or mismatch repair deficient (dMMR), solid tumors enrolled in one of five uncontrolled, open-label, single-arm trials. A total of 149 individuals were evaluated across the five trials. The ORR was 39.6% (95% CI 31.7 to 47.9) across all trials, and the duration of response was not reached.

Locally Advanced or Metastatic Urothelial Carcinoma

The efficacy of pembrolizumab in combination with enfortumab vedotin was evaluated in individuals with locally advanced or metastatic urothelial carcinoma in multi-cohort study, EV-103/Keynote-869. Dose escalation cohort and cohort A, single-arm cohorts, included individuals who received pembrolizumab in combination with enfortumab vedotin, while cohort K included individuals who were randomized to receive either pembrolizumab in combination with enfortumab vedotin or enfortumab alone. In these studies, individuals did not receive prior systemic therapy and were not eligible for cisplatin-containing chemotherapy. A total of 121 individuals received the combination therapy where the individuals' objective response rate (ORR) and duration of response (doR) were evaluated. The individuals' overall response rate was 68% including 12% of individuals with complete response. The median doR for the dose escalation cohort plus cohort A was 22 months, and the medial doR was not reached for cohort K.

Stage 1B, II, or IIIA non-small cell lung cancer

The efficacy of pembrolizumab was evaluated in a multicenter, randomized, triple-blind, placebo-controlled KEYNOTE-091 trial where 1177 individuals with stage IB, II or IIIA non-small cell lung cancer randomized 1:1 to receive pembrolizumab 200 mg or placebo intravenously every 3 weeks for up to 1 year. Out of 1177 individuals, 1010 received adjuvant platinum-based chemotherapy following complete resection. The primary outcome was disease-free survival. Overall, the study did achieve statistical significance in the disease-free survival. In 167 individuals who did not receive adjuvant chemotherapy, the disease-free survival hazard ratio was 1.25. In the individuals who received adjuvant chemotherapy, the median disease-free survival was 58.7 months in the treatment group and 34.9 months in the placebo group with hazard ratio of 0.73.

Muscle Invasive Bladder Cancer (MIBC)

The efficacy of intravenous pembrolizumab in combination with enfortumab vedotin as neoadjuvant treatment and continued after radical cystectomy as adjuvant treatment was investigated in KEYNOTE-905/EV-303 (NCT03924895), an open-label, randomized, multicenter, active-controlled trial in 344 individuals with previously untreated MIBC who were candidates for radical cystectomy (RC) with pelvic lymph node dissection (PLND) but were ineligible for or declined cisplatin-based chemotherapy. Individuals were randomized (1:1) to receive neoadjuvant pembrolizumab and enfortumab vedotin-ejfv followed by surgery followed by adjuvant enfortumab vedotin-ejfv in combination with pembrolizumab followed by pembrolizumab as a single agent or to undergo immediate surgery alone. The major efficacy outcome measure was event-free survival (EFS) assessed by blinded independent central review. Overall survival (OS) was an additional efficacy outcome. The trial demonstrated statistically significant improvements in EFS and OS in individuals treated with pembrolizumab and enfortumab vedotin-ejfv before and after RC and PLND compared with surgery alone. Median EFS was not reached (NR) (95% CI: 37.3, NR) in the pembrolizumab and enfortumab vedotin arm and was 15.7 months (95% CI: 10.3, 20.5) in the RC and PLND arm (Hazard Ratio [HR] 0.40 [95% CI: 0.28, 0.57]; p-value <0.0001). Median OS was NR (95% CI: NR, NR) and 41.7 months (95% CI: 31.8, NR) in the respective arms (HR 0.50 [95% CI: 0.33, 0.74]; p-value 0.0002).

The overall safety profile of enfortumab vedotin-ejfv with pembrolizumab in KEYNOTE-905/EV-303 was similar to that observed in prior trials in advanced urothelial cancer. The pembrolizumab prescribing information includes warnings and precautions for immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic hematopoietic stem cell transplantation, and embryo-fetal toxicity. The enfortumab vedotin-ejfv prescribing information includes warnings and precautions for skin reactions, hyperglycemia,

pneumonitis/interstitial lung disease (ILD), peripheral neuropathy, ocular disorders, infusion site extravasation, and embryo-fetal toxicity.

Ovarian Cancer

The efficacy of intravenous pembrolizumab in combination with paclitaxel, with or without bevacizumab, was evaluated in KEYNOTE-B96 (NCT05116189), a multicenter, randomized, double-blind, placebo controlled trial that enrolled 643 individuals with platinum-resistant, epithelial ovarian, fallopian tube, or primary peritoneal carcinoma who received one or two prior lines of systemic therapy for ovarian carcinoma. Individuals must have received at least one line of platinum-based chemotherapy for ovarian cancer with radiographic evidence of disease progression within 6 months after the last dose. Prior therapy with an anti-PD-1/PD-L1 inhibitor, PARP inhibitor, or bevacizumab was permitted. Individuals were enrolled regardless of PD-L1 tumor expression status. Individuals with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by investigator decision to use bevacizumab, geographic region (U.S. or European Union or Rest of World), and PD-L1 status according to the PD-L1 IHC 22C3 pharmDx assay (CPS less than 1 or CPS 1 to less than 10 or CPS at least 10). Individuals were randomized (1:1) to one of the two treatment groups: (1) Intravenous pembrolizumab 400 mg every 6 weeks plus paclitaxel 80 mg/m2 with or without bevacizumab 10 mg/kg; (2) Placebo every 6 weeks plus paclitaxel 80 mg/m2 with or without bevacizumab 10 mg/kg. Assessment of tumor status was performed every 9 weeks for the first year, followed by every 12 weeks thereafter. The major efficacy outcome measure was PFS as assessed by investigator according to RECIST v1.1. An additional efficacy outcome measure was OS. In individuals whose tumors express PD-L1 (CPS at least 1), the median PFS was 8.3 months (95% CI, 7.0-9.4) for those receiving Keytruda plus paclitaxel, with or without bevacizumab, versus 7.2 months (95% CI, 6.2-8.1) for those receiving placebo plus paclitaxel with or without bevacizumab. The median OS for these individuals receiving the Keytruda regimen was 18.2 months (95% CI, 15.3-21.0) versus 14.0 months (95% CI, 12.5-16.1) for those receiving the placebo regimen.

Libtayo (cemiplimab)

There is currently limited published data available on the efficacy of cemiplimab in the treatment of malignancies. In one fair quality Phase 1, non-randomized, open-label, expansion cohort study, 26 individuals with advanced cutaneous squamous cell carcinoma received cemiplimab

showed response to treatment in 50% of individuals and a durable response in 65% of individuals who had a response.

In a fair quality Phase 2, non-randomized, open-label, pivotal cohort study, 59 individuals with metastatic cutaneous squamous cell carcinoma received cemiplimab monotherapy and treatment response was seen in 47% of individuals. Among the 28 individuals who had a response, a durable disease control rate of 61% was observed.

Other potentially supportive studies of cemiplimab in individuals with advanced cutaneous squamous cell carcinoma, lung cancer, ovarian cancer, cervical cancer, and glioblastoma are ongoing.

The most common adverse events seen with cemiplimab in the Phase 1 study were fatigue (27%), constipation, decreased appetite, diarrhea, hypercalcemia, hypophosphatemia, nausea, and urinary tract infection (15%). The most common grade 3 to 5 adverse events were hypercalcemia, skin infection, and failure to thrive. Discontinuation due to adverse events occurred in two individuals in the study.

In the phase 2 study, the most common adverse events were diarrhea (27%), fatigue (24%), nausea (17%), constipation (15%), and rash (15%). Grade 3 to 5 adverse events occurred in more than one individual were pneumonitis, cellulitis, hypercalcemia, pleural effusion, and adverse events resulting in death. Four individuals discontinued due to adverse events during this study.

Loqtorzi (toripalimab-tpzi)

In the JUPITER-02 Phase 3 study, Loqtorzi combined with chemotherapy reduced the risk of disease progression or death by 48% compared to chemotherapy alone. Loqtorzi treatment resulted in a 37% reduction in the risk of death versus chemotherapy alone. The incidence of Grade ≥3 adverse events (AEs) (89.7% vs 90.2%) and fatal AEs (3.4% vs 2.8%) was similar between the two arms. AEs leading to discontinuation of Loqtorzi versus placebo (11.6% vs 4.9%), immune-related adverse events (irAEs) (54.1% vs. 21.7%), and Grade ≥3 irAEs (9.6% vs. 1.4%) were more frequent in the Loqtorzi arm. In the POLARIS-02 study, Loqtorzi for individuals with recurrent or metastatic nasopharyngeal carcinoma who failed previous chemotherapy saw an objective response rate (ORR) of 20.5%, a disease control rate (DCR) of 40.0%, and a median OS of 17.4 months.

Opdivo (nivolumab)

The advanced melanoma indication for nivolumab received accelerated biologics license application approval based on tumor response rate and durability of response in one open-label, Phase III trial of nivolumab in adults with unresectable or metastatic melanoma following progression on Yervoy (ipilimumab) and, if BRAF V600 mutation–positive, a BRAF inhibitor (dabrafenib or vemurafenib). An improvement in survival or disease-related symptoms has not yet been established. Phase III trials are to be submitted by the end of 2016. CheckMate-372 was a randomized (2:1), open-label trial in which 370 individuals with unresectable or metastatic melanoma received nivolumab 3 mg/kg every 2 weeks (n=268) or investigator's choice of chemotherapy (n=102), either dacarbazine or carboplatin plus paclitaxel. Primary end points were objective response rate (ORR), by independent radiology review committee, and overall survival (OS). Secondary end points included progression-free survival (PFS); PD-L1 expression; and health-related quality of life (HRQOL).

Efficacy was assessed in a single-arm, noncomparative, preplanned interim analysis in the first 120 individuals who received nivolumab in Trial 1 and in whom the minimum duration of follow-up was 6 months. Data are unpublished and taken from the label. ORR in the efficacy subset was 32% (95% confidence interval [CI], 23 to 41), consisting of 4 complete responses and 34 partial responses in nivolumab-treated individuals. Of the 38 individuals with responses, 33 individuals (87%) had ongoing responses with durations ranging from 2.6+ to 10+ months, which included 13 individuals with ongoing responses of 6 months or longer. There were objective responses in individuals with and without BRAF V600 mutation–positive melanoma.

Warnings and precautions are generally related to the development of moderate-to-severe immune-mediated reactions in a small number of individuals. This results in administration of corticosteroids and either withholding the drug (in the majority of cases) or discontinuation of the drug. Such reactions included immune-mediated pneumonitis (2.2%), colitis (2.2%), hepatitis (1.1%), nephritis or renal dysfunction (0.7%), hyperthyroidism (3%) or hypothyroidism (8%), or other immune-mediated events (<1%). Nivolumab was discontinued for adverse reactions in 9% of individuals, while 26% of individuals receiving nivolumab had a drug delay for an adverse reaction. Serious adverse reactions occurred in 41% of individuals receiving nivolumab. The most frequent grade 3 and 4 adverse reactions reported in 2% to less than 5% of individuals receiving nivolumab were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase. The most common adverse reaction was rash (> 20%).

Penpulimab-kcqx

Approval of penpulimab-kcqx was based on two pivotal clinical trials: The Phase 3 Study AK105-304 compared penpulimab-kcqx plus chemotherapy versus placebo plus chemotherapy in first-line recurrent or metastatic non-keratinizing NPC. The median progression-free survival (PFS) was 9.6 months for the penpulimab-kcqx arm versus 7.0 months for placebo. The 12- month progression-free survival (PFS) rate was 31% versus 11%, respectively. Overall survival (OS) data were immature but numerically favored penpulimab-kcqx. The Phase 2 Study AK105-202 evaluated single-agent penpulimab-kcqx in individuals with disease progression after platinum-based chemotherapy and one additional prior systemic therapy. The overall response rate (ORR) was 28%, and the median duration of response (DOR) was not reached.

Tecentriq (atezolizumab)

Tecentriq (atezolizumab) was approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Tecentriq (atezolizumab) was investigated in Study 1, a multicenter, open-label, two-cohort trial that included individuals with locally advanced or metastatic urothelial carcinoma. In Cohort 2 of Study 1, 310 individuals with locally advanced or metastatic urothelial carcinoma who had disease progression during or following a platinum-containing chemotherapy regimen or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen were treated with Tecentriq. This study excluded individuals who had: a history of autoimmune disease, active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 28 days prior to enrollment, or administration of systemic immunostimulatory agents or systemic immunosuppressive medications. Individuals received an intravenous infusion of 1200 mg of Tecentriq every 3 weeks until unacceptable toxicity or either radiographic or clinical progression. Tumor response assessments were conducted every 9 weeks for the first 54 weeks and every 12 weeks thereafter.

Major efficacy outcome measures included confirmed ORR as assessed by independent review facility (IRF) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and duration of response (DoR). In this cohort, the median age was 66 years, 78% were male, 91% individuals were Caucasian. Twenty-six percent had non-bladder urothelial carcinoma and 78% of individuals had visceral metastases. Sixty-two percent of individuals had an Eastern Cooperative Oncology Group (ECOG) score of 1 and 35% of individuals had a baseline creatinine clearance of < 60 mL/min. Nineteen percent of individuals had disease progression following prior platinum-

containing neoadjuvant or adjuvant chemotherapy. Forty-one percent of individuals had received ≥ 2 prior systemic regimens in the metastatic setting. Seventy-three percent of individuals received prior cisplatin, 26% had prior carboplatin, and 1% were treated with other platinum-based regimens. Tumor specimens were evaluated prospectively using the Ventana PD-L1 (SP142) Assay at a central laboratory, and the results were used to define subgroups for pre-specified analyses.

Of the 310 individuals, 32% were classified as having PD-L1 expression of ≥ 5% (defined as PD-L1 stained tumor-infiltrating immune cells [ICs] covering ≥ 5% of the tumor area). The remaining 68% of individuals were classified as having PD-L1 expression of <5% (PD-L1 stained tumor infiltrating ICs covering < 5% of the tumor area). The median follow-up time for this cohort was 14.4 months. In 59 individuals with disease progression following neoadjuvant or adjuvant therapy, the ORR was 22.0% (95% CI: 12.3%, 34.7%).

The efficacy of Tecentriq (atezolizumab) was investigated in two multi-center, international, randomized, open-label trials in individuals with metastatic NSCLC who progressed during or following a platinum-containing regimen. Study 2 was a trial in 1225 individuals with the primary analysis population consisting of the first 850 randomized individuals and Study 3 was a trial in 287 individuals. In both studies, eligible individuals were stratified by PD-L1 expression status in tumor-infiltrating immune cells (IC), by the number of prior chemotherapy regimens, and by histology. Individuals were randomized (1:1) to receive either TECENTRIQ administered intravenously at 1200 mg every 3 weeks until unacceptable toxicity or either radiographic or clinical progression, or docetaxel administered intravenously at 75 mg/m^2 every 3 weeks until unacceptable toxicity or disease progression.

These studies excluded individuals who had: a history of autoimmune disease, had active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 28 days prior to enrollment, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to enrollment. Tumor assessments were conducted every 6 weeks for the first 36 weeks, and every 9 weeks thereafter. In Study 2, tumor specimens were evaluated prospectively for PD-L1 expression on tumor cells (TC) and IC using the VENTANA PD-L1 (SP142) Assay and the results were used to define the PD-L1 expression subgroups for the analyses described below.

In Study 2, among individuals in the primary analysis population, the median age was 64 years (range: 33 to 85), and 61% of individuals were male. The majority of individuals were white (70%). Approximately three-fourths of individuals had non-squamous disease (74%), 10% had known EGFR mutation, 0.2% had known ALK rearrangements, and most individuals were current or previous smokers (82%). Baseline ECOG performance status was 0 (37%) or 1 (63%). Seventy-five percent of individuals received only one prior platinum-based therapeutic regimen.

In Study 3, the median age was 62 years (range: 36 to 84), and 59% of individuals were male. The majority of individuals were white (79%). Approximately two-thirds of individuals had non-squamous disease (66%), 7% had known EGFR mutation, 1% had ALK rearrangements, and most individuals were current or previous smokers (80%). Baseline ECOG performance status was 0 (33%) or 1 (67%). Approximately two-thirds of individuals received only one prior platinum-based therapeutic regimen.

The major efficacy outcome measure of Study 2 was OS in the primary analysis population (first 850 randomized individuals).

The major efficacy outcome measure of Study 3 was OS. Other efficacy outcome measures for Study 3 included investigator-assessed objective response rates and duration of response per RECIST v1.1. Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define the PD-L1 expression subgroups for prespecified analyses. Of the 850 individuals, 16% were classified as having high PD-L1 expression, which is defined as having PD-L1 expression on ≥ 50% of TC or ≥ 10% of IC. In an exploratory efficacy subgroup analysis of OS based on PD-L1 expression, the hazard ratio was 0.41 (95% CI: 0.27, 0.64) in the high PD-L1 expression subgroup and 0.82 (95% CI: 0.68, 0.98) in individuals who did not have high PD-L1 expression. Results of an updated survival analysis in Study 3 with a median follow-up of 22 months are provided for all randomized individuals.

Tecentriq (atezolizumab) was approved for the treatment of adult and pediatric individuals 2 years of age and older with unresectable or metastatic alveolar soft part sarcoma (ASPS). The efficacy of atezolizumab was evaluated in an open-label, single-arm study where 49 adult and pediatric individuals with unresectable or metastatic ASPS. The adult individuals received atezolizumab 1200 mg intravenously and pediatric individuals received 15mg/kg (max 1200 mg) intravenously every 21 days until disease progression or unacceptable toxicity. The primary efficacy endpoints were overall response rate (ORR) and duration of response (DOR). The study's overall response rate was 24% (12 individuals). Out of 12 individuals, 67% of individuals had DOR of 6 months or more and 42% had a DOR of 12 months or more. Most common adverse reactions in the trial were musculoskeletal pain, fatigue, rash, cough, nausea, headache and hypertension.

Tevimbra (tislelizumab-jsgr)

Tevimbra (tislelizumab-jsgr) was approved based on the RATIONALE 302 trial, which met its primary endpoint in the intention-to-treat (ITT) population with a statistically significant and clinically meaningful survival benefit for Tevimbra compared with chemotherapy. In the ITT

population, the median overall survival (OS) in the Tevimbra arm was 8.6 months (95% CI: 7.5, 10.4) compared to 6.3 months (95% CI: 5.3, 7.0) in the chemotherapy arm (p=0.0001; hazard ratio [HR]=0.70 [95% CI: 0.57, 0.85]). The most common (≥20%) adverse reactions for Tevimbra, including laboratory abnormalities, were increased glucose, decreased hemoglobin, decreased lymphocytes, decreased sodium, decreased albumin, increased alkaline phosphatase, anemia, fatigue, increased AST, musculoskeletal pain, decreased weight, increased ALT and cough.

The efficacy of Tevimbra in combination with zanidatamab-hrii and fluoropyrimidine-and platinum-containing chemotherapy for the treatment of GEA was evaluated in HERIZON-GEA 01 (NCT05152147), a randomized, multicenter, 3-arm, open-label, active-comparator study. Individuals had untreated, unresectable locally advanced/metastatic, HER2-positive (IHC 3+ or IHC 2+/ISH+) per central testing, an ECOG PS of 0 or 1, and adequate organ function, including left ventricular ejection fraction (LVEF) ≥50%. Individuals were enrolled regardless of their PD-L1 expression. Randomization was stratified by geographic region (Asian, EU/North America, Rest of World), HER2 status (3+ IHC staining, 2+ IHC staining with ISH-positivity), and Eastern Cooperative Oncology Group (ECOG) performance status (0, 1). Individuals were randomized to receive one of the following treatment arms, each with investigator's choice of a fluoropyrimidine-and platinum-containing chemotherapy – CAPOX (capecitabine 1,000 mg/m2 administered orally twice a day from the evening of Day 1 to the morning of Day 15 of each 21-day cycle plus oxaliplatin 130 mg/m2 administered intravenously on Day 1 of each 21-day cycle) or FP (5-Fluorouracil 800 mg/m2/day administered as continuous intravenous infusion on Days 1 to 5 of each 21-day cycle plus cisplatin 80 mg/m2 administered intravenously on Day 1 of each 21-day cycle) for at least 6 cycles: Tevmibra 200 mg administered intravenously with zanidatamab-hrii 1800 mg (for individuals with a body weight of < 70 kg) or 2400 mg (for individuals with a body weight ≥70 kg) administered intravenously on Day 1 of each 21-day cycle, or Zanidatamab-hrii 1800 mg (for individuals with a body weight of < 70 kg) or 2400 mg (for individuals with a body weight ≥70 kg) administered intravenously on Day 1 of each 21-day, or Trastuzumab 6 mg/kg administered intravenously on day 1 of each 21-day cycle (8 mg/kg loading dose administered intravenously on Cycle 1, Day 1) (control arm).

Treatment with Tevimbra and zanidatamab-hrii continued in each arm until disease progression, unacceptable toxicity, or other discontinuation criteria were met. Efficacy assessments were based on individuals randomized to the Tevimbra plus zanidatamab-hrii and chemotherapy versus the trastuzumab and chemotherapy arms. The dual major efficacy endpoints were progression-free survival (PFS) assessed by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) and overall survival (OS). Additional efficacy outcome measures included objective response rate (ORR) and duration of response (DoR). A total of 914 individuals were enrolled into the HERIZON-GEA-01 trial with 610 individuals randomized to the Tevimbra and control arms. Of these individuals, 434 had gastric

adenocarcinoma, 134 had gastroesophageal junction adenocarcinoma, and 42 had esophageal adenocarcinoma. The trial population characteristics were median age 64 years (range: 21 to 84 years), 47% ≥65 years of age, 79% male; 55% Asian, 40% White, 2% American Indian or Alaskan Native, and 1.6% of other or multiple races; 40% ECOG performance status of 0 or 60% performance status of 1. Overall survival (OS): The arm in which Tevimbra was added to Ziihera and chemotherapy resulted in a statistically significant improvement in OS (median OS of 26.4 months) at IA1. There was statistically significant improvement in overall survival, with median overall survival of 26.4 months for the Tevimbra combination versus 19.2 months for the control. Progression-free survival was also significantly improved, with a median of 12.4 months compared to 8.1 months. Benefits were consistent regardless of PD-L1 status and across HER2 expression levels.

Unloxcyt (cosibelimab-ipdl)

Efficacy was evaluated in Study CK-301-101, a multicenter, multicohort, open-label trial in 109 individuals with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC) who were not candidates for curative surgery or curative radiation. Individuals were excluded if they had any of the following: active or suspected autoimmune disease, allogeneic transplant within 6 months prior to treatment, prior treatment with anti-PD-1/PD-L1 blocking antibodies or other immune checkpoint inhibitor therapy, uncontrolled or significant cardiovascular disease, ECOG PS ≥ 2, or infection with HIV, hepatitis B, or hepatitis C. The major efficacy outcome measures were objective response rate (ORR) and duration of response (DOR) as assessed by an independent central review committee (IRC) according to RECIST version 1.1. For individuals with laCSCC with externally visible target lesions not assessable by radiologic imaging, ORR was determined by ICR assessments of digital photography (WHO criteria). ORR was 50% (95% CI: 38, 62) for individuals with mCSCC (n=78) and 55% (95% CI: 36, 73) for individuals with laCSCC (n=31). Median DOR was not reached (range: 1.4+, 45.3+) in individuals with mCSCC and was not reached (range: 8.3, 31.3+) in individuals with laCSCC.

Yervoy (ipilimumab)

Phase III trials suggested a survival benefit in individuals with stage III or IV metastatic melanoma compared to gp-100 (10.1 months vs. 6.4 months). However, the investigators' report of 2 to 3.5 months of increased median overall survival is uncertain due to limitations in the trial design. A majority of immune-related adverse events (irAEs) were reduced upon treatment

below their respective baselines. With immediate medical attention and treatment, irAEs are manageable and resolvable.

Clinical trials investigated the safety and efficacy of Yervoy (ipilimumab) in a randomized, double-blind, placebo-controlled trial in individuals with resected Stage IIIA (> 1 mm nodal involvement), IIIB, and IIIC (with no in-transit metastases) histologically confirmed cutaneous melanoma. Individuals were randomized to receive ipilimumab 10 mg/kg or placebo every 3 weeks for 4 doses. Enrollment required complete resection of melanoma with full lymphadenectomy within 12 weeks prior to randomization. Forty-nine percent of the ipilimumab arm experienced recurrence-free survival (RFS), whereas it was 62% in the placebo arm. Fourteen deaths occurred with the intervention and 5 in placebo. The adverse event (AE) rate was more severe at this higher dose compared to 3 mg/kg. Common AEs included rash, pruritus, GI disorders, fatigue, pyrexia, and headache. More severe irAEs included enterocolitis, hepatitis, dermatitis, neuropathy, and endocrinopathy. Endocrine AEs eventually require hormone supplementation.

Zynyz (retifanlimab-dlwr)

Zynyz (retifanlimab-dlwr), a programmed death receptor -1 (PD-1) inhibitor, is approved for the treatment of adult individuals with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC). The efficacy and safety of Zynyz was evaluated in the PODIUM-201 study, which was a single-arm, open-label, multiregional phase II study involving 65 individuals with locally advanced MCC who had not received prior systemic therapy. Individuals were administered Zynyz 500 mg intravenously every 4 weeks until disease progression, unacceptable toxicity, or up to 24 months. The study's primary efficacy endpoint was objective response rate and duration of response. The objective response rate for the study was 52%, with 18% complete responses and 34% partial responses. Of the 34 individuals with the response, 76% individuals had duration of response for at least 6 months, while 62% individual had duration of response of at least 12 months. The indication was granted accelerated approval based on the tumor objective response rate and duration of response observed in the trial. Continued approval for this indication may be subject to confirmation and description of clinical benefit in confirmatory trials.

The most common adverse effects in the clinical trial were fatigue, musculoskeletal pain, pruritus, diarrhea, rash, pyrexia and nausea. Severe adverse events, such as fatigue, arrythmia and pneumonitis, were reported in approximately 22% of the individuals. In the trial, about 11% of the individuals permanently discontinued Zynyz due to adverse reactions, such as asthenia, atrial fibrillation, and concomitant disease progression of chronic lymphocytic leukemia, etc.

2019 Update

Reviewed prescribing information for all drugs in policy. Added a new indication identified for Keytruda (pembrolizumab) for esophageal cancer. Bavencio (avelumab), a PD-L1 inhibitor, was moved from policy **5.01.540 Miscellaneous Oncology Drugs** into policy **5.01.591 Immune Checkpoint Inhibitors**. Added a new indication for Bavencio for renal cell carcinoma. No additional evidence was identified that would require changes to other drugs listed in this policy.

2020 Update

Reviewed prescribing information for all drugs in policy. Added a new indication identified for Tecentriq (atezolizumab) for the treatment of individuals with BRAF V600 mutation-positive unresectable or metastatic melanoma when used in combination with Cotellic (cobimetinib) and Zelboraf (vemurafenib).

2021 Update

Reviewed prescribing information for all drugs in policy. Added a new indication to Keytruda (pembrolizumab) for 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 when used in combination with platinum- and fluoropyrimidine- containing chemotherapy. Removed from Keytruda (pembrolizumab) coverage for small cell lung cancer as the indication was withdrawn due to lack of efficacy in follow-up trials. Added two new indications to Libtayo (cemiplimab). The first indication is locally advanced or metastatic basal cell carcinoma previously treated with a hedgehog pathway inhibitor (e.g., Erivedge [vismodegib], Odomzo [sonidegib]) or for whom a hedgehog pathway inhibitor is not appropriate. The second indication is for locally advanced, where individuals are not candidates for surgical resection or definitive chemoradiation, or metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥ 50%] with no EGFR, ALK or ROS1 aberrations when Libtayo is used as first-line treatment. Added new indication to Opdivo (nivolumab) for first-line treatment of individuals with advanced renal cell carcinoma in combination with Cabometyx (cabozantinib). Removed from Imfinzi (durvalumab) coverage for urothelial carcinoma as the indication was withdrawn due to

lack of efficacy in follow-up trials. Removed from Tecentriq (atezolizumab) coverage for prior platinum containing chemotherapy for metastatic urothelial carcinoma as indication was withdrawn due to lack of efficacy in follow-up trials.

2022 Update

Reviewed prescribing information for all drugs in policy. Removed from Keytruda (pembrolizumab) coverage as 3rd line monotherapy treatment for individuals with PD-L1-positive gastric or gastroesophageal junction (GEJ) cancer as the indication was withdrawn due to lack of efficacy in follow-up trials. Added site of service review for Keytruda (pembrolizumab) and for Opdivo (nivolumab). Keytruda and Opdivo are subject to review for site of service administration except when it is used concurrently with other IV medications for cancer treatment.

2023 Update

Reviewed prescribing information for all drugs in policy. Updated coverage criteria for Tecentriq (atezolizumab) to include the indication for the treatment of adult and pediatric individuals 2 years of age and older with unresectable or metastatic alveolar soft part sarcoma (ASPS). Updated coverage criteria for Keytruda (pembrolizumab) to include the indication for the treatment of for adjuvant treatment following resection and platinum-based chemotherapy for adult individuals with stage IB, II, or IIIA NSCLC, as a single agent. Updated coverage criteria for Keytruda (pembrolizumab) to include the indication for the treatment of adult individuals with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy, when used in combination with enfortumab vedotin. Added coverage criteria for Zynyz (retifanlimab-dlwr) for the treatment of adult individuals with metastatic or recurrent locally advanced Merkel cell carcinoma. Added language of "adult individuals" for Keytruda's indication of locally advanced or metastatic urothelial carcinoma when used in combination with Padcev to match FDA label. Grouped the Keytruda indications (NSCLS and urothelial carcinoma) together. Updated coverage criteria for Jemperli (dostarlimab-gxly) to include treatment of certain adult individuals with primary advanced or recurrent endometrial cancer. Updated coverage criteria for Keytruda (pembrolizumab) to include treatment of certain individuals with resectable non-small cell lung cancer (NSCLC) and locally advanced unresectable or metastatic biliary tract cancer. Removed from Opdivo (nivolumab) coverage for BRAF V600 wild type and BRAF V600 mutation-positive unresectable or metastatic melanoma due to removal from FDA

approved indications. Updated coverage criteria for Opdivo (nivolumab) to include treatment of certain individuals with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma.

2024 Update

Reviewed prescribing information for all drugs in policy. Added coverage criteria for Loqtorzi (toripalimab-tpzi). Updated Opdivo (nivolumab) to remove coverage criteria for hepatocellular carcinoma in individuals who have been previously treated with sorafenib as this indication was withdrawn. Updated Keytruda (pembrolizumab) to add coverage criteria for the treatment of certain individuals with Stage III-IVA cervical cancer, and HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma. Updated Keytruda (pembrolizumab) to add coverage criteria for the treatment of adults with locally advanced or metastatic urothelial cancer in combination with Padcev (enfortumab vedotin). Updated Opdivo (nivolumab) to add coverage criteria for adults with unresectable or metastatic urothelial carcinoma in combination with cisplatin and gemcitabine. Updated Keytruda (pembrolizumab) to add coverage criteria for certain individuals with non-small cell lung cancer (NSCLC) in combination with Pemfexy (pemetrexed). Updated Imjudo (tremelimumab-actl) to add coverage criteria for certain individuals with metastatic NSCLC in combination with Imfinzi (durvalumab). Updated Imfinzi (durvalumab) to add coverage criteria for certain individuals with metastatic NSCLC in combination with Imjudo (tremelimumab-actl). Added coverage criteria for Tevimbra (tislelizumab-jsgr). Updated Keytruda (pembrolizumab) to add coverage criteria for certain individuals with hepatocellular carcinoma (HCC) secondary to hepatitis B. Updated Imfinzi (durvalumab) to add coverage criteria for certain individuals with primary advanced or recurrent endometrial cancer. Updated Keytruda (pembrolizumab) to add coverage criteria for certain individuals with primary advanced or recurrent endometrial carcinoma. Clarified that Tecentriq (atezolizumab) use for hepatocellular carcinoma is limited to adults. Updated Imfinzi (durvalumab) to add coverage criteria for certain individuals with non-small cell lung cancer (NSCLC) used in combination with platinum-containing chemotherapy. Updated Opdivo (nivolumab) to add coverage criteria for certain individuals with stage I or II Hodgkin lymphoma with one or more high-risk features. Updated Opdivo (nivolumab) to add coverage criteria for certain individuals with stage IIb through IV Hodgkin lymphoma. Updated Jemperli (dostarlimab-gxly) to include coverage criteria for adults with primary advanced or recurrent endometrial cancer regardless of whether the cancer is mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H). Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

2025 Update

Reviewed prescribing information for all drugs in policy. Added a new indication to Opdivo (nivolumab) for the treatment of resectable (tumors ≥4 cm or node positive) non-small cell lung cancer with no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements in the neoadjuvant setting when Opdivo is used in combination with platinum-doublet chemotherapy, followed by single-agent Opdivo as adjuvant treatment after surgery. Added a new indication to Keytruda (pembrolizumab) for the treatment of unresectable advanced or metastatic malignant pleural mesothelioma as first-line treatment in adult individuals when used in combination with pemetrexed and platinum chemotherapy. Added a new product Tecentriq Hybreza (atezolizumab and hyaluronidase-tqjs), which is a subcutaneous dosage form of Tecentriq (atezolizumab), to policy for the treatment of non-small cell lung cancer, small cell lung cancer, hepatocellular carcinoma, melanoma, and alveolar soft part sarcoma. Tecentriq is an intravenous formulation that is administered over 30–60 minutes while Tecentriq Hybreza only takes about 7 minutes to administer. Added a new indication to Tevimbra (tislelizumab-jsgr) for the first-line treatment of adults with unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 (≥1) when used in combination with platinum and fluoropyrimidine-based chemotherapy. Added a new indication to Imfinzi (durvalumab) for the treatment of adults with limited-stage small cell lung cancer whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy and Imfinzi is used as a single agent. Reviewed evidence published November 2024 in the New England Journal of Medicine (NEJM) on Nivolumab plus Ipilimumab in Microsatellite-Instability–High Metastatic Colorectal Cancer along with NCCN Guidelines for Colon Cancer Version 5.2024 published August 22, 2024, for the first-line treatment of checkpoint inhibitor immunotherapy for microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer. Based on the published evidence from the NEJM article and supported by the NCCN Guidelines, coverage was added for Opdivo (nivolumab) and Yervoy (ipilimumab) combination therapy for the first-line treatment of MSI-H or dMMR unresectable or metastatic colorectal cancer. Policy updated to indicate that Site of Service Medical Necessity criteria does not apply to Alaska fully-insured members pursuant to **Alaska HB 226** (accessed January 3, 2025). Added an exception to the site-of-service requirements for certain individuals receiving treatment for cytokine release syndrome (CRS). Updated Tevimbra (tislelizumab-jsgr) coverage criteria to include first-line treatment of certain adults with esophageal cancer. Added a new indication to Imfinzi (durvalumab) for the treatment of muscle invasive bladder cancer (MIBC). Added a new indication to Yervoy (ipilimumab) for the first-line treatment of unresectable or metastatic HCC when used in combination with Opdivo (nivolumab). Updated Yervoy criteria for the treatment of MSI-H or dMMR unresectable or metastatic CRC allowing coverage for all lines of therapy

when used in combination with Opdivo. Added a new indication to Opdivo (nivolumab) for the first-line treatment of unresectable or metastatic HCC when used in combination with Yervoy (ipilimumab). Updated Opdivo criteria for the treatment of MSI-H or dMMR unresectable or metastatic CRC allowing coverage for all lines of therapy when used in combination with Yervoy. Added site of service review for the following drugs: Imfinzi (durvalumab), Jemperli (dostarlimab-gxly), Opdivo Qvantig (nivolumab-hyaluronidase-nvhy), Tecentriq (atezolizumab), and Tecentriq Hybreza (atezolizumab-hyaluronidase-tqjs). Clarified that the Site of Service Medical Necessity criteria can apply to injection drugs. Updated Keytruda (pembrolizumab) coverage criteria to include treatment of certain individuals with resectable locally advanced head and neck squamous cell cancer. Updated Keytruda (pembrolizumab) gastric cancer coverage criteria to clarify that use is limited to adults whose tumors that express PD-L1. Updated Opdivo (nivolumab) esophageal cancer coverage criteria to clarify that use for first-line treatment is limited to tumors that express PD-L1. Updated Opdivo (nivolumab) stage IIb-IV classical Hodgkin lymphoma coverage criteria age requirement from 18 years or older to 12 years or older. Updated Zynyz (retifanlimab-dlwr) coverage criteria to include treatment of certain individuals with squamous cell carcinoma of the anal canal (SCAC) when used for first-line treatment in combination with carboplatin and paclitaxel or as a single agent in adults with locally recurrent or metastatic disease. Added coverage criteria for penpulimab-kcqx.

2026 Update

Reviewed prescribing information for all drugs in policy. Updated coverage criteria for Keytruda (pembrolizumab) and Keytruda Qlex (pembrolizumab and berahyaluronidase alfa-pmph) adding new indication for the treatment of adult individuals with muscle invasive bladder cancer (MIBC) who are ineligible for cisplatin-containing chemotherapy and used in combination with enfortumab vedotin, as neoadjuvant treatment and then continued after cystectomy as adjuvant treatment. Updated Keytruda Qlex to include indication for adult individuals with resectable locally advanced HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) is at least 1] as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy with or without cisplatin and then as a single agent. Updated coverage criteria for Imfinzi (durvalumab) adding new indication for the treatment of adult individuals with resectable gastric or gastroesophageal junction adenocarcinoma (GC/GEJC) and used in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by single agent durvalumab. Updated coverage criteria for Tecentriq Hybreza (atezolizumab and hyaluronidase-tqjs) for unresectable or metastatic alveolar soft part sarcoma changing requirement from adult to individuals aged 12 years and older who weigh at least 40 kg. Updated coverage criteria for Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) to include

unresectable or metastatic HCC, as a first-line treatment following combination treatment with intravenous Opdivo (nivolumab) and Yervoy (ipilimumab). Reformatted policy with no change to criteria except where noted above.

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37. Opdualag (nivolumab and relatlimab-rmbw). Prescribing Information. Bristol-Myers Squibb Company, Princeton, NJ. Revised March 2024.

38. Imjudo (tremelimumab-actl). Prescribing Information. AstraZeneca Pharmaceuticals LP, Wilmington, DE. Revised July 2024.

39. Zynyz (retifanlimab-dlwr). Prescribing Information. Incyte Corporation; Wilmington, DE. Revised December 2025

40. Tevimbra (tislelizumab-jsgr). Prescribing Information. BeOne Medicines USA, Inc.; Pennington, NJ. Revised August 2026.
41. Unloxcyt (cosibelimab-ipdl). Prescribing Information. Checkpoint Therapeutics, Inc, Waltham, MA. Revised November 2025.
42. Loqtorzi (toripalimab-tpzi). Prescribing Information. Coherus BioSciences, Inc.; Redwood City, CA. Revised October 2024.
43. Penpulimab-kcqx. Prescribing Information.. Akeso Biopharma Co., Ltd. Revised April 2025.

History

Date	Comments
11/01/18	New policy, approved October 9, 2018. Add to Prescription Drug section. Immunotherapy drugs (atezolizumab, ipilimumab, nivolumab and pembrolizumab) were moved from policy 5.10.540. Medical necessity and reauthorization criteria are provided for these four agents in this policy. Added criteria and information for Cemiplimab.
03/01/19	Interim Review, approved February 12, 2019. Updated criteria for Tecentriq (atezolizumab). Added HCPCS code J9173.
05/01/19	Interim Review, approved April 9, 2019. Updated criteria for Tecentriq (atezolizumab).
08/01/19	Interim Review, approved July 9, 2019. Updated criteria for Keytruda (pembrolizumab).
10/01/19	Annual Review, approved September 5, 2019. Updated criteria for Bavencio (avelumab) and Keytruda (pembrolizumab). Added HCPCS codes J9023 and J9119. Removed J3490.
02/01/20	Annual Review, approved January 23, 2020. Added new indications for Keytruda (endometrial carcinoma in combination with lenvatinib) and Tecentriq (NSCLC with paclitaxel protein-bound and carboplatin).
03/01/20	Interim Review, approved February 20, 2020. Added a new indication to Keytruda (pembrolizumab) for the treatment of patients with BCG.
06/01/20	Interim Review, approved May 21, 2020. Updated indication for Opdivo for hepatocellular carcinoma for use as monotherapy or in combination with Yervoy. Added new indication to Yervoy for treatment of hepatocellular carcinoma when used in combination with Opdivo.
07/01/20	Interim Review, approved June 9, 2020. Added new indication to Imfinzi (durvalumab) for the treatment of ES-SCLC. Updated Keytruda (pembrolizumab) indications for NSCLC and added a new indication for HNSCC when used in combination with platinum and FU for the first-line treatment. Added new indication to Tecentriq (atezolizumab) for NSCLC whose tumors have high PD-L1 expression and for the treatment of HCC. Added new indication to Opdivo and Yervoy for treatment of NSCLC expressing PD-L1.

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08/01/20	Interim Review, approved July 14, 2020. Added new indication to Opdivo for the treatment of ESCC. Added three new indications to Keytruda for the treatment of TMB-H cancer, cSCC and first-line treatment of MSI-H or dMMR CRC. Added new indication to Bavencio for the maintenance treatment of UC.
10/01/20	Interim Review, approved September 17, 2020. Added a new indication to Tecentriq for the treatment of patients with melanoma when used in combination with cobimetinib and vemurafenib.
12/01/20	Interim Review, approved November 10, 2020. Added new indication to Opdivo and Yervoy for treatment of unresectable malignant pleural mesothelioma.
02/01/21	Interim Review, approved January 12, 2021. Updated Keytruda coverage criteria for adults and pediatric patients with R/R cHL. Added new indication to Keytruda for the treatment of TNBC. Removed from Opdivo coverage for metastatic SCLC as indication was withdrawn due to lack of efficacy in follow-up trials. Added new indication to Opdivo and Yervoy when combined and with 2 cycles of platinum-doublet chemotherapy for treatment of metastatic or recurrent NSCLC.
05/01/21	Annual Review, approved April 13, 2021. Added a new indication to Keytruda in combination with platinum- and fluoropyrimidine-based chemotherapy for patients with locally advanced or metastatic esophageal or GEJ carcinoma. Removed from Keytruda coverage for SCLC as indication was withdrawn due to lack of efficacy in follow-up trials. Added new indications to Libtayo for locally advanced or metastatic basal cell carcinoma and for locally advanced or metastatic NSCLC. Added new indication to Opdivo for first-line treatment of advanced RCC in combination with cabozantinib. Removed from Imfinzi coverage for urothelial carcinoma as indication was withdrawn due to lack of efficacy in follow-up trials. Removed from Tecentriq coverage for prior platinum containing chemotherapy for metastatic urothelial carcinoma as the indication was withdrawn due to lack of efficacy in follow-up trials.
06/01/21	Interim Review, approved May 11, 2021. Added criteria for Jemperli (dostarlimab-gxly) for the treatment of mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer. Added a new indication to Keytruda (pembrolizumab) for treatment of patients with HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma. Added a new indication to Opdivo (nivolumab) for the treatment of advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma. Added HCPCS code J3590.
08/01/21	Interim Review, approved July 22, 2021. Updated Keytruda (pembrolizumab) criteria when used in combination with pemetrexed and platinum chemotherapy for metastatic NSCLC to require patients have no EGFR or ALK genomic tumor aberrations.
09/01/21	Interim Review, approved August 10, 2021. Updated Keytruda (pembrolizumab) indication for cutaneous squamous cell carcinoma (cSCC) to include locally advanced cSCC. Added a new indication to Keytruda (pembrolizumab) for the treatment of high-risk early-stage TNBC. Updated criteria for Opdivo (nivolumab) for the treatment of

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	HCC removing use as a single agent in patients previously treated with sorafenib (Opdivo must be used in combination with Yervoy).
10/01/21	Interim Review, approved September 14, 2021. Added a new indication to Keytruda (pembrolizumab) for the treatment of RCC in combination with lenvatinib. Added a new indication to Jemperli (dostarlimab-gxly) for the treatment of solid tumors. Added a new indication to Opdivo (nivolumab) for the adjuvant treatment of UC in patients who are at high risk of recurrence after undergoing radical resection of UC. Removed from Tecentriq (atezolizumab) coverage for TNBC whose tumors express PD-L1 as the indication was withdrawn due to lack of efficacy in follow-up trials. Added HCPCS C9082.
12/01/21	Interim Review, approved November 9, 2021. Added a new indication to Keytruda (pembrolizumab) for the treatment of persistent, recurrent, or metastatic cervical cancer in combination with chemotherapy, with or without bevacizumab. Added a new indication to Tecentriq (atezolizumab) as an adjuvant treatment for adult patients with Stage II and IIIA NSCLC following resection and platinum-based chemotherapy.
01/01/22	Interim Review, approved December 14, 2021. Added a new indication to Keytruda (pembrolizumab) for the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma following complete resection. Added a new indication to Keytruda for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions. Added HCPCS code J9272 and removed HCPCS code J3590.
04/01/22	Annual Review, approved March 8, 2022. Removed from Keytruda (pembrolizumab) coverage as 3rd line monotherapy treatment for patients with PD-L1-positive gastric or gastroesophageal junction (GEJ) cancer as the indication was withdrawn due to lack of efficacy in follow-up trials. Added site of service review for Keytruda (pembrolizumab) and for Opdivo (nivolumab) for dates of service on or after July 7, 2022.
06/01/22	Interim Review, approved May 10, 2022. Added a new indication to Keytruda (pembrolizumab) for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR when used as a single agent. Added a new indication to Opdivo (nivolumab) for neoadjuvant treatment of resectable NSCLC.
08/01/22	Interim Review, approved July 12, 2022. Added coverage to Opdivo (nivolumab) for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer in adult patients who have received neoadjuvant CRT. Added coverage to Opdivo (nivolumab) for the first-line treatment of adult patients with unresectable advanced or metastatic ESCC when used in combination with fluoropyrimidine- and platinum-containing chemotherapy OR when used in combination in combination with Yervoy (ipilimumab). Added coverage to Yervoy (ipilimumab) for the first-line treatment of adult patients with unresectable advanced or metastatic ESCC when used in combination with Opdivo (nivolumab).
11/01/22	Interim Review, approved October 11, 2022. Added coverage to Imfinzi for use in combination with gemcitabine and cisplatin for the treatment of adult individuals with locally advanced or metastatic biliary tract cancer. Added Opdualag for the treatment

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	of adult and pediatric individuals 12 years of age or older with unresectable or metastatic melanoma. Updated Keytruda criteria when used in combination with lenvatinib for the treatment of advanced endometrial carcinoma by removing the requirement the cancer is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). Updated Keytruda when used as a single agent for esophageal or GEJ carcinoma to require the tumor to be of squamous cell histology. Added HCPCS code J9298. Changed the wording from "patient" to "individual" throughout the policy for standardization.
01/01/23	Interim Review, approved December 13, 2022. Added coverage for Imjudo (tremelimumab-actl), in combination with Imfinzi (durvalumab), for the treatment of unresectable hepatocellular carcinoma (uHCC). Added a new indication to Imfinzi (durvalumab), when used in combination with Imjudo (tremelimumab-actl), for the treatment of uHCC. Updated Keytruda indication for NSCLC when used in combination with pemetrexed and platinum chemotherapy for first-line treatment to require the NSCLC is non-squamous and to allow for coverage initiation while awaiting the results of confirmed genomic testing. Added a new indication to Libtayo (cemiplimab) for use in combination with platinum-based chemotherapy for first-line advanced NSCLC. Removed coverage from Tecentriq (atezolizumab) for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma as indication was withdrawn due to lack of efficacy in follow-up trials. Removed termed HCPC code C9082 and new code effective date from HCPC code J9272. Added HCPC code J3590 to report Imjudo.
04/01/23	Coding update. Added new HCPCS code C9147.
06/01/23	Annual Review, approved May 9, 2023. Reviewed prescribing information for all drugs in policy. Updated coverage criteria for Tecentriq (atezolizumab) to include the indication for the treatment of adult and pediatric individuals 2 years of age and older with unresectable or metastatic alveolar soft part sarcoma (ASPS). Updated coverage criteria for Keytruda (pembrolizumab) to include the indication for the treatment of for adjuvant treatment following resection and platinum-based chemotherapy for adult individuals with stage IB, II, or IIIA NSCLC, as a single agent. Updated coverage criteria for Keytruda (pembrolizumab) to include the indication for the treatment of adult individuals with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy, when used in combination with enfortumab vedotin. Added coverage criteria for Zynyz (retifanlimab-dlwr) for the treatment of adult individuals with metastatic or recurrent locally advanced Merkel cell carcinoma.
07/01/23	Interim Review, approved June 26, 2023. Made minor update to Zynyz criteria. Updated Zynyz criteria to include individuals “who may have received surgery or radiation” for the indication Merkel cell carcinoma (MCC). Made minor update and added T2a > 4cm to Keytruda’s criteria for stage IB, II, or IIIA NSCLC to match FDA label. Added language of “adult individuals” for Keytruda's indication of locally advanced or metastatic urothelial carcinoma when used in combination with Padcev to match FDA label. Grouped the Keytruda indications (NSCLC and urothelial carcinoma) together. Added termed date for deleted code C9147 and added new HCPCS code J9347.

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10/01/23	Coding update. Added new HCPCS code J9345.
01/01/24	Interim Review, approved December 12, 2023. Updated coverage criteria for Jemperli (dostarlimab-gxly) to include treatment of certain adult individuals with primary advanced or recurrent endometrial cancer. Updated coverage criteria for Keytruda (pembrolizumab) to include treatment of certain individuals with resectable non-small cell lung cancer (NSCLC) and locally advanced unresectable or metastatic biliary tract cancer. Removed from Opdivo (nivolumab) coverage for BRAF V600 wild type and BRAF V600 mutation-positive unresectable or metastatic melanoma due to removal from FDA approved indications. Updated coverage criteria for Opdivo (nivolumab) to include treatment of certain individuals with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma. Added new HCPCS code J9258.
05/01/24	Annual Review, approved April 9, 2024. Added coverage criteria for Loqtorzi (toripalimab-tpzi). Updated Opdivo (nivolumab) to remove coverage criteria for hepatocellular carcinoma in individuals who have been previously treated with sorafenib as this indication was withdrawn. Updated Keytruda (pembrolizumab) to add coverage criteria for the treatment of certain individuals with Stage III-IVA cervical cancer, and HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma. Updated Keytruda (pembrolizumab) to add coverage criteria for the treatment of adults with locally advanced or metastatic urothelial cancer in combination with Padcev (enfortumab vedotin). Updated Opdivo (nivolumab) to add coverage criteria for adults with unresectable or metastatic urothelial carcinoma in combination with cisplatin and gemcitabine. Updated Keytruda (pembrolizumab) to add coverage criteria for certain individuals with non-small cell lung cancer (NSCLC) in combination with Pemfexy (pemetrexed). Updated Imjudo (tremelimumab-actl) to add coverage criteria for certain individuals with metastatic NSCLC in combination with Imfinzi (durvalumab). Updated Imfinzi (durvalumab) to add coverage criteria for certain individuals with metastatic NSCLC in combination with Imjudo (tremelimumab-actl). Added coverage criteria for Tevimbra (tislelizumab-jsgr).
07/01/24	Coding update. Added new HCPCS code J3263 effective 7/1/2024. Removed drug name Loqtorzi from unlisted code, J3590.
09/01/24	Interim Review, approved August 13, 2024. Updated Keytruda (pembrolizumab) to add coverage criteria for certain individuals with hepatocellular carcinoma (HCC) secondary to hepatitis B. Updated Imfinzi (durvalumab) to add coverage criteria for certain individuals with primary advanced or recurrent endometrial cancer. Updated Keytruda (pembrolizumab) to add coverage criteria for certain individuals with primary advanced or recurrent endometrial carcinoma. Removed HCPCS J9258.
10/01/24	Coding update. Added new HCPCS code J9329 effective 10/1/2024 for Tevimbra. Removed unlisted HCPCS code, J3590.
11/01/24	Interim Review, approved October 8, 2024. Clarified that Tecentriq (atezolizumab) use for hepatocellular carcinoma is limited to adults. Updated Imfinzi (durvalumab) to add coverage criteria for certain individuals with non-small cell lung cancer (NSCLC) used in combination with platinum-containing chemotherapy. Updated Opdivo (nivolumab) to

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	add coverage criteria for certain individuals with stage I or II Hodgkin lymphoma with one or more high-risk features. Updated Opdivo (nivolumab) to add coverage criteria for certain individuals with stage IIb through IV Hodgkin lymphoma. Updated Jemperli (dostarlimab-gxly) to include coverage criteria for adults with primary advanced or recurrent endometrial cancer regardless of whether the cancer is mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H).
01/01/25	Interim Review, approved December 23, 2024. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.
02/01/25	Annual Review, approved January 14, 2025. Added a new indication to Opdivo (nivolumab) for the treatment of resectable NSCLC with no known EGFR mutations or ALK rearrangements in the neoadjuvant setting, in combination with platinum-doublet chemotherapy, followed by single-agent nivolumab as adjuvant treatment after surgery. Added a new indication to Keytruda (pembrolizumab) for the treatment of unresectable advanced or metastatic MPM as first-line treatment in adult individuals when used in combination with pemetrexed and platinum chemotherapy. Added a new product Tecentriq Hybreza (atezolizumab and hyaluronidase-tqjs), which is a SC dosage form of Tecentriq (atezolizumab), to policy for the treatment of NSCLC, SCLC, HCC, melanoma, and ASPS. Added a new indication to Imfinzi (durvalumab) for the treatment of adults with LS-SCLC whose disease has not progressed following cCRT and Imfinzi is used as a single agent. Added coverage for Opdivo (nivolumab) and Yervoy (ipilimumab) combination therapy for the first-line treatment of MSI-H or dMMR unresectable or metastatic colorectal cancer. Added a new indication to Tevimbra (tislelizumab-jsgr) for the first-line treatment of adults with unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 (≥1) when used in combination with platinum and fluoropyrimidine-based chemotherapy. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Policy updated to indicate that Site of Service Medical Necessity criteria does not apply to Alaska fully-insured members; only Medical Necessity criteria for the infusion drug applies pursuant to Alaska HB 226 (link added). Added an exception to the site-of-service requirements for certain individuals receiving treatment for cytokine release syndrome (CRS). Added unlisted HCPCS codes C9399 and J9999 for Tecentriq Hybreza.
04/01/25	Interim Review, approved March 11, 2025. Added coverage criteria for Unloxcyt (cosibelimab-ipdl) for the treatment of adults with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC). Added Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) to the policy as monotherapy, monotherapy maintenance following completion of intravenous Opdivo (nivolumab) and Yervoy (ipilimumab) combination therapy, or in combination with other therapy for the treatment of renal cell carcinoma, melanoma, non-small cell lung cancer, squamous cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer, hepatocellular carcinoma, esophageal cancer, gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma. Added new HCPCS code J9024.

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05/01/25	Interim Review, approved April 8, 2025. Updated Tevimbra (tislelizumab-jsgr) coverage criteria to include first-line treatment of certain adults with esophageal cancer.
07/01/25	Interim Review, approved June 10, 2025. Added a new indication to Imfinzi (durvalumab) for the treatment of muscle invasive bladder cancer (MIBC). Added a new indication to Yervoy (ipilimumab) for the first-line treatment of unresectable or metastatic HCC when used in combination with Opdivo (nivolumab). Updated Yervoy criteria for the treatment of MSI-H or dMMR unresectable or metastatic CRC allowing coverage for all lines of therapy when used in combination with Opdivo. Added a new indication to Opdivo (nivolumab) for the first-line treatment of unresectable or metastatic HCC when used in combination with Yervoy (ipilimumab). Updated Opdivo criteria for the treatment of MSI-H or dMMR unresectable or metastatic CRC allowing coverage for all lines of therapy when used in combination with Yervoy. Added new HCPCS codes J9275 (Unloxcyt) and J9289 (Opdivo Qvantig) due to quarterly coding updates. The following policy changes are effective October 3, 2025, following 90-day provider notification. Added site of service review for the following drugs: Imfinzi (durvalumab), Jemperli (dostarlimab-gxly), Opdivo Qvantig (nivolumab-hyaluronidase-nvhy), Tecentriq (atezolizumab), and Tecentriq Hybreza (atezolizumab-hyaluronidase-tqjs). Clarified that the Site of Service Medical Necessity criteria can apply to injection drugs.
08/01/25	Interim Review, approved July 8, 2025. Updated Keytruda (pembrolizumab) coverage criteria to include treatment of certain individuals with resectable locally advanced head and neck squamous cell cancer. Updated Keytruda (pembrolizumab) gastric cancer coverage criteria to clarify that use is limited to adults whose tumors that express PD-L1. Updated Opdivo (nivolumab) esophageal cancer coverage criteria to clarify that use for first-line treatment is limited to tumors that express PD-L1. Updated Opdivo (nivolumab) stage IIb-IV classical Hodgkin lymphoma coverage criteria age requirement from 18 years or older to 12 years or older. Updated Zynyz (retifanlimab-dlwr) coverage criteria to include treatment of certain individuals with squamous cell carcinoma of the anal canal (SCAC) when used for first-line treatment in combination with carboplatin and paclitaxel or as a single agent in adults with locally recurrent or metastatic disease. Added coverage criteria for penpulimab-kcqx. Added HCPCS code J9999 for penpulimab-kcqx.
11/01/25	Interim Review, approved October 14, 2025. Added coverage criteria for Keytruda Qlex (pembrolizumab and berahyaluronidase alfa-pmph). Added HCPCS Code J3590 for Keytruda Qlex. The following changes are effective February 6, 2026, following a 90-day provider notification: Updated Yervoy (ipilimumab) criteria for the treatment of ESCC to require the tumors express PD-L1 (at least 1). Updated Opdivo (nivolumab) and Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) criteria for the treatment of gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma to require the tumors express PD-L1 (at least 1). Updated Opdivo Qvantig for the first-line treatment of unresectable advanced or metastatic ESCC to require the tumors express PD-L1 (at least 1).

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12/01/25	Interim Review, approved November 11, 2025. Added a new indication to Libtayo (cemiplimab) for the adjuvant treatment of adults with CSCC at high risk of recurrence after surgery and radiation. Added a new indication to Tecentriq (atezolizumab) and Tecentriq Hybreza (atezolizumab and hyaluronidase-tqjs) for the maintenance treatment of adult individuals with ES-SCLC when used in combination with Zepzelca (lurbinectedin).
03/01/26	Annual Review, approved February 10, 2026. Updated coverage criteria for Keytruda (pembrolizumab) and Keytruda Qlex (pembrolizumab and berahyaluronidase alfa-pmph) adding new indication for the treatment of adult individuals with muscle invasive bladder cancer (MIBC) who are ineligible for cisplatin-containing chemotherapy and used in combination with enfortumab vedotin, as neoadjuvant treatment and then continued after cystectomy as adjuvant treatment. Updated Keytruda Qlex to include indication for adult individuals with resectable locally advanced HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) is at least 1] as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy with or without cisplatin and then as a single agent. Updated coverage criteria for Imfinzi (durvalumab) adding new indication for the treatment of adult individuals with resectable gastric or gastroesophageal junction adenocarcinoma (GC/GEJC) and used in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by single agent durvalumab. Updated coverage criteria for Tecentriq Hybreza (atezolizumab and hyaluronidase-tqjs) for unresectable or metastatic alveolar soft part sarcoma changing requirement from adult to individuals aged 12 years and older who weigh at least 40 kg. Updated coverage criteria for Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) to include unresectable or metastatic HCC, as a first-line treatment following combination treatment with intravenous Opdivo (nivolumab) and Yervoy (ipilimumab). Reformatted policy with no change to criteria except where noted above.
04/01/26	Interim Review, approved March 10, 2026. Updated criteria for Keytruda (pembrolizumab) and Keytruda Qlex (pembrolizumab and berahyaluronidase alfa-pmph) adding new indication in combination with paclitaxel, with or without bevacizumab, for the treatment of adult individuals with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinoma whose tumors express PD-L1 (CPS at least 1), and who have received one or two prior systemic treatment regimens. Removed reference to non-formulary exception reviews. Added new HCPCS code J9277. Removed reference note regarding Keytruda Qlex related to J3590 and C9399 for reporting now that there is a code specific to this drug. The following policy changes are effective July 2, 2026, following 90-day provider notification. Added site of service review for Keytruda Qlex (pembrolizumab and berahyaluronidase alfa-pmph) SC.
09/01/26	Interim Review, approved August 11, 2026. Updated Imfinzi adding criteria when used combination with BCG for the treatment of adult individuals with BCG-naive, high-risk NMIBC. Updated Keytruda and Keytruda Qlex for treatment of MIBC removing requirement individual is ineligible for cisplatin-containing chemotherapy, adding criteria when used in combination with belzutifan for the adjuvant treatment of ccRCC,

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	and adding criteria for when used in combination with sacituzumab govitecan-hziy for the first line treatment of unresectable locally advanced or metastatic TNBC. Updated Tecentriq and Tecentriq Hybreza adding criteria for adjuvant treatment of adult individuals with MIBC after cystectomy who have ctDNA MRD.
11/01/26	Interim Review, approved October 13, 2026. Updated Tevimbra (tislelizumab-jsgr) adding criteria for the treatment of HER2 positive (IHC 3+ or ISH+) unresectable locally advanced or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma. Removed HCPCS code J3590. The following policy changes are effective February 5, 2027, following 90-day provider notification. Updated criteria for Keytruda Qlex adding requirement individual must receive Keytruda (pembrolizumab) IV. Updated criteria for Opdivo Qvantig adding requirement individual must receive Opdivo (nivolumab) IV. Updated criteria for Tecentriq Hybreza adding requirement individual must receive Tecentriq (atezolizumab) IV.

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