CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Pembrolizumab (Keytruda®)

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NantHealth® | Eviti®

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Pembrolizumab (Keytruda®)

Discussion

Pembrolizumab is a type of targeted immunotherapy called an immune checkpoint inhibitor. It is a monoclonal antibody that binds to the protein PD-1 on the surface of immune cells called T cells. It works by keeping cancer cells from suppressing the immune system, which allows the immune system to attack and kill the cancer cells.[1]

The most common adverse reactions occurring in at least 20% of patients treated with single agent are fatigue, musculoskeletal pain, rash, diarrhea, pyrexia, cough, decreased appetite, pruritus, dyspnea, constipation, pain, abdominal pain, nausea, and hypothyroidism. For patients treated with combination therapy, the most common adverse effects include fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, stomatitis, headache, weight loss, abdominal pain, arthralgia, myalgia, insomnia, palmar-plantar erythrodysesthesia, urinary tract infection, hypothyroidism, radiation skin injury, dysphagia, dry mouth, musculoskeletal pain, anemia, neutropenia, hypertension, thrombocytopenia, leukopenia, hepatotoxicity, dysphonia, proteinuria, hemorrhagic events, acute kidney injury, pruritus, dry eye, dysgeusia. Clinically significant adverse reactions include severe and fatal immune-mediated reactions and infusion-related reactions.

Pembrolizumab is approved by the Food and Drug Administration (FDA) for the following cancer types: biliary tract, cervical, classical Hodgkin lymphoma, cutaneous squamous cell carcinoma, endometrial, esophageal, gastric, head and neck squamous cell, hepatocellular, malignant pleural mesothelioma, melanoma, Merkel cell, microsatellite instability-high or mismatch repair deficient, microsatellite instability-high or mismatch repair deficient colorectal, non-small cell lung, primary mediastinal large B-cell lymphoma, renal cell, triple-negative breast cancer, tumor mutational burden-high, and urothelial.[2]

The National Comprehensive Cancer Network (NCCN) endorses pembrolizumab in the following cancer types: ampullary adenocarcinoma, anal, appendiceal neoplasms, B-cell lymphoma, biliary tract, bladder, bone, breast, central nervous system, cervical, chronic lymphocytic leukemia/small lymphocytic lymphoma, colon, esophageal and esophagogastric junction, gastric, gestational trophoblastic neoplasia, head and neck, hepatocellular, Hodgkin lymphoma, Kaposi sarcoma, kidney, cutaneous and uveal melanoma, Merkel cell, peritoneal and pleural mesothelioma, neuroendocrine and adrenal tumors, non-small cell lung, occult primary, ovarian, pancreatic, pediatric aggressive mature B-cell lymphoma, pediatric central nervous system, pediatric Hodgkin lymphoma, penile, primary cutaneous lymphoma, prostate, rectal, small bowel adenocarcinoma, small cell lung, soft tissue sarcoma, squamous cell skin, T-cell lymphoma, thymomas and thymic, thyroid, uterine, vaginal, and vulvar.[3,45,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49]

Definitions

- **Anaplastic Lymphoma Kinase (ALK) Rearrangement** - ALK is a tyrosine kinase that can be aberrantly expressed in several tumor types. ALK-positive tumors (tumors harboring

a rearranged ALK gene/fusion protein) are highly sensitive to therapy with ALK-targeted inhibitors.[50]

- **Deficient Mismatch Repair/Microsatellite Instability-High (dMMR/MSI-H)** - When microsatellite DNA segments in cancer cells show changes (mutations), this indicates that the tumor cells are deficient in the repair of mismatch errors. These cancers have microsatellite instability (also called MSI-High, MSI-H, or mismatch repair deficiency, dMMR).[51]
- **Del(17p)/TP53 Mutation** - The loss of all or part of the short arm (also called the p arm) of chromosome 17. The deletion 17p leads to the loss of the tumor suppressor gene TP53.[52] TP53 gene makes a protein that is found inside the nucleus of cells and plays a key role in controlling cell division and cell death. Mutations (changes) in the TP53 gene may cause cancer cells to grow and spread in the body.[52,53]
- **Epidermal Growth Factor Receptor (EGFR) Exon 19 Deletion and Epidermal Growth Factor Receptor 21 L858R Mutations** - The two most commonly found EGFR gene mutations are deletions in exon 19 in 45% of patients and a point mutation in exon 21 (L858R in 40%). These mutations are predictive of treatment benefit from EGFR tyrosine kinase inhibitor (EGFR TKI) therapy. Most patients harboring them have adenocarcinoma histology and have either never smoked or have a light smoking history.[54]
- **Food and Drug Administration (FDA)** - The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.[55]
- **Immune Checkpoint Inhibitors (ICIs)** - Immunotherapy drugs called immune checkpoint inhibitors work by blocking checkpoint proteins from binding with their partner proteins. This prevents the "off" signal from being sent, allowing the T cells to kill cancer cells. One such drug acts against a checkpoint protein called CTLA-4. Other immune checkpoint inhibitors act against a checkpoint protein called PD-1 or its partner protein PD-L1.[56]
- **National Comprehensive Cancer Network (NCCN)** - An alliance of 33 leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.[57]
- **Oncogenic Drivers** - Genes whose mutation facilitates tumor growth are called driver genes. Cancer develops because of the accumulation of a somatic (after conception) mutation and other genetic alterations that impair cell division, checkpoints, etc., which result in abnormal cell proliferation and eventually to a cancer – such mutations are called "driver mutations". The discovery of oncogenic drivers led to the design of therapies targeting tumors harboring specific gene alterations that cause aberrant signaling and growth.[58]
- **Programmed Cell Death Protein 1 (PD-1)/Programmed Cell Death-Ligand 1 (PD-L1)** - Checkpoint proteins, such as PD-L1 on tumor cells and PD-1 on T-cells, help keep immune responses in check. The binding of PD-L1 to PD-1 keeps T cells from killing tumor cells, which in the body. Blocking the binding of PD-L1 to PD-1 with an immune checkpoint inhibitor (anti-PD-L1 or anti-PD-1) allows the T cells to kill tumor cells.[59]

- **Richter's Transformation** - Histologic transformation to a more aggressive lymphoma such as diffuse large B-cell lymphoma or Hodgkin lymphoma (HL) in the setting of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and occurs in about 2% to 10% of patients during the course of their treatment. Clinical outcomes for these patients are exceedingly poor.[60]
- **ROS1 Rearrangement** - A distinct receptor tyrosine kinase that is very similar to ALK and members of the insulin receptor family. It is estimated that ROS1 gene rearrangements occur in about 1-2% of patients with NSCLC. These mutations most frequently occur in nonsquamous histology but can also occur in squamous cell histology, although at a lower rate.[61]
- **Tumor Mutational Burden High (TMB-H)** - Mutations are changes in the DNA of a cancer cell that are not present in your normal cells. TMB is the number of mutations found in the DNA of cancer cells. A high number of mutations is considered "high TMB." High values are an indicator of potential response to immunotherapy.[62]
- **Yp Staging** - Abbreviation for posttherapy staging and applies to patients who have been treated with neoadjuvant therapy including neoadjuvant chemotherapy (NAC), radiation, or hormonal therapy.[63]

Policy

Coverage will be considered for FDA approved indications and for NCCN category 1, 2A, or 2B recommendations when the following criteria are met:

Ampullary Adenocarcinoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single agent therapy for metastatic disease as first-line therapy if microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR), or tumor mutational burden-high (TMB-H ≥ 10 mut/Mb); OR
4. Single agent therapy for disease progression if the patient did not receive prior immunotherapy and if microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR), or tumor mutational burden-high (TMB-H ≥ 10 mut/Mb).[3]

Anal Carcinoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single agent for one of the following:
   a) Before proceeding to abdominoperineal resection for locally recurrent, progressive disease; OR

b) Second-line and subsequent therapy for metastatic disease if no prior immunotherapy was received prior.[4]

Appendiceal Neoplasms and Cancers

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Neoadjuvant systemic therapy as a single agent (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation with ultra-hypermutated phenotype [eg, TMB >50 mut/Mb]), if no previous treatment with a checkpoint inhibitor, for one of the following:
   a) Biopsy-proven recurrence of high-risk disease and no previous cytoreductive surgery
   b) Metastatic disease in peritoneal-only; OR
4. Single agent (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation with ultra-hypermutated phenotype [eg, TMB >50 mut/Mb]), if no previous treatment with a checkpoint inhibitor, for one of the following:
   a) Recurrence with serial tumor marker elevation or radiographic progression and progressive or positive findings
   b) Biopsy-proven recurrence of high-risk disease if cytoreductive surgery was previously received or not possible
   c) Progressive disease or inadequate response after neoadjuvant systemic therapy for metastatic peritoneal-only disease
   d) extraperitoneal disease.[5]

B-Cell Lymphoma

1. Prescribed by or in consultation with an oncologist; AND

Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

For **FDA** required criteria coverage:

2. For adult or pediatric patients; AND
3. Refractory disease or for patients who have relapsed after two or more prior lines of therapy

   Note: Pembrolizumab is not recommended for the treatment of patients with PMBCL who require urgent cytoreductive therapy;[2] OR

For **NCCN** required criteria coverage:

4. At least 18 years of age; AND
5. Single agent for relapsed or refractory disease.[6]

Biliary Tract Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. In combination with gemcitabine and cisplatin for locally advanced unresectable or metastatic disease;[2] OR

Gallbladder Cancer

For **NCCN** required criteria coverage:

4. Neoadjuvant systemic therapy for one of the following:
   a) In combination with cisplatin and gemcitabine (or carboplatin if ineligible for cisplatin)
   b) Single agent for disease that is microsatellite instability-high (MSI-H) and/or deficient mismatch repair (dMMR)

   The above regimens may be used for resectable locoregionally advanced disease that presents as one of the following:
   i. Incidental finding of a suspicious mass during surgery where hepatobiliary surgery expertise is unavailable
   ii. Incidental finding on pathologic review (cystic duct node positive)
   iii. Mass on imaging
   iv. Jaundice; OR
5. In combination with cisplatin and gemcitabine (or carboplatin if ineligible for cisplatin) as primary treatment for unresectable or resected gross residual (R2) disease, or metastatic disease; OR
6. Single agent as primary treatment for unresectable or gross residual (R2) disease, or metastatic disease that is microsatellite instability-high (MSI-H) and/or deficient mismatch repair (dMMR); OR
7. Subsequent treatment for progression on or after systemic treatment for unresectable or resected gross residual (R2) disease, or metastatic disease in combination with cisplatin (or carboplatin if ineligible for cisplatin) and gemcitabine for patients that have not been previously treated with a checkpoint inhibitor; OR
8. Subsequent treatment as a single agent for progression on or after systemic treatment for unresectable or gross residual (R2) disease, or metastatic disease that is microsatellite instability-high (MSI-H) and/or deficient mismatch repair (dMMR) or tumor mutational burden high (TMB-H) in those who have not been previously treated with a checkpoint inhibitor; OR

Intrahepatic and Extrahepatic Cholangiocarcinoma

For **NCCN** required criteria coverage:

9. In combination with gemcitabine and cisplatin (or carboplatin if ineligible for cisplatin) as primary treatment for unresectable or gross residual (R2) disease, or metastatic disease; OR
10. Primary treatment as a single agent for unresectable or gross residual (R2) disease, or metastatic disease that is microsatellite instability-high (MSI-H) and/or deficient mismatch repair (dMMR); OR

11. Subsequent treatment for progression on or after systemic treatment for unresectable or gross residual (R2) disease, or metastatic disease in combination with cisplatin and gemcitabine (or carboplatin if ineligible for cisplatin) in those who have not been previously treated with a checkpoint inhibitor; OR
12. Subsequent treatment as a single agent for progression on or after systemic treatment for unresectable or gross residual (R2) disease, or metastatic disease that is microsatellite instability-high (MSI-H) and/or deficient mismatch repair (dMMR) or tumor mutational burden high (TMB-H) in those who have not been previously treated with a checkpoint inhibitor.[7]

Bladder Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. BCG-unresponsive, high-risk, non-muscle invasive bladder cancer with one of the following:
   a) CIS (with or without papillary) tumors who are ineligible for or have elected not to undergo cystectomy for one of the following:
      i. As initial management
      ii. Cytology-positive, imaging- and cystoscopy-negative, bladder positive recurrent or persistent disease; OR
   b) High-grade papillary Ta/T1 only tumors without ~~Tis~~ CIS who are ineligible for or have elected not to undergo cystectomy for one of the following:
      i. As initial management
      ii. For cytology-positive, imaging- and cystoscopy-negative, bladder positive recurrent or persistent disease; OR
4. Adjuvant therapy for patients who value an opportunity to delay recurrence even if the chance of cure was not improved, and for whom the risk of side effects was acceptable for one of the following:
   a) Stage II (cT2, N0) disease following cystectomy based on pathologic risk if no cisplatin neoadjuvant treatment was given and pT3, pT4a, or pN+
   b) Stage II (cT2, N0) disease following cystectomy based on pathologic risk if cisplatin neoadjuvant treatment was given and ypT2-ypT4a or ypN+
   c) Stage IIIA (cT3, N0; cT4a, N0; cT1-4a, N1) disease following cystectomy based on pathologic risk if no cisplatin neoadjuvant treatment was given and pT3, pT4a, or pN+
   d) Stage IIIA (cT3, N0; cT4a, N0; cT1-4a, N1) disease following cystectomy based on pathologic risk if cisplatin neoadjuvant treatment was given ypT2-ypT4a or ypN+; OR
5. First-line systemic therapy as a single agent in cisplatin ineligible patients who are not eligible for any platinum-containing chemotherapy or in combination with enfortumab vedotin-ejfv for one of the following:
   a) Stage II (cT2, N0) disease or stage IIIA (cT3, N0; cT4a, N0; cT1-T4a, N1) disease if the tumor is present following reassessment of tumor status 2-3 months after primary treatment with bladder preserving concurrent chemoradiotherapy and maximal TURBT or after primary treatment with radiotherapy alone, or TURBT
   b) Stage II (cT2, N0) disease or stage IIIA (cT3, N0; cT4a, N0; cT1-T4a, N1) disease if tumor is present following reassessment of tumor status 2-3 months after primary treatment with radiotherapy alone

c) Stage IIIB (cT1-T4a, N2,3) disease as downstaging systemic therapy
d) Stage IVA (cT4b, any N, M0; any T, any N, M1a) disease
e) Stage IVA (cT4b, any N, M0) disease as consolidation systemic therapy if no tumor present following reassessment of tumor status 2-3 months after primary treatment with concurrent chemoradiotherapy
f) Stage IVA (cT4b, any N, M0) disease if tumor present following reassessment of tumor status 2-3 months after primary treatment with concurrent chemoradiotherapy
g) Metastatic stage IVB (any T, any N, M1b) disease
h) Muscle invasive local recurrence or persistent disease in a preserved bladder treated with curative intent
i) Metastatic or local recurrence post cystectomy treated with curative intent; OR

6. Second-line systemic therapy as a single agent or in combination with enfortumab vedotin-ejfv for one of the following:
   a) Stage II (cT2, N0) disease or stage IIIA (cT3, N0; cT4a, N0; cT1-T4a, N1) disease if tumor is present following reassessment of tumor status 2-3 months after primary treatment with concurrent bladder preserving chemoradiotherapy and maximal TURBT
   b) Stage IIIB (cT1-T4a, N2,3) disease following progression after primary treatment with downstaging systemic therapy
   c) Stage IVA (cT4b, any N, M0) disease if tumor is present following reassessment of tumor status after primary treatment with first-line systemic therapy or concurrent chemoradiotherapy
   d) Stage IVA (any T, any N, M1a) disease if stable disease or progression following reassessment of tumor status after primary treatment with first-line systemic therapy
   e) Metastatic stage IVB (any T, any N, M1b) disease
   f) Muscle invasive local recurrence or persistent disease in a preserved bladder treated with curative intent
   g) Metastatic or local recurrence post cystectomy treated with curative intent; OR

Upper GU Tract Tumors

For **NCCN** required criteria coverage:

7. Adjuvant therapy for pathologic stage T2-4 or nodal disease (N+) of the renal pelvis or urothelial carcinoma of the ureter for one of the following:
   a) Platinum-based neoadjuvant chemotherapy not given and pT3, pT4, or pN+
   b) Platinum-based neoadjuvant chemotherapy given and ypT2-ypT4 or ypN+; OR
8. Metastatic disease in combination with enfortumab vedotin-ejfv as first-line systemic therapy; OR
9. Metastatic disease for first-line systemic therapy as a single agent in patients who are not eligible for any platinum-containing chemotherapy (useful in certain circumstances, cisplatin-ineligible); OR
10. Metastatic disease as a single agent (preferred if previous chemotherapy, no previous immunotherapy or enfortumab vedotin-ejfv) as second-line systemic therapy; OR

Urothelial Carcinoma of the Prostate

For **NCCN** required criteria coverage:

11. Primary treatment for tumors with stromal invasion as adjuvant therapy if platinum-based neoadjuvant chemotherapy not given and pT3, pT4a, pN+; OR
12. Metastatic disease in combination with enfortumab vedotin-ejfv as first-line systemic therapy; OR
13. First-line systemic therapy for metastatic disease as a single agent in patients who are not eligible for any platinum-containing chemotherapy; OR
14. Single agent for metastatic disease for second-line systemic therapy; OR
15. Therapy for metastatic disease in combination with enfortumab vedotin-ejfv as second-line systemic therapy; OR

Primary Carcinoma of the Urethra

For **NCCN** required criteria coverage:

16. Adjuvant therapy for pathologic stage T2-4 or nodal disease N1-2 disease in the male bulbar urethra for one of the following:
    a) Platinum-based neoadjuvant chemotherapy not given and pT3, pT4, or pN+
    b) Platinum-based neoadjuvant chemotherapy given and ypT2-ypT4 or ypN+; OR
17. Primary treatment as a single agent for stage T3-4, cN1-2 disease or cN1-2 palpable inguinal lymph nodes as first-line systemic therapy in patients who are not eligible for any platinum-containing chemotherapy; OR
18. Metastatic disease in combination with enfortumab vedotin-ejfv as first-line systemic therapy; OR
19. Recurrent or metastatic disease as first-line systemic therapy as a single agent in patients who are not eligible for any platinum-containing chemotherapy; OR
20. Recurrent or metastatic disease as a single agent for second-line systemic therapy; OR
21. Recurrent or metastatic disease in combination with enfortumab vedotin-ejfv as second-line systemic therapy;[8] OR

Urothelial Cancer

For **FDA** required criteria coverage:

22. In combination with enfortumab vedotin, for locally advanced or metastatic disease; OR
23. Single agent for locally advanced or metastatic disease for one of the following:
    a) Patient is not eligible for any platinum-containing chemotherapy
    b) Disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; OR
24. Single agent for patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.[2]

Bone Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

Chondrosarcoma

For **NCCN** required criteria coverage:

3. Single-agent therapy for unresectable or metastatic disease that has progressed following prior treatment and with no satisfactory alternative treatment options for one of the following:
   a) Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors
   b) Tumor mutational burden-high (TMB-H) tumors with 10 or more mutations per megabase; OR

Chordoma

For **NCCN** required criteria coverage:

4. Single-agent therapy for unresectable or metastatic disease that has progressed following prior treatment and with no satisfactory alternative treatment options for one of the following:
   a) Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors
   b) Tumor mutational burden-high (TMB-H) tumors with 10 or more mutations per megabase; OR
5. Single-agent therapy for recurrent conventional disease; OR

Ewing Sarcoma

For **NCCN** required criteria coverage:

6. Single-agent therapy for unresectable or metastatic disease that has progressed following prior treatment and with no satisfactory alternative treatment options for one of the following:
   a) Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors
   b) Tumor mutational burden-high (TMB-H) tumors with 10 or more mutations per megabase

   Note: Other primary round cell tumors of the bone (eg, CIC::DUX4, BCOR::CCNB3) can be treated like Ewing Sarcoma; OR

Osteosarcoma

For **NCCN** required criteria coverage:

7. Single-agent therapy for unresectable or metastatic disease that has progressed following prior treatment and with no satisfactory alternative treatment options for one of the following:
   a) Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors
   b) Tumor mutational burden-high (TMB-H) tumors with 10 or more mutations per megabase; OR
8. Single agent for dedifferentiated chondrosarcoma.[9]

Breast Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. High-risk early-stage triple negative disease (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery; OR
4. In combination with chemotherapy, for locally recurrent unresectable, or metastatic TNBC whose tumors express PD-L1 (CPS ≥10);[2] OR

Invasive Breast Cancer

For **NCCN** required criteria coverage:

5. Preoperative systemic therapy for patients with locally advanced c≥T2 or cN+ and M0 disease (preferred) or cT1c, cN0 triple negative breast cancer in combination with carboplatin and docetaxel for triple negative tumors; OR
6. High-risk (stage II-III) TNBC when used as part of one of of the following regimen: preoperative therapy for patients with locally advanced c≥T2 or cN+ and M0 disease, or cT1c, cN0 disease with pembrolizumab in combination with carboplatin and paclitaxel, followed by preoperative pembrolizumab in combination with cyclophosphamide and either doxorubicin or epirubicin, followed by mastectomy or breast-conserving surgery (BCS) with surgical axillary staging, followed by adjuvant single agent pembrolizumab* if ypT0N0 or pCR, or if ypT1-4,N0 or ypN≥1; OR
7. Single agent therapy for recurrent unresectable (local or regional) or stage IV (M1) disease that is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), or tumor mutational burden-high (TMB-H) tumors (≥10 muts/mb) that have progressed following prior treatment and with no satisfactory alternative treatment options for one of the following:
   a) Third-line therapy and beyond for hormone receptor positive and human epidermal growth factor receptor 2 (HER2)-negative with visceral crisis or endocrine therapy refractory or for TNBC
   b) Fourth-line and beyond for HER2-positive disease; OR
8. In combination with either albumin-bound paclitaxel, paclitaxel, or gemcitabine with carboplatin for PD-L1 positive (PD-L1 CPS ≥10) triple negative recurrent unresectable (local or regional) or stage IV (M1) disease for one of the following:
   a) First-line therapy
   b) Second and subsequent lines of therapy if PD-1/PD-L1 inhibitor has not been previously used; OR

Inflammatory Breast Cancer

For **NCCN** required criteria coverage:

9. Preoperative systemic therapy in combination with carboplatin and docetaxel for triple negative tumors; OR
10. High-risk (stage II-III) triple negative breast cancer when used as part of the following regimen: preoperative pembrolizumab in combination with carboplatin and paclitaxel,

followed by preoperative pembrolizumab in combination with cyclophosphamide and either doxorubicin or epirubicin, followed by surgery, followed by adjuvant single agent pembrolizumab

Note: There is no data on sequencing or combining adjuvant pembrolizumab with capecitabine or olaparib in patients who meet criteria for treatment with one or more of these agents. However, their sequential/combined use may be considered given high-risk of recurrence in patients with residual disease; OR

11. Single agent therapy for patients with no response to preoperative systemic therapy, or recurrent unresectable (local or regional) or stage IV (M1) disease that is MSI-H or dMMR, or tumor mutational burden-high (TMB-H) tumors (≥10 muts/mb) that have progressed following prior treatment and with no satisfactory alternative treatment options for one of the following:
    a) Third-line therapy and beyond for hormone receptor positive and HER2 with visceral crisis or endocrine therapy refractory or for TNBC
    b) Fourth-line and beyond for HER2-positive disease; OR
12. In combination with either albumin-bound paclitaxel, paclitaxel, or gemcitabine with carboplatin for PD-L1 positive (PD-L1 CPS ≥10) triple negative disease for patients with no response to preoperative systemic therapy, or recurrent unresectable (local or regional) or stage IV (M1) disease
    a) First-line therapy
    b) Second and subsequent lines of therapy if PD-1/PD-L1 inhibitor has not been previously used.[10]

Central Nervous System Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

Limited Brain Metastases

For **NCCN** required criteria coverage:

3. Single agent treatment for limited brain metastases in microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) or tumor mutational burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) tumors, or for isolated brain metastases for one of the following:
    a) Initial treatment in select cases (e.g., small asymptomatic brain metastases) for newly diagnosed or stable systemic disease or if reasonable systemic treatment options exist
    b) Recurrent brain metastases; OR
4. Single agent therapy for limited brain metastases in BRAF non-specific melanoma or PD-L1-positive (Tumor Proportion Score [TPS] ≥1%) non-small cell lung cancer for one of the following:
    a) Initial treatment in select cases (e.g., small asymptomatic brain metastases) for newly diagnosed or stable systemic disease or if reasonable systemic treatment options exist
    b) Recurrent brain metastases; OR

Extensive Brain Metastases

For **NCCN** required criteria coverage:

5. Single agent for extensive brain metastases in microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) or tumor mutational burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) tumors for isolated brain metastases for one of the following:
   a) Primary treatment in select cases (eg, small asymptomatic brain metastases)
   b) Recurrent disease with stable systemic disease or reasonable systemic treatment options; OR
6. Single agent for extensive brain metastases in BRAF non-specific melanoma or PD-L1-positive (Tumor Proportion Score [TPS] ≥1%) non-small cell lung cancer for one of the following:
   a) Primary treatment in select cases (eg, small asymptomatic brain metastases)
   b) Recurrent disease with stable systemic disease or reasonable systemic treatment options.[11]

Cervical Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. In combination therapy with chemoradiotherapy, for the treatment of patients with locally advanced cervical cancer involving the lower third of the vagina, with or without extension to pelvic sidewall, or hydronephrosis/non-functioning kidney, or spread to adjacent pelvic organs (FIGO 2014 Stage III-IVA cervical cancer); OR
4. In combination therapy with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1); OR
5. Single agent for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1);[12] OR

For **NCCN** required criteria coverage:

6. Primary treatment in combination with chemoradiation with cisplatin or carboplatin (if patient is cisplatin intolerant) for patients with FIGO 2014 stage III-IVA disease or select FIGO 2018 stage III-IVA; OR
7. First-line, second-line, or subsequent therapy as clinically appropriate (if not used previously as first-line) in combination with cisplatin or carboplatin, paclitaxel, and with or without bevacizumab and continued for maintenance therapy for PD-L1 positive (combined positive score [CPS] ≥1) for one of the following:
   a) Local/regional recurrence
   b) Stage IVB or recurrence with distant metastases

   Note: Pembrolizumab may be continued as a maintenance therapy; OR

8. Second-line or subsequent therapy as a single agent if PD-L1 positive (combined positive score [CPS] ≥1), or for microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors for one of the following:
   a) Local/regional recurrence
   b) Stage IVB or recurrence with distant metastases; OR
9. Second-line or subsequent treatment of patients with unresectable or metastatic tumor mutational burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) tumors that have progressed following prior treatment and with no satisfactory alternative treatment options; OR
10. Second-line or subsequent therapy in combination with tisotumab vedotin-tftv (useful in certain circumstances) for PD-L1 positive tumors (combined positive score [CPS] ≥ 1) if no prior immuno-oncology therapy has been received for one of the following:
    a) Locoregional recurrence
    b) Stage IVB or recurrence with distant metastases.[12]

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Non-chemoimmunotherapy (Immune Checkpoint Inhibitor) based regimen used as a single agent or in combination with ibrutinib for Richter transformation in patients with one of the following:
   a) Untreated CLL or clonally unrelated disease at initial diagnosis as additional therapy for partial response, refractory disease, or progression while on treatment with chemoimmunotherapy regimens
   b) Previously treated CLL and clonally related or clonal relation unknown as first-line treatment
   c) Previously treated CLL and clonally related or clonal relation unknown as continuation therapy for complete response until progression or as additional therapy not previously used for partial response, refractory disease, or progression while on treatment with CIT or non-CIT regimens).[13]

Colon Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Unresectable or metastatic microsatellite instability-high or mismatch repair deficient (MSI-H or dMMR);[2] OR

For **NCCN** required criteria coverage:

4. Single agent for (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation) or polymerase epsilon/delta

[POLE/POLD1] mutation with ultra-hypermutated phenotype (candidate for immunotherapy and no prior immunotherapy received) for one of the following:
   a) Locally unresectable or medically inoperable disease
   b) Primary treatment for synchronous abdominal/peritoneal metastases that are nonobstructing, or following local therapy for patients with existing or imminent obstruction
   c) Unresectable synchronous metastases or
   d) Unresectable metachronous metastases; OR
5. Single agent therapy for dMMR/MSI-H or POLE/POLD1 mutation with ultra-hypermutated phenotype [e.g., TMB >50 mut/Mb]) for one of the following:
   a) Neoadjuvant therapy in clinical T4b or bulky nodal disease
   b) Neoadjuvant therapy for resectable synchronous liver and/or lung metastases (if no previous treatment with a checkpoint inhibitor); OR
6. Initial treatment for resectable metachronous metastases if no previous immunotherapy.[14]

Cutaneous Squamous Cell Carcinoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Recurrent or metastatic disease or for locally advanced disease that is not curable by surgery or radiation.[2]

Esophageal and Esophagogastric Junction Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Locally advanced or metastatic disease (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation for one of the following:
   a) In combination with platinum-and fluoropyrimidine-based chemotherapy for patients whose tumors express PD-L1 (CPS ≥1)
   b) Single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10);[2] OR

For **NCCN** required criteria coverage:

4. Induction systemic therapy for relieving dysphagia in select patients with PD-L1 CPS ≥ 1 who are medically fit and planned for esophagectomy with cT2, N0 (high-risk lesions: lymphovascular invasion, ≥ 3cm, poorly differentiated), cT1b-cT2, N+ or cT3-cT4a, Any N disease in combination with one of the following:
   a) Oxaliplatin and capecitabine or fluorouracil
   b) Cisplatin and capecitabine or fluorouracil; OR

5. Induction systemic therapy for relieving dysphagia in select patients with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors (independent of PD-L1 status) who are medically fit and planned for esophagectomy with cT2, N0 (high-risk lesions: lymphovascular invasion, ≥ 3cm, poorly differentiated), cT1b-cT2, N+, or cT3-cT4a, Any N disease as a single agent or in combination with oxaliplatin and capecitabine or fluorouracil; OR
6. Neoadjuvant or perioperative immunotherapy as a single agent for adenocarcinoma if the tumor is MSI-H or dMMR for one of the following:
   a) Primary treatment in patients who are medically fit for surgery with cT2, N0 (high-risk lesions: lymphovascular invasion, ≥ 3cm, poorly differentiated), cT1b-cT2, N+ or cT3-cT4a, any N disease
   b) Postoperative management following R0 resection in patients who have received preoperative therapy with the same regimen; OR
7. Palliative therapy for patients who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease and a Karnofsky performance score ≥60% or an ECOG performance score ≤2 as first-line therapy for one of the following:
   a) HER2 overexpression negative adenocarcinoma and PD-L1 CPS ≥ in combination for one of the following:
      i. Oxaliplatin and fluorouracil or capecitabine (if no prior checkpoint inhibitor or no prior tumor progression while on therapy with a checkpoint inhibitor
      ii. Cisplatin and fluorouracil or capecitabine (if no prior checkpoint inhibitor or no prior tumor progression while on therapy with a checkpoint inhibitor); OR
   b) Squamous cell carcinoma with PD-L1 CPS ≥ 1 for one of the following:
      i. Oxaliplatin and fluorouracil or capecitabine (if no prior checkpoint inhibitor or no prior tumor progression while on therapy with a checkpoint inhibitor
      ii. Cisplatin and fluorouracil or capecitabine (if no prior checkpoint inhibitor or no prior tumor progression while on therapy with a checkpoint inhibitor); OR
   c) HER2 overexpression positive adenocarcinoma and PD-L1 CPS ≥ in combination for one of the following:
      i. Fluorouracil, cisplatin or oxaliplatin, and trastuzumab (if no prior checkpoint inhibitor or no tumor progression while on therapy with a checkpoint inhibitor)
      ii. Capecitabine, cisplatin or oxaliplatin, and trastuzumab (if no prior checkpoint inhibitor or no tumor progression while on therapy with a checkpoint inhibitor); OR
8. Palliative therapy for patients who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease and Karnofsky performance score ≥60% or ECOG performance score ≤2 and if no prior checkpoint inhibitor or no tumor progression while on therapy with a checkpoint inhibitor for one of the following:
   a) First-line therapy as a single agent or in combination with oxaliplatin and fluorouracil or capecitabine if microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumor and independent of PD-L1 status
   b) Second-line therapy as a single agent for esophageal squamous cell carcinoma (SCC) with PD-L1 expression by CPS of ≥10
   c) Second-line or subsequent therapy as a single agent for microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors
   d) Second-line or subsequent therapy as a single agent for tumor mutational burden (TMB) high (≥ 10 mutations/megabase) tumors.[15]

Gastric Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. In combination with trastuzumab, fluoropyrimidine, and platinum-containing chemotherapy, for first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1); OR
4. In combination with fluoropyrimidine and platinum-containing chemotherapy, for first-line treatment of locally advanced unresectable or metastatic HER2 negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1);[2] OR

For **NCCN** required criteria coverage:

5. Palliative therapy for patients who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease (including peritoneal only metastatic disease, including positive cytology) with HER2 overexpression positive adenocarcinoma with PD-L1 CPS ≥ 1 and Karnofsky performance score ≥60% or ECOG performance score ≤2 as first-line therapy in combination with one of the following:
   a) Cisplatin, trastuzumab and fluorouracil or capecitabine (if no prior checkpoint inhibitor therapy or no tumor progression while on therapy with a checkpoint inhibitor)
   b) Oxaliplatin, trastuzumab and fluorouracil or capecitabine (if no prior checkpoint inhibitor therapy or no tumor progression while on therapy with a checkpoint inhibitor); OR
6. Palliative therapy for HER2 overexpression negative patients and PD-L1 CPS ≥ 1 who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease (including peritoneal only metastatic disease, including positive cytology) and Karnofsky performance score ≥60% or ECOG performance score ≤2 as first-line therapy in combination with one of the following:
   a) Oxaliplatin and fluorouracil or capecitabine (if no prior checkpoint inhibitor therapy or no tumor progression while on therapy with a checkpoint inhibitor)
   b) Cisplatin and fluorouracil or capecitabine (if no prior checkpoint inhibitor therapy or no tumor progression while on therapy with a checkpoint inhibitor); OR
7. Palliative therapy for patients with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors (independent of PD-L1 status) who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease (including peritoneal only metastatic disease, including positive cytology) and a Karnofsky performance score ≥60% or an ECOG performance score ≤2 as preferred first-line therapy for one of the following:
   a) Single agent (if no prior checkpoint inhibitor therapy or no tumor progression while on therapy with a checkpoint inhibitor)
   b) In combination with oxaliplatin and fluorouracil or capecitabine (if no prior checkpoint inhibitor therapy or no tumor progression while on therapy with a checkpoint inhibitor); OR
8. Palliative therapy for locoregional disease in patients who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease (including peritoneal only metastatic disease, including positive cytology) and Karnofsky performance score

≥60% or ECOG performance score ≤2 as second-line or subsequent therapy as a single agent for microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors or tumor mutational burden (TMB) high (≥ 10 mutations/megabase) tumors (if no prior checkpoint inhibitor therapy or no tumor progression while on therapy with a checkpoint inhibitor); OR

9. Primary treatment for patients who are medically fit for surgery but with surgically unresectable locoregional HER2 overexpression positive adenocarcinoma and PD-L1 CPS ≥ 1 is given in combination with one of the following:
   a) Cisplatin, trastuzumab and fluorouracil or capecitabine
   b) Oxaliplatin, trastuzumab and fluorouracil or capecitabine; OR
10. Primary treatment for patients who are medically fit for surgery but with surgically unresectable locoregional HER2 overexpression negative disease and a PD-L1 CPS ≥ 1 in combination with one of the following:
   a) Oxaliplatin and fluorouracil or capecitabine
   b) Cisplatin and fluorouracil or capecitabine; OR
11. Primary treatment for patients with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors (independent of PD-L1 status) who are medically fit for surgery but with surgically unresectable locoregional disease for one of the following:
   a) Single agent
   b) In combination with oxaliplatin and fluorouracil or capecitabine; OR
12. Neoadjuvant or perioperative immunotherapy as a single agent for patients with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors for one of the following:
   a) Primary treatment prior to surgery for potentially resectable locoregional disease (cT2 or higher, any N) if medically fit for surgery
   b) Postoperative management following R0 resection in patient who have received systemic therapy.[16]

Gestational Trophoblastic Neoplasia

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single agent therapy for multiagent chemotherapy-resistant disease for one of the following:
   a) High-risk disease
   b) Recurrent or progressive intermediate trophoblastic tumor (placental site trophoblastic tumor or epithelioid trophoblastic tumor.[17]

Head and Neck Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Resectable locally advanced disease whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1], as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without cisplatin, and then as a single agent; OR
4. In combination with platinum and fluorouracil (FU) for the first-line treatment of patients with metastatic or unresectable, recurrent disease; OR
5. Single agent for the first-line treatment of patients with metastatic or unresectable, recurrent disease whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1]; OR
6. Single agent for the treatment of patients with recurrent or metastatic disease with disease progression on or after platinum-containing chemotherapy;[2] OR

Oral Cavity (Including Mucosal Lip)

For **NCCN** required criteria coverage:

7. Neoadjuvant therapy as a single agent if PD-L1 CPS ≥ 1 for stage III-IVa disease for one of the following:
   a) T3, N0
   b) T1-3, N1-2
   c) T4a, N0-2; OR
8. Neoadjuvant pembrolizumab (if PD-L1 CPS ≥ 1) and resection, used as adjuvant therapy as a component of pembrolizumab + radiation therapy (with cisplatin if extranodal extension and/or positive margin) followed by adjuvant pembrolizumab for stage III-IVa disease for one of the following:
   a) T3, N0
   b) T1-3, N1-2
   c) T4a, N0-2; OR

Oropharynx

For **NCCN** required criteria coverage:

9. Neoadjuvant therapy as a single agent if PD-L1 CPS ≥ 1 for p16-negative stage III-IVa disease for one of the following:
   a) T1-2, N1
   b) T3-4a, N0-1
   c) T1-4a, N2; OR
10. Neoadjuvant pembrolizumab (if PD-L1 CPS ≥ 1) and resection, used as adjuvant therapy as a component of pembrolizumab + radiation therapy (with cisplatin if extranodal extension and/or positive margin) followed by adjuvant pembrolizumab for p16-negative stage III-IVa disease for one of the following:
    a) T1-2, N1
    b) T3-4a, N0-1
    c) T1-4a, N2; OR

Hypopharynx

For **NCCN** required criteria coverage:

11. Neoadjuvant therapy as a single agent if PD-L1 CPS ≥ 1 for stage III-IVa disease for one of the following:
    a) T2, N1-2 or T3, N0-2 (if requiring amenable to pharyngectomy with partial or total laryngectomy); T1, N1-2
    b) T4a, N0-2; OR
12. Neoadjuvant pembrolizumab (if PD-L1 CPS ≥ 1) and resection, used as adjuvant therapy as a component of pembrolizumab + radiation therapy (with cisplatin if extranodal extension and/or positive margin) followed by adjuvant pembrolizumab for stage III-IVa disease for one of the following:
    a) T2, N1-2 or T3, N0-2 (if requiring amenable to pharyngectomy with partial or total laryngectomy); T1, N1-2
    b) T4a, N0-2; OR

Nasopharynx

For **NCCN** required criteria coverage:

13. First-line systemic therapy in combination with cisplatin and gemcitabine for T1-4, N0-3, metastatic (M1) disease for one of the following:
    a) Oligometastatic disease and performance status (PS) 0-2
    b) Widely metastatic disease and good PS (0-2); OR
14. Subsequent-line single agent systemic therapy in combination with cisplatin and gemcitabine for T1-4, N0-3, M1 disease, if previously treated, for one of the following:
    a) Oligometastatic disease and PS 0-2
    b) Widely metastatic disease and good PS (0-2); OR
15. Subsequent-line single agent systemic therapy if previously treated, PD-L1–positive, recurrent or metastatic disease, or for tumor mutational burden-high (TMB-H) tumors (≥ 10 mut/Mb) for T1-4, N0-3, M1 disease for one of the following:
    c) Oligometastatic disease and PS 0-2
    d) Widely metastatic disease and a good PS 0-2; OR

Glottic Larynx

For **NCCN** required criteria coverage:

16. Neoadjuvant therapy as a single agent if PD-L1 CPS ≥ 1 for stage III-IVa disease for one of the following:
    a) T3, N0-2 requiring (amenable to) total laryngectomy
    b) T4a, N0-2; OR
17. Following neoadjuvant pembrolizumab (if PD-L1 CPS ≥ 1) and resection, used as adjuvant therapy as a component of pembrolizumab + radiation therapy (with cisplatin if extranodal extension and/or positive margin), followed by adjuvant pembrolizumab for stage III-IVa disease for one of the following:
    a) T3, N0-2 requiring (amenable to) total laryngectomy,
    b) T4a, and N0-2; OR

Supraglottic Larynx

For **NCCN** required criteria coverage:

18. Neoadjuvant therapy as a single agent if PD-L1 CPS ≥ 1 for stage III-IVa disease for one of the following:
    a) T3, N0 requiring (amenable to) total laryngectomy
    b) T1-2, N1-2 and selected T3, N1 amenable to larynx preserving (conservation) surgery
    c) T3, N1-2 requiring (amenable to) total laryngectomy
    d) T4a, N0-2; OR
19. Neoadjuvant pembrolizumab (if PD-L1 CPS ≥ 1) and resection, used as adjuvant therapy as a component of pembrolizumab + radiation therapy (with cisplatin if extranodal extension and/or positive margin) followed by adjuvant pembrolizumab for stage III-IVa disease for one of the following:
    a) T3, N0 requiring (amenable to) total laryngectomy
    b) T1-2, N1-2 and selected T3, N1 amenable to larynx preserving surgery
    c) T3, N1-2 requiring amenable to total laryngectomy
    d) T4a, N0-2; OR

Very Advanced Head and Neck Cancer

For **NCCN** required criteria coverage:

20. Systemic therapy as a single agent for non-nasopharyngeal cancer tumors that express PD-L1 with CPS ≥1 for one of the following:
    a) First-line option for a PS of 3 for newly diagnosed disease for one of the following:
        i. T4b, N0-3, M0 disease
        ii. Unresectable nodal disease with no metastases
        iii. Non-metastatic disease for patients who are unfit for surgery
    b) First-line or alternate subsequent-line option, if not previously used, for a PS 0-3 for M1 disease at initial presentation
    c) First-line or subsequent-line option, if not previously used, for a PS 3 and unresectable locoregional recurrence without prior radiation therapy (RT) or unresectable persistent disease without prior RT
    d) First-line or alternate subsequent-line option, if not previously used, for a PS 0-3 for one of the following:
        i. Unresectable locoregional recurrence with prior RT
        ii. Unresectable second primary with prior RT
        iii. Unresectable persistent disease with prior RT
        iv. Recurrent/persistent disease with distant metastases; OR
21. Single agent for non-nasopharyngeal cancer in patients with MSI-H, dMMR, TMB-H (≥10 mut/Mb) tumors for one of the following:
    a) First-line option for a PS 3 for a newly diagnosed disease for one of the following:
        i. T4b, N0-3, M0 disease
        ii. newly diagnosed unresectable nodal disease with no metastases
        iii. newly diagnosed non-metastatic disease for patients who are unfit for surgery
    b) First-line or alternate subsequent-line option for a PS 0-3 for metastatic (M1) disease at initial presentation
    c) First-line or subsequent-line option for a PS 3 and unresectable locoregional recurrence without prior RT or unresectable persistent disease without prior RT
    d) First-line or alternate subsequent-line option for a PS 0-3 for one of the following:
        i. Unresectable locoregional recurrence with prior RT
        ii. Unresectable second primary with prior RT

iii. Unresectable persistent disease with prior RT
iv. Recurrent/persistent disease with distant metastases; OR

22. Systemic therapy as a first-line or subsequent-line option in patients with non-nasopharyngeal cancer and a PS 0-1 for one of the following:
    a) M1 disease at initial presentation
    b) Recurrent/persistent disease with distant metastases
    c) Unresectable locoregional recurrence with prior RT
    d) Unresectable second primary with prior RT
    e) Unresectable persistent disease with prior RT

    Given in combination with one of the following:
    i. Fluorouracil and carboplatin
    ii. Fluorouracil and cisplatin
    iii. Docetaxel and carboplatin
    iv. Docetaxel and cisplatin
    v. Paclitaxel and carboplatin
    vi. Paclitaxel and cisplatin
    vii. Cetuximab; OR
23. In combination systemic therapy in non-nasopharyngeal cancer for resectable locoregional recurrence or persistent disease without prior RT when given with one of the following:
    a) Fluorouracil and carboplatin
    b) Fluorouracil and cisplatin
    c) Docetaxel and carboplatin
    d) Docetaxel and cisplatin
    e) Paclitaxel and carboplatin
    f) Paclitaxel and cisplatin
    g) Cetuximab; OR
24. Single agent subsequent-line option for non-nasopharyngeal cancer if disease progression on or after platinum therapy in patients with one of the following:
    a) PS 0-3 and persistent or progressive M1 at initial presentation following first-line therapy
    b) PS 3 and unresectable locoregional recurrence without prior RT or unresectable persistent disease without prior RT
    c) PS 0-3 for one of the following:
    i. Unresectable locoregional recurrence with prior RT
    ii. Unresectable second primary with prior RT
    iii. Unresectable persistent disease with prior RT
    iv. Recurrent/persistent disease with distant metastases; OR
25. First-line or subsequent-line option in patients with nasopharyngeal cancer and a PS 0-1 for one of the following:
    a) Unresectable locoregional recurrence with prior RT
    b) Unresectable second primary with prior RT
    c) Unresectable persistent disease with prior RT
    d) Recurrent/persistent disease with distant metastases in combination with cisplatin and gemcitabine

    Note: If not previously used, may be considered in subsequent-lines of therapy; OR

26. Single agent subsequent-line option in patients with TMB-H (≥10 mut/Mb) or for previously treated PD-L1-positive nasopharyngeal cancer and a PS of 0-3 for one of the following:

a) Unresectable locoregional recurrence with prior RT
b) Unresectable second primary with prior RT,
c) Unresectable persistent disease with prior RT
d) Recurrent/persistent disease with distant metastases; OR

Salivary Gland Tumors

For **NCCN** required criteria coverage:

27. Single-agent systemic therapy for MSI-H, dMMR, TMB-H (≥10 mut/Mb), or PD-L1 positive recurrent disease for one of the following:
    a) Distant metastases in patients with a PS of 0-3
    b) Unresectable locoregional recurrence or second primary with prior RT.[18]

Hepatocellular Carcinoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Disease secondary to hepatitis B who have received prior systemic therapy other than a PD1/PD-L1-containing regimen;[2] OR

For **NCCN** required criteria coverage:

4. First-line systemic therapy as a single agent for those who may or may not have microsatellite instability high (MSI-H) tumors and have one of the following:
    a) Liver-confined, unresectable disease, and are deemed ineligible for transplant
    b) Extrahepatic/metastatic disease and are deemed ineligible for resection, transplant, or locoregional therapy; OR
5. Subsequent-line systemic therapy as a single agent if progression on or after systemic therapy in patients who have not been previously treated with a checkpoint inhibitor or who may or may not have MSI-H tumors.[19]

Hodgkin Lymphoma

1. Prescribed by or in consultation with an oncologist; AND

Classical Hodgkin Lymphoma (cHL)

For **FDA** required criteria coverage:

2. Relapsed or refractory disease for patients at least 18 years of age; OR
3. Refractory disease for patients less than 18 years of age that have relapsed after 2 or more lines of therapy;[2] OR

For **NCCN** required criteria coverage:

4. At least 18-60 years of age; AND
5. Second-line systemic therapy for primary refractory disease or suspected relapse (within any time frame) and are a candidate for high-dose therapy and autologous stem cell rescue (HDT/ASCR) in combination with one of the following:
   a) GVD (gemcitabine, vinorelbine, liposomal doxorubicin)
   b) ICE (ifosfamide, carboplatin, etoposide) (preferred if no prior checkpoint inhibitor exposure); OR
6. Second-line systemic therapy for primary refractory disease or suspected relapse and not a candidate for high-dose therapy and autologous stem cell rescue (HDT/ASCR) if no prior checkpoint inhibitor (CPI) or progression after ≥3 months of a CPI-containing regimen for one of the following:
   a) In combination with GVD (gemcitabine, vinorelbine, liposomal doxorubicin)
   b) In combination with ICE (ifosfamide, carboplatin, etoposide)
   c) Single agent palliative therapy; OR
7. Second-line systemic therapy for primary refractory disease or suspected relapse and the patient is not a candidate for high-dose therapy and autologous stem cell rescue (HDT/ASCR) if prior checkpoint inhibitor (CPI) or progression after ≥3 months of a CPI or BV-containing regimen containing regimen for one of the following:
   a) In combination with GVD (gemcitabine, vinorelbine, liposomal doxorubicin)
   b) In combination with ICE (ifosfamide, carboplatin, etoposide)
   c) Single agent palliative therapy; OR
8. Subsequent systemic therapy (if not previously used) in combination with one off the following:
   a) GVD (gemcitabine, vinorelbine, liposomal doxorubicin)
   b) ICE (ifosfamide, carboplatin, etoposide)

   The above regimens are used for primary refractory disease or suspected relapse for one of the following:
      i. Within 3 months and a candidate for high-dose therapy and autologous stem cell rescue (HDT/ASCR) (only if Deauville 4 or 5 following restaging with FDG-PET/CT)
      ii. After ≥3 months and candidate for HDT/ASCR
      iii. Not a candidate for HDT/ASCR; OR
9. Subsequent systemic therapy (if not previously used) for primary refractory disease or suspected relapse and not a candidate for high-dose therapy and autologous stem cell rescue (HDT/ASCR) as a single agent palliative therapy option; OR
10. Disease refractory to at least 3 prior lines of subsequent therapy in combination with one of the following:
    a) Decitabine
    b) Vorinostat; OR
11. Single agent post-allogeneic hematopoietic cell transplant; OR
12. Primary treatment for patients any age and not a candidate for anthracycline as a single agent + ISRT (if contraindications to brentuximab vedotin) in adults aged>60 years or adults unfit for intensive therapy.[20]

Kaposi Sarcoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. As a single agent given alone (no HIV) or with antiretroviral therapy (ART) for people with HIV (PWH) for subsequent systemic therapy for relapsed/refractory advanced disease that has progressed on or not responded to first-line systemic therapy, and progressed on alternate first-line systemic therapy

   Notes:
   1. Immune checkpoint inhibitors should not be used in patients with multicentric Castleman disease (MCD) or KSHV–associated inflammatory cytokine syndrome (KICS) due to risk of flare of these conditions. If the patient has a history of KSHV-associated diseases, ICIs should be used with caution and consideration of more frequent monitoring for signs and symptoms of KICS or MCD
   2. Advanced disease refers to T1 disease, extensive T0 cutaneous disease, or nodal disease.[21]

Kidney Cancer (Renal Cell Carcinoma)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. In combination with axitinib for the first-line treatment of advanced disease; OR
4. In combination with lenvatinib for the first-line treatment of adult patients with advanced disease; OR
5. Adjuvant treatment for intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions;[2] OR

For **NCCN** required criteria coverage:

6. Single agent adjuvant treatment for clear cell histology for one of the following:
   a) Nephrectomy or SBRT in stage II disease (grade 4, with or without sarcomatoid features)
   b) Nephrectomy or SBRT in stage III disease
   c) Metastasectomy with complete resection of disease within 1 year of nephrectomy for stage IV or relapsed disease; OR
7. Adjuvant single agent treatment following nephrectomy for resectable stage IV (T4, M0) disease with clear cell histology; OR
8. In combination with axitinib for stage IV or relapsed disease with clear cell histology for one of the following:
   a) First-line therapy
   b) Subsequent therapy if immuno-oncology therapy naïve
   c) Subsequent therapy if prior history includes immuno-oncology therapy; OR
9. In combination with lenvatinib for stage IV or relapsed disease for one of the following:
   a) First-line therapy for clear cell histology
   b) Subsequent therapy for clear cell histology if immuno-oncology therapy naive
   c) Subsequent therapy for clear cell histology if prior history includes immuno-oncology therapy

d) Systemic therapy for non-clear cell histology; OR

10. Single-agent therapy for stage IV or relapsed disease as systemic therapy for non-clear cell histology

Note: If first-line therapy and stage IV, then M1 or unresectable T4, M0 only.[22]

Melanoma

1. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

2. At least 18 years of age; AND
3. Unresectable or metastatic diseases; OR
4. At least 12 years of age; AND
5. Adjuvant treatment for stages IIB, IIC, or III following complete resection;[2] OR

Cutaneous

For **NCCN** required criteria coverage:

6. At least 18 years of age; AND
7. Adjuvant systemic therapy option as a single agent for pathologically staged IIB/IIC disease following a wide excision alone or a wide excision with negative sentinel lymph node (SLN) biopsy; OR
8. Adjuvant systemic therapy option as a single agent for one of the following:
   a) Stage IIIB/C/D disease following a wide excision alone or a wide excision with negative sentinel lymph node (SLN) biopsy after microscopic satellites are found in the biopsy specimen from primary lesion
   b) Stage IIIB/C/D disease if SLN negative or SLN biopsy not performed after microscopic satellites found in the wide excision specimen
   c) Resected stage III sentinel node positive disease (based on risk of recurrence) during radiographic surveillance or after completion lymph node dissection (CLND)
   d) Stage III disease with clinically positive node(s) following a wide excision of the primary tumor with therapeutic lymph node dissection (TLND)
   e) Stage III disease with clinical satellite/in-transit metastases if no evidence of disease (NED) after a complete excision to clear margins or consider if NED after initial treatment with local or regional therapy
   f) Local satellite/in-transit recurrence if NED after complete excision to clear margins or consider if NED after initial treatment with local or regional therapy
   g) Resectable disease limited to nodal recurrence following excision of the recurrence with TLND
   h) If NED following metastasis-directed therapy (complete resection, stereotactic ablative therapy, or T-VEC/intralesional therapy) or systemic therapy followed by resection for oligometastatic disease; OR
9. Neoadjuvant systemic therapy option as a single agent for one of the following:
   a) Primary treatment for stage III clinically positive, resectable nodal disease
   b) Initial and/or subsequent treatment for limited resectable stage III disease with clinical satellite/in-transit metastases

c) Initial and/or subsequent treatment for limited resectable local satellite/in-transit recurrence
d) Resectable disease limited to nodal recurrence; OR

10. First-line systemic therapy option for metastatic or unresectable disease for one of the following:
    a) Single agent
    b) In combination with low dose ipilimumab

    Note: Metastatic disease includes stage III unresectable/borderline resectable disease with clinically positive node(s) or clinical satellite/in-transit metastases, as well as unresectable/borderline resectable local satellite/in-transit recurrence, unresectable nodal recurrence, and widely disseminated distant metastatic disease; OR

11. Second-line or subsequent systemic therapy option for metastatic or unresectable disease for disease progression, intolerance, and/or projected risk of progression with BRAF-targeted therapy for one of the following:
    a) Single agent
    b) Combination with low-dose ipilimumab for disease progression following anti-PD-1 therapy
    c) Re-induction therapy as a single agent if prior anti-PD-1 therapy resulted in disease control (complete response, partial response, or stable disease) with no residual toxicity, and disease progression/relapse occurred >3 months after treatment discontinuation
    d) Re-induction therapy in combination with low-dose ipilimumab if prior combination ipilimumab/anti-PD-1 therapy resulted in disease control (complete response, partial response, or stable disease) and no residual toxicity, and disease progression/relapse occurred >3 months after treatment discontinuation

    Note: Metastatic disease includes stage III unresectable/borderline resectable disease with clinically positive node(s) or clinical satellite/in-transit metastases, as well as unresectable/borderline resectable local satellite/in-transit recurrence, unresectable nodal recurrence, and widely disseminated distant metastatic disease; OR

12. Subsequent systemic therapy option in combination with lenvatinib for metastatic or unresectable disease that has progressed following treatment with anti-PD-1/PD-L1-based therapy, including in combination with anti-CTLA-4 for ≥2 doses; OR
13. Metastatic or unresectable disease in combination with trametinib and dabrafenib if BRAF V600 mutation positive for one of the following:
    a) Second-line or subsequent therapy for disease progression, intolerance, and/or projected risk of progression with BRAF-targeted therapy
    b) Re-induction therapy if prior combination BRAF/MEK + PD(L)-1 checkpoint inhibition resulted in disease control (complete response, partial response, stable disease) with no residual toxicity, and disease progression/relapse >3 months after treatment discontinuation;[23] OR

Uveal

For **NCCN** required criteria coverage:

14. Single agent therapy for metastatic or unresectable disease.[24]

Merkel Cell Carcinoma

1. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

2. For adult or pediatric patients; AND
3. Recurrent locally advanced or metastatic disease;[2] OR

For **NCCN** required criteria coverage:

4. At least 18 years of age; OR
5. Single agent for one of the following:
   a) Primary clinical N0 locally advanced disease if curative surgery and curative radiation therapy (RT) are not feasible
   b) Recurrent N0 locally advanced disease if curative surgery and curative RT are not feasible or for progression on neoadjuvant nivolumab
   c) Primary N+, M0 regional disease with biopsy positive draining nodal basin if curative surgery and curative RT are not feasible
   d) Recurrent N+ regional disease if curative surgery and curative RT are not feasible
   e) M1 disseminated disease.[25]

Mesothelioma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

Peritoneal

For **NCCN** required criteria coverage:

3. In combination with cisplatin or carboplatin and pemetrexed for first-line systemic therapy for one of the following:
   a) Adjuvant treatment of medically operable and a complete cytoreduction is achievable; with pre-operative low risk features following cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC), if there is the presence of any surgical/pathologic high-risk features
   b) Medically operable disease and a complete cytoreduction is achievable, with pre-operative low risk features if progression is noted following CRS + HIPEC and if no prior adjuvant systemic therapy was given
   c) Medically inoperable disease; complete cytoreduction is not achievable, or there is a presence of any high-risk features

   Notes:
   1. May also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma
   2. Low-risk features: epithelioid histology; absence of any high-risk features

3. High-risk features: biphasic/sarcomatoid histology, nodal metastasis, Ki-67 >9%, thrombocytosis, PS=2, bicavitary disease, high disease burden/incomplete cytoreduction (peritoneal cancer index [PCI] >17, completeness of cytoreduction [cc] score >1);[26] OR

Pleural

For **FDA** required criteria coverage:

4. In combination with pemetrexed and platinum chemotherapy for first-line treatment unresectable advanced or metastatic disease;[2] OR

For **NCCN** required criteria coverage:

5. Induction systemic therapy in combination with cisplatin or carboplatin and pemetrexed prior to a surgical exploration for clinical stage I disease and epithelioid histology; OR
6. First-line systemic therapy in combination with cisplatin or carboplatin and pemetrexed for one of the following:
   a) Stage I disease with epithelioid histology as initial treatment
   b) Stage II-IV with epithelioid histology, sarcomatoid, or biphasic histology (any stage), or if medically inoperable as initial treatment
   c) Stage I disease with epithelioid histology following surgical exploration if induction systemic therapy was not given

Notes:
1. May also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma
2. Best supportive care is recommended for patients presenting with PS 3-4.[27]

Microsatellite Instability-High or Mismatch Repair Deficient Cancer

1. For adult or pediatric patients; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and with no satisfactory alternative treatment options.[2]

Neuroendocrine and Adrenal Tumors

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Unresectable locally advanced/metastatic disease with favorable biology (e.g., relatively low Ki-67 [<55%], slow growing, positive SSTR-based PET imaging) that has clinically significant tumor burden or evidence of disease progression with mismatch repair-deficient

(dMMR), microsatellite instability-high (MSI-H), or tumor mutational burden high (TMB-H) (≥10 mut/Mb) that has progressed following prior treatment and has no satisfactory alternative treatment options; OR
4. Locally advanced/metastatic disease with unfavorable biology (relative high Ki-67 [≥55%], rapid growth rate, negative SSTR-based PET imaging) with mismatch repair-deficient (dMMR), microsatellite instability-high (MSI-H), or tumor mutational burden high (TMB-H) (≥10 mut/Mb) that has progressed following prior treatment and with no satisfactory alternative treatment options; OR
5. Locoregional unresectable or metastatic adrenocortical carcinoma with or without mitotane; OR
6. Subsequent therapy for locoregional unresectable or metastatic disease as treatment for patients with dMMR, MSI-H, or advanced TMB-H (≥10 mut/Mb) tumors that have progressed following prior treatment and with no satisfactory alternative treatment options.[28]

Non-Small Cell Lung Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. In combination with pemetrexed and platinum chemotherapy for first-line for metastatic nonsquamous disease with no EGFR or ALK genomic tumor aberrations; OR
4. In combination with carboplatin and either paclitaxel or paclitaxel protein-bound for first-line metastatic squamous disease; OR
5. Single agent for first-line treatment with expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] and no EGFR or ALK genomic tumor aberrations for one of the following:
   a) Stage III when the patient is not a candidate for surgical resection or definitive chemoradiation
   b) Metastatic disease; OR
6. Single agent for metastatic disease and tumors express PD-L1 (TPS ≥1%) with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on therapy for these aberrations prior to receiving pembrolizumab; OR
7. Resectable (tumors ≥4 cm or node positive) disease in combination with platinum-containing chemotherapy as neoadjuvant treatment and then continued as a single agent for adjuvant treatment after surgery; OR
8. Single agent for adjuvant treatment following a resection and platinum-based chemotherapy for patient with stage IB (T2a ≥4 cm), II, or IIIA;[2] OR

For **NCCN** required criteria coverage:

9. Neoadjuvant systemic therapy for resectable (tumors ≥4 cm or node positive) disease in patients who are candidates for immune checkpoint inhibitors and given in combination with one of the following:
   a) Pemetrexed and cisplatin for nonsquamous cell histology
   b) Gemcitabine and cisplatin for squamous cell histology

The above regimen are used for one of the following:

i. Operable clinical stage IB (T2a, N0), stage II (T1abc-2ab, N1 or T2b, N0), stage IIB (T3, N0), or stage IIIA (T3, N1) disease with pathologic N0 or N1 disease
ii. Clinical presentation of chest wall, trachea/carina, mediastinum, or diaphragm; T3 invasion, N0-1; resectable T4 invasion, N0-1 disease
iii. Clinical presentation of resectable stage IIIA (T4 [size], N0-1)
iv. Operable T2a-3, N0 or T1-3, N1 nodes positive, M0 findings on mediastinal biopsy
v. T1-3, N2 nodes positive and M0 findings on mediastinal biopsy
vi. Clinical presentation of separate pulmonary nodule(s), same lobe (T3, N0-1), or ipsilateral non-primary lobe (T4, N0-1); OR

10. Single-agent systemic therapy for patients with completely resected tumors ≥ 4 cm or node positive disease with stages IB-IIIA, IIIB (T3-4, N2) that is negative for EGFR exon 19 deletion or exon 21 L858R mutations, or ALK rearrangements, and who received previous adjuvant chemotherapy and with no contraindications to immune checkpoint inhibitors; OR
11. Single-agent systemic therapy for those with completely resected tumors ≥ 4 cm or node positive NSCLC stages IB-IIIA, IIIB (T3-4, N2) who received previous neoadjuvant pembrolizumab plus chemotherapy; OR
12. First- line therapy for recurrent, advanced, or metastatic disease for PD-L1 expression-positive (≥1%) tumors that are negative for actionable molecular biomarkers (may be KRAS G12C mutation positive) and no contraindications to PD-1 or PD-L1 inhibitors and a performance status 0-2 for one of the following:
    a) Single agent
    b) In combination with pemetrexed and either carboplatin or cisplatin for nonsquamous cell histology
    c) In combination with carboplatin and either paclitaxel or albumin-bound paclitaxel for squamous cell histology; OR
13. Continuation maintenance therapy for recurrent, advanced, or metastatic disease for PD-L1 expression positive (≥1%) tumors that are negative for actionable molecular biomarkers (may be KRAS G12C mutation positive) and no contraindications to PD-1 or PD-L1 inhibitors and a performance status 0-2, who achieve tumor response or stable disease following systemic or first-line therapy for one of the following:
    a) Single agent if pembrolizumab monotherapy was given first-line for nonsquamous cell histology
    b) Combination with pemetrexed if given first-line as part of a pembrolizumab/pemetrexed treatment and either cisplatin or carboplatin regimen for nonsquamous cell histology
    c) Single agent if pembrolizumab was given as monotherapy or as part of a pembrolizumab/carboplatin/(paclitaxel or albumin-bound paclitaxel) regimen for squamous cell histology; OR
14. Recurrent, advanced, or metastatic disease for patients with a performance status 0-2 and no contraindications to PD-1 or PD-L1 inhibitors and no EGFR exon 19 deletion or L858R; ALK, RET, or ROS1 rearrangements in combination with one of the following:
    a) Pemetrexed and either carboplatin or cisplatin for nonsquamous cell histology
    b) Carboplatin and either paclitaxel or albumin-bound paclitaxel for squamous cell histology

    The above regimens are used for one of the following:
    i. Initial systemic therapy for PD-L1 <1% and negative for actionable molecular biomarkers (maybe KRAS G12C mutation positive)

ii. First-line therapy for EGFR exon 20 insertion mutation positive tumors
iii. First-line or subsequent therapy for BRAF V600E mutation positive tumors
iv. First-line or subsequent therapy for NTRK1/2/3 gene fusion positive tumors
v. First-line or subsequent therapy for MET exon 14 skipping mutation positive tumors
vi. First-line therapy for ERBB2 (HER2) mutation positive tumors
vii. First-line therapy for NRG1 gene fusion positive tumors
viii. Subsequent therapy for EGFR S768I, L861Q, and/or G719X mutation positive tumors and prior afatinib, osimertinib, erlotinib, gefitinib, or dacomitinib therapy; OR

14. Continuation maintenance therapy in combination with pemetrexed if given first line as part of a pembrolizumab/pemetrexed and either cisplatin or carboplatin regimen for recurrent, advanced, or metastatic disease with PD-L1 expression <1% tumors that are negative for actionable molecular biomarkers (may be KRAS G12C mutation positive) and no contraindications to PD-1 or PD-L1 inhibitors, and have nonsquamous cell histology in those with performance status 0-2, who achieve tumor response or stable disease following initial systemic therapy; OR
15. Single-agent continuation maintenance therapy if given first line as part of a pembrolizumab/carboplatin/(paclitaxel or albumin-bound paclitaxel) regimen for recurrent, advanced, or metastatic disease with PD-L1 expression <1% tumors that are negative for actionable molecular biomarkers (may be KRAS G12C mutation positive) and with no contraindications to PD-1 or PD-L1 inhibitors, and squamous cell histology, in patients with a performance status 0-2 who achieve tumor response or stable disease following initial systemic therapy; OR
16. Single agent as subsequent therapy for recurrent, advanced, or metastatic disease if no contraindications to PD-1 or PD-L1 inhibitors in patients with a performance status 0-2 and tumors with PD-L1 expression levels ≥1% and no prior progression on a PD-1/PD-L1 inhibitor

Notes:

1. Complete genotyping for EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, NRG1, and ERBB2 (HER2), via biopsy and/or plasma testing. Treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.
2. Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents, and some oncogenic drivers (ie, EGFR exon 19 deletion or exon 21 L858R; ALK, RET, or ROS1 rearrangements) have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors.[29]

Occult Primary

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single agent in symptomatic patients with a performance status (PS) 1-2 or asymptomatic patients with a PS 0 and aggressive disease for one of the following:

a) Axillary involvement in patients with a prostate or post-prostatectomy if clinically indicated
b) Lung nodules or breast marker-negative pleural effusion
c) Resectable liver disease
d) Peritoneal mass or ascites with non-ovarian histology
e) Retroperitoneal mass of non-germ cell histology in selected patients
f) Unresectable liver disease or disseminated metastases; OR

4. Single agent in symptomatic patients with a PS 1-2 or asymptomatic patients with PS 0 and aggressive disease for systemic therapy in patients with multiple lung nodules, pleural effusion, or disseminated metastases.[30]

Ovarian, Fallopian Tube, and Primary Peritoneal Cancers

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. In combination with carboplatin and paclitaxel, followed by pembrolizumab as a single agent, for the treatment of primary advanced or recurrent endometrial carcinoma; OR
4. In combination with lenvatinib, for the treatment of advanced disease that is mismatch repair proficient (pMMR) or not MSI-H and have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation; OR
5. Single agent for advanced disease is MSI-H or dMMR and have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation;[2] OR

Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer

For **NCCN** required criteria coverage:

6. Platinum-resistant persistent disease or recurrence in combination with oral cyclophosphamide and bevacizumab for one of the following:
   a) Immediate treatment for serially rising CA-125 in patients who previously received chemotherapy
   b) Progression on primary, maintenance, or recurrence therapy
   c) Stable or persistent disease (if not on maintenance therapy)
   d) Complete remission and relapse <6 months after completing chemotherapy; OR
7. Single-agent therapy for persistent disease or recurrence, if microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), or tumor mutational burden-high (TMB-H) tumors ≥10 mutations/megabase for one of the following:
   a) Immediate treatment for serially rising CA-125 in patients that previously received chemotherapy
   b) Progression on primary, maintenance, or recurrence therapy (platinum-resistant disease)
   c) Stable or persistent disease (if not on maintenance therapy) (platinum-resistant disease)
   d) Complete remission and relapse <6 months after completing chemotherapy (platinum-resistant disease)

e) Radiographic and/or clinical relapse in patients with previous complete remission and relapse ≥6 months after completing prior chemotherapy (platinum-sensitive disease); OR

Carcinosarcoma (Malignant Mixed Müllerian Tumors)

For **NCCN** required criteria coverage:

8. Single-agent therapy for persistent disease or recurrence, if microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), or tumor mutational burden-high (TMB-H) tumors ≥10 mutations/megabase for one of the following:
   a) Immediate treatment for serially rising CA-125 in patients who previously received chemotherapy
   b) Progression on primary, maintenance, or recurrence therapy (platinum-resistant disease)
   c) Stable or persistent disease (if not on maintenance therapy) (platinum-resistant disease)
   d) Complete remission and relapse <6 months after completing chemotherapy (platinum-resistant disease)
   e) Radiographic and/or clinical relapse in patients with previous complete remission and relapse ≥6 months after completing prior chemotherapy (platinum-sensitive disease); OR
9. Platinum-resistant persistent disease or recurrence in combination with oral cyclophosphamide and bevacizumab for one of the following:
   a) Immediate treatment for serially rising CA-125 in patients that previously received chemotherapy
   b) Progression on primary, maintenance, or recurrence therapy
   c) Stable or persistent disease (if not on maintenance therapy)
   d) Complete remission and relapse <6 months after completing chemotherapy; OR

Clear Cell Carcinoma of the Ovary

For **NCCN** required criteria coverage:

10. Platinum-resistant persistent disease or recurrence in combination with oral cyclophosphamide and bevacizumab for one of the following:
    a) Immediate treatment for serially rising CA-125 in patients that previously received chemotherapy
    b) Progression on primary, maintenance, or recurrence therapy (platinum-resistant disease)
    c) Stable or persistent disease (if not on maintenance therapy) (platinum-resistant disease)
    d) Complete remission and relapse <6 months after completing chemotherapy (platinum-resistant disease); OR
11. Single-agent therapy for persistent disease or recurrence if microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), or tumor mutational burden-high (TMB-H) tumors ≥10 mutations/megabase for one of the following:
    a) Immediate treatment for serially rising CA-125 in patients that previously received chemotherapy
    b) Progression on primary, maintenance, or recurrence therapy (platinum-resistant disease)
    c) Stable or persistent disease (if not on maintenance therapy) (platinum-resistant disease)
    d) Complete remission and relapse <6 months after completing chemotherapy (platinum-resistant disease)

e) Radiographic and/or clinical relapse in patients with previous complete remission and relapse ≥6 months after completing prior chemotherapy (platinum-sensitive disease); OR

Mucinous Neoplasms of the Ovary

For **NCCN** required criteria coverage:

12. Platinum-resistant persistent disease or recurrence in combination with oral cyclophosphamide and bevacizumab for one of the following:
    a) Immediate treatment for serially rising CA-125 in patients that previously received chemotherapy
    b) Progression on primary, maintenance, or recurrence therapy
    c) Stable or persistent disease (if not on maintenance therapy)
    d) Complete remission and relapse <6 months after completing chemotherapy; OR
13. Single-agent therapy for persistent disease or recurrence if microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), or tumor mutational burden-high (TMB-H) tumors ≥10 mutations/megabase for one of the following:
    a) Immediate treatment for serially rising CA-125 in patients that previously received chemotherapy
    b) Progression on primary, maintenance, or recurrence therapy (platinum-resistant disease)
    c) Stable or persistent disease (if not on maintenance therapy) (platinum-resistant disease)
    d) Complete remission and relapse <6 months after completing chemotherapy (platinum-resistant disease)
    e) Radiographic and/or clinical relapse in patients with previous complete remission and relapse ≥6 months after completing prior chemotherapy (platinum-sensitive disease); OR

Endometrioid Carcinoma

For **NCCN** required criteria coverage:

14. Platinum-resistant persistent disease or recurrence in combination with oral cyclophosphamide and bevacizumab for one of the following:
    a) Immediate treatment for serially rising CA-125 in patients that previously received chemotherapy
    b) Progression on primary, maintenance, or recurrence therapy
    c) Stable or persistent disease (if not on maintenance therapy)
    d) Complete remission and relapse <6 months after completing chemotherapy; OR
15. Single-agent therapy for persistent disease or recurrence if microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), or tumor mutational burden-high (TMB-H) tumors ≥10 mutations/megabase for one of the following:
    a) Immediate treatment for serially rising CA-125 in patients that previously received chemotherapy
    b) Progression on primary, maintenance, or recurrence therapy (platinum-resistant disease)
    c) Stable or persistent disease (if not on maintenance therapy) (platinum-resistant disease)
    d) Complete remission and relapse <6 months after completing chemotherapy (platinum-resistant disease)

e) Radiographic and/or clinical relapse in patients with previous complete remission and relapse ≥6 months after completing prior chemotherapy (platinum-sensitive disease); OR

Low-Grade Serous Carcinoma

For **NCCN** required criteria coverage:

16. Platinum-resistant recurrence in combination with oral cyclophosphamide and bevacizumab; OR
17. Single-agent therapy for platinum-sensitive or platinum-resistant recurrence if microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), or tumor mutational burden-high (TMB-H) tumors ≥10 mutations/megabase; OR

Malignant Germ Cell Tumors

For **NCCN** required criteria coverage:

18. Single agent for recurrent disease as palliative therapy only in patients with abnormal markers, definitive recurrent disease following initial complete clinical response and microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), or tumor mutational burden-high (TMB-H) tumors ≥10 mutations/megabase.[31]

Pancreatic Adenocarcinoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. First-line therapy as a single agent (if microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR), or tumor mutational burden high (TMB-H) [≥ 10 mut/Mb] for one of the following:
   a) Locally advanced or metastatic disease if the patient has a good performance status (defined as ECOG PS 0-1, with good biliary drainage and adequate nutritional intake)
   b) Locally advanced or metastatic disease if the patient has an intermediate PS (ECOG 2)
   c) Metastatic disease if poor PS (ECOG 3); OR
4. Subsequent therapy as a single agent (if no prior immunotherapy and if microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) or tumor mutational burden-high (TMB-H) [≥ 10 mut/Mb]) for locally advanced or metastatic disease and disease progression for one of the following:
   a) Good performance status (defined as ECOG PS 0-1, with good biliary drainage and adequate nutritional intake)
   b) Intermediate PS (ECOG 2)
   c) Poor PS (ECOG 3); OR
5. Single agent as an alternate systemic therapy if not previously used and no prior immunotherapy and if microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR) or tumor mutational burden-high (TMB-H) [≥ 10 mut/Mb]) for one of the following:
   a) Local recurrence in the pancreatic operative bed after resection

b) Recurrent metastatic disease with or without local recurrence after resection.[32]

Pediatric Aggressive Mature B-Cell Lymphomas

1. Less than 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Relapsed or refractory disease as a single agent; OR
4. Consolidation/additional therapy in combination with brentuximab vedotin, if partial response was achieved after therapy for relapsed or refractory disease.[33]

Pediatric Central Nervous System Cancer

1. Less than 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Adjuvant treatment for hypermutant tumor pediatric diffuse high-grade glioma for one of the following:
   a) Following standard brain radiation therapy (RT) with or without concurrent temozolomide in patients ≥3 years old
   b) Patients <3 years old

   Note: Except diffuse midline glioma, H3 K27-altered or pontine location; OR

4. Recurrent or progressive disease for hypermutant tumor pediatric diffuse high-grade glioma

   Note: Except oligodendroglioma, IDH-mutant and 1p/19q co-deleted or astrocytoma IDH-mutant.[34]

Pediatric Hodgkin Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single agent for relapsed or refractory disease as a consideration in patients with heavily pretreated disease (with platinum or anthracycline-based chemotherapy), or if there is a decrease in cardiac function observed, or for patients who have relapsed after 2 or more prior lines of therapy; OR
4. Relapsed or refractory disease as one of the following:
   a) ICE (ifosfamide, carboplatin, etoposide) regimen (there is no pediatric data for this regimen)
   b) GVD (gemcitabine, vinorelbine, doxorubicin hydrochloride liposome) regimen; OR

5. Maintenance therapy following high-dose therapy and autologous stem cell rescue (HDT/ASCR) for relapsed or refractory disease

   Note: There is no pediatric data for this regimen.[35]

Penile Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single agent for subsequent-line systemic therapy if disease is unresectable or metastatic for one of the following:
   a) Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumor that has progressed following prior treatment and with no satisfactory alternative treatment options
   b) Tumor mutational burden-high (TMB ≥10 mut/Mb) in patients who have progressed on previously approved lines of therapy; OR
4. First-line treatment in combination with fluorouracil and either cisplatin or carboplatin followed by pembrolizumab maintenance for one of the following:
   a) Local recurrence in the inguinal region in patients that received prior inguinal lymphadenectomy or radiotherapy
   b) Systemic chemotherapy for metastatic disease.[36]

Primary Cutaneous Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Systemic therapy as primary treatment for one of the following:
   a) Stage IB-IIA mycosis fungoides (MF), in combination with skin-directed therapy in selected cases (consider for patients with extensive skin involvement, higher skin disease burden, predominantly plaque disease, blood involvement, and/or inadequate response to skin-directed therapy)
   b) Stage IIB MF with limited tumor lesions, with or without local radiation therapy and with or without skin-directed therapy
   c) Stage IIB MF with generalized tumor lesions, in combination with skin-directed therapy
   d) Stage III MF, in combination with skin-directed therapy
   e) Stage IVA1 or IVA2 Sezary syndrome, in combination with skin-directed therapy
   f) Generalized cutaneous or extracutaneous lesions with large cell transformation (LCT), in combination with systemic therapy; OR
4. Systemic therapy as subsequent treatment for one of the following:
   a) Stage IA mycosis fungoides (MF) that is refractory to multiple previous therapies, in combination with skin-directed therapy in selected cases (consider for patients with extensive skin involvement, higher skin disease burden, predominantly plaque disease, blood involvement, and/or inadequate response to skin-directed therapy)

b) Relapsed or persistent stage IB-IIA MF with a lower skin disease burden (eg, predominantly patch disease), in combination with skin-directed therapy in selected cases (consider for patients with extensive skin involvement, higher skin disease burden, predominantly plaque disease, blood involvement, and/or inadequate response to skin-directed therapy)
c) Stage IB-IIA MF with a higher skin disease burden (eg, predominantly plaque disease) that is relapsed or persistent with T1-T2 disease, in combination with skin-directed therapy in selected cases (consider for patients with extensive skin involvement, higher skin disease burden, predominantly plaque disease, blood involvement, and/or inadequate response to skin-directed therapy)
d) Stage IB-IIA MF that is refractory to multiple previous therapies, in combination with skin-directed therapy
e) Relapsed stage IIB T1-2 MF with limited tumor lesions, in combination with skin-directed therapy in selected cases (consider for patients with extensive skin involvement, higher skin disease burden, predominantly plaque disease, blood involvement, and/or inadequate response to skin-directed therapy)
f) Relapsed stage IIB T3 MF with limited tumor lesions, with or without local radiation therapy and with or without skin-directed therapy
g) Persistent stage IIB T1-3 MF with limited tumor lesions, with or without local radiation therapy and with or without skin-directed therapy
h) Stage IIB MF with limited tumor lesions that are refractory to multiple previous therapies, in combination with skin-directed therapy
i) Relapsed stage IIB T1-2 MF with generalized tumor lesions, in combination with skin-directed therapy in selected cases (consider for patients with extensive skin involvement, higher skin disease burden, predominantly plaque disease, blood involvement, and/or inadequate response to skin-directed therapy)
j) Relapsed stage IIB T3 MF with generalized tumor lesions, in combination with skin-directed therapy
k) Persistent stage IIB T1-3 MF with generalized tumor lesions, in combination with skin-directed therapy
l) Stage IIB MF with generalized tumor lesions that are refractory to multiple previous therapies, in combination with skin-directed therapy
m) Relapsed or persistent stage III MF, in combination with skin-directed therapy
n) Stage III MF that is refractory to multiple previous therapies, in combination with skin-directed therapy
o) Relapsed or persistent stage IVA1 or IVA2 Sezary syndrome, in combination with skin-directed therapy
p) Limited cutaneous lesions with large cell transformation (LCT) that are refractory to multiple previous therapies, in combination with skin-directed therapy
q) Relapsed or persistent generalized cutaneous or extracutaneous lesions with LCT, in combination with skin-directed therapy; OR

5. Systemic therapy as a single agent for subsequent treatment for refractory disease to multiple previous therapies for one of the following:
   a) Stage IIB MF with limited tumor lesions
   b) Stage IIB MF with generalized tumor lesions
   c) Stage III MF
   d) Stage IVA1 or IVA2 Sezary syndrome
   e) Stage IVA2 non-Sezary or stage IVB visceral disease (solid organ)
   f) Limited cutaneous lesions with LCT

g) Generalized cutaneous or extracutaneous lesions with LCT; OR

6. For primary cutaneous anaplastic large cell lymphoma (ALCL) with multifocal lesions, or cutaneous ALCL with regional node (N1) (excludes systemic ALCL), as a single agent for relapsed/refractory disease.[37]

Prostate Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single agent (Continue androgen deprivation therapy (ADT) to maintain castrate levels of serum testosterone <50 ng/dL) for castration-resistant distant metastatic (M1) disease for one of the following:
   a) Irrespective of prior androgen receptor pathway inhibitor (ARPI) or prior docetaxel as molecular biomarker-directed therapy if microsatellite instability-high (MSI-H)/ mismatch repair deficient (dMMR)
   b) TMB ≥10 mutations/megabase.[38]

Rectal Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Unresectable or metastatic microsatellite instability-high or mismatch repair deficient (MSI-H or dMMR);[2] OR

For **NCCN** required criteria coverage:

4. Single agent for patients (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation with ultra-hypermutated phenotype [eg, TMB >50 mut/Mb]) if the patient is a candidate for immunotherapy and no prior immunotherapy received for one of the following:
   a) Primary treatment for synchronous abdominal/peritoneal metastases that are nonobstructing, or following local therapy for patients with existing or imminent obstruction
   b) Primary treatment for synchronous unresectable metastases
   c) Primary treatment for potentially resectable or unresectable isolated pelvic/anastomotic recurrence
   d) Primary treatment for unresectable metachronous metastases; OR
5. Single agent for patients with dMMR/MSI-H or POLE/POLD1 mutation with ultra-hypermutated phenotype [eg, TMB >50 mut/Mb]) for one of the following:
   a) Neoadjuvant treatment for resectable synchronous liver only and/or lung only metastases (no previous treatment with a checkpoint inhibitor)
   b) Initial treatment for resectable metachronous metastases and no previous immunotherapy; OR

6. Single agent for neoadjuvant/definitive immunotherapy for stage T3, N Any; T1-2, N1-2; T4, N Any; or locally unresectable or medically inoperable disease for dMMR/MSI-H or POLE/POLD1 mutation with ultra-hypermutated phenotype [e.g., TMB >50 mut/Mb]) with no previous treatment with a checkpoint inhibitor.[39]

Small Bowel Adenocarcinoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single agent as primary treatment for locally unresectable or medically inoperable disease (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation with ultra-hypermutated phenotype [eg, tumor mutational burden (TMB) > 50 mut/Mb]); OR
4. Single agent for advanced or metastatic disease with dMMR/MSI-H or POLE/POLD1 mutation with ultra-hypermutated phenotype [eg, TMB > 50 mut/Mb), if no previous treatment with a checkpoint inhibitor, for any line of therapy; OR
5. Single agent for advanced or metastatic disease TMB-H ≥ 10 mut/Mb, if no previous treatment with a checkpoint inhibitor for one of the following:
   a) Initial therapy if proficient mismatch repair/microsatellite-stable (pMMR/MSS) and patient received previous FOLFOX/CAPEOX in the adjuvant setting within past 12 months or contraindication
   b) Second-line and subsequent therapy if not previously given.[40]

Small Cell Lung Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Subsequent systemic therapy as a single agent if not previously treated with an immune checkpoint inhibitor and if performance status 0-2 for progression or relapse.[41]

Soft Tissue Sarcoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

Extremity/Body Wall, Head/Neck

For **NCCN** required criteria coverage:

3. Palliative single-agent therapy for subsequent lines of therapy for advanced/metastatic disease with disseminated metastases for one of the following:
   a) Myxofibrosarcoma
   b) Undifferentiated pleomorphic sarcoma (UPS)

c) Dedifferentiated liposarcoma
d) Cutaneous angiosarcoma
e) Undifferentiated sarcomas; OR

4. Palliative single-agent therapy for unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] or microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors regardless of the soft tissue sarcoma sub-type that have progressed following prior treatment and for patients with no satisfactory alternative treatment options, given as subsequent lines of therapy for advanced/metastatic disease with disseminated metastases; OR

Retroperitoneal/Intra-Abdominal

For **NCCN** required criteria coverage:

5. Single agent as alternative systemic therapy for unresectable or progressive disease after initial therapy for unresectable localized disease or as palliative subsequent lines of therapy for stage IV disease with disseminated metastases for one of the following:
   a) Myxofibrosarcoma
   b) Undifferentiated pleomorphic sarcoma (UPS)
   c) Dedifferentiated liposarcoma
   d) Cutaneous angiosarcoma
   e) Undifferentiated sarcomas; OR
6. Single agent for unresectable or metastatic TMB-H ≥10 mut/Mb or MSI-H or dMMR tumors regardless of the soft tissue sarcoma sub-type that have progressed following prior treatment and and the patient does not have any for one of the following:
   a) Alternative systemic therapy for unresectable or progressive disease after initial therapy for unresectable localized disease
   b) Palliative subsequent lines of therapy for stage IV disease with disseminated metastases

   Note: Treat well-differentiated liposarcoma (WDLPS) (retroperitoneum, paratesticular) with or without evidence of de-differentiation as other soft tissue sarcomas; OR

Rhabdomyosarcoma

For **NCCN** required criteria coverage:

7. Single agent for advanced/metastatic pleomorphic rhabdomyosarcoma as subsequent line of therapy (including for unresectable or metastatic TMB-H ≥10 mut/Mb or MSI-H or dMMR tumors that have progressed following prior treatment and the patient with no satisfactory alternative treatment options); OR

Alveolar Soft Part Sarcoma

For **NCCN** required criteria coverage:

8. Single-agent therapy or in combination with axitinib; OR

Angiosarcoma

For **NCCN** required criteria coverage:

9. Single-agent therapy for cutaneous angiosarcoma; OR

Dedifferentiated Liposarcoma with or without Concurrent Well-Differentiated Liposarcoma

For **NCCN** required criteria coverage:

10. Single-agent therapy for dedifferentiated liposarcoma with or without concurrent well-differentiated liposarcoma; OR

Epithelioid Hemangioendothelioma

For **NCCN** required criteria coverage:

11. Single-agent therapy for unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] or microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) epithelioid hemangioendothelioma, that have progressed following prior treatment and who have no satisfactory alternative treatment options.[42]

Squamous Cell Skin Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single agent treatment if curative radiation therapy or surgery is not feasible for a disease that is one of the following:
   a) Locally advanced
   b) Recurrent
   c) Metastatic
   d) Satellitosis/in-transit metastasis that is unresectable or incompletely resected.[43]

T-Cell Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Relapsed/refractory disease following additional therapy with an alternate combination chemotherapy regimen (asparaginase-based) if not previously used and if a clinical trial is unavailable.[44]

Thymomas and Thymic Carcinomas

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

5. Postoperative treatment as a single agent for those who cannot tolerate first-line combination regimens for thymic carcinoma after R1 or R2 resection; OR
6. First-line systemic therapy for thymic carcinoma for recurrent, advanced, or metastatic disease as a single agent for those who cannot tolerate first-line combination regimens for one of the following:
   a) Consideration following surgery for solitary metastasis or ipsilateral pleural metastasis
   a) Medically inoperable/unresectable solitary metastasis or ipsilateral pleural metastasis
   c) Extrathoracic metastatic disease; OR
7. Subsequent systemic therapy for thymic carcinoma as a single agent for one of the following:
   a) Unresectable locally advanced disease
   b) Solitary metastasis or ipsilateral pleural metastasis
   c) Extrathoracic metastatic disease.[45]

Thyroid Carcinoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

Papillary Carcinoma

For **NCCN** required criteria coverage:

3. Tumor mutational burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) tumors, consider for treatment of progressive and/or symptomatic disease for one of the following:
   a) Unresectable locoregional recurrent or persistent disease not amenable to radioactive iodine (RAI) therapy
   b) Distant metastatic disease not amenable to RAI therapy; OR
4. For microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors, if progressed following prior treatment and with no satisfactory alternative treatment options, consider for treatment of progressive and/or symptomatic for one of the following:
   a) Unresectable locoregional recurrent or persistent disease not amenable to RAI therapy
   b) Distant metastatic disease RAI refractory disease; OR
5. Disease progression on lenvatinib, consider for treatment in combination with Lenvatinib of progressive and/or symptomatic disease for one of the following:
   a) Unresectable locoregional recurrent or persistent radioactive iodine (RAI)-refractory disease
   b) Distant metastatic RAI-refractory disease; OR

Follicular Carcinoma

For **NCCN** required criteria coverage:

6. For TMB-H ≥10 mut/Mb tumors, consider for treatment of progressive and/or symptomatic for one of the following:
   a) Unresectable locoregional recurrent or persistent disease not amenable to RAI therapy
   b) Metastatic disease RAI therapy; OR

7. For MSI-H or dMMR tumors, if progressed following prior treatment and with no satisfactory alternative treatment options, consider for treatment of progressive and/or symptomatic for one of the following:
   a) Unresectable locoregional recurrent or persistent radioactive iodine (RAI)-refractory disease
   b) Distant metastatic RAI-refractory disease; OR
8. Disease progression on lenvatinib, consider for treatment in combination with lenvatinib of progressive and/or symptomatic for one of the following:
   a) Unresectable locoregional recurrent or persistent radioactive iodine (RAI)-refractory disease
   b) Distant metastatic RAI-refractory disease; OR

Oncocytic Carcinoma

For **NCCN** required criteria coverage:

9. For TMB-H ≥10 mut/Mb tumors of progressive and/or symptomatic for one of the following:
   a) Unresectable locoregional recurrent or persistent disease
   b) Metastatic disease; OR
10. For MSI-H or dMMR tumors, if progressed following prior treatment and with no satisfactory alternative treatment options, consider for treatment of progressive and/or symptomatic disease for one of the following:
   a) Unresectable locoregional recurrent or persistent disease
   b) Distant metastatic disease; OR
11. Disease progression on lenvatinib, consider for treatment in combination with lenvatinib of progressive and/or symptomatic for one of the following:
   a) Unresectable locoregional recurrent or persistent disease
   b) Distant metastatic disease; OR

Anaplastic Carcinoma

For **NCCN** required criteria coverage:

12. Single agent or in combination for metastatic disease with lenvatinib for one of the following:
   a) Aggressive first-line therapy for stage IVC (metastatic) disease
   b) Second-line therapy for stage IVC (metastatic) disease.[46]

Tumor Mutational Burden-High (TMB-H) Cancer

1. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

2. For adults or pediatric patients; AND
3. Unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors that have progressed following prior treatment and with no satisfactory alternative treatment options.[2]

Uterine Neoplasm

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

Endometrial Carcinoma

For **FDA** required criteria coverage:

3. In combination with carboplatin and paclitaxel, followed by pembrolizumab as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma; OR
4. In combination with lenvatinib, for advanced endometrial carcinoma that is mismatch repair proficient (pMMR) or not MSI-H, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation; OR
5. Single agent, for advanced endometrial carcinoma that is MSI-H or dMMR, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation;[2] OR

For **NCCN** required criteria coverage:

6. Primary treatment in combination with carboplatin and paclitaxel and continued as a single agent for maintenance therapy for patients with stage III-IV endometrioid adenocarcinoma for one of the following:
   a) Preoperatively for patients presenting with abdominal/pelvic-confined disease that is suitable for primary surgery
   b) With or without external beam radiation therapy (EBRT), stereotactic body radiation therapy, and/or total hysterectomy/bilateral salpingo-oophorectomy (TH/BSO) for distant metastases that are suitable for primary surgery
   c) With sequential EBRT and with or without brachytherapy for locoregional extrauterine disease that is not suitable for primary surgery
   d) Locoregional extrauterine disease or distant metastases hat are not suitable for primary surgery; OR
7. Adjuvant treatment in combination with carboplatin and paclitaxel and continued as a single agent for maintenance therapy with or without external beam radiation therapy (EBRT) and with or without vaginal brachytherapy for surgically staged patients with stage III-IV endometrioid adenocarcinoma

   Notes:
   1. May be continued as a maintenance therapy. Refer to the original study protocol for maintenance therapy schedules
   2. For stage III or IVA with measurable disease post-surgery or stage IVB with or without measurable disease. For patients not meeting the eligibility criteria for NRG-GY018 carboplatin/paclitaxel + pembrolizumab should be considered for stage III-IV deficient mismatch repair (dMMR) tumors; OR

8. First-line therapy (or second-line or subsequent therapy as clinically appropriate if not used previously) in combination with carboplatin and paclitaxel for recurrent endometrial carcinoma with or without measurable disease, and continued as a single agent for

maintenance therapy for recurrent disease (except for carcinosarcoma) for one of the following:
a) Isolated metastases
b) Disseminated metastases with or without sequential palliative external beam radiation therapy (EBRT)
c) With sequential EBRT and with or without brachytherapy for locoregional recurrence in patients with no prior RT to site of recurrence, or previous vaginal brachytherapy only
d) After surgical exploration, with sequential EBRT for locoregional recurrence in patients with disease confined to the vagina or paravaginal soft tissue, or in pelvic or para-aortic lymph nodes
e) After surgical exploration, with or without sequential EBRT for locoregional recurrence in patients with upper abdominal or peritoneal disease
f) With or without sequential palliative EBRT or brachytherapy for locoregional recurrence in patients who have received prior EBRT to site of recurrence; OR

9. In combination with carboplatin and paclitaxel and continued as a single agent for maintenance therapy for stage III-IV tumors (except for carcinosarcoma) including serous carcinoma, clear cell carcinoma, or undifferentiated/dedifferentiated carcinoma for one of the following:
   a) That is suitable for primary surgery as additional treatment with or without sequential external beam radiation therapy (EBRT) and with or without vaginal brachytherapy after total hysterectomy/bilateral salpingo-oophorectomy (TH/BSO)
   b) That is not suitable for primary surgery as primary treatment with or without sequential EBRT and with or without brachytherapy; OR

   Notes:
   1. May be continued as a maintenance therapy. Refer to the original study protocol for maintenance therapy schedules
   2. For stage III or IVA with measurable disease post-surgery or stage IVB with or without measurable disease. For patients not meeting the eligibility criteria for NRG-GY018 carboplatin/paclitaxel + pembrolizumab should be considered for stage III-IV deficient mismatch repair (dMMR) tumors; OR

10. First-line therapy or second-line or subsequent therapy as clinically appropriate if not used previously in combination with lenvatinib for recurrent disease that is mismatch repair proficient (pMMR) for one of the following:
    a) Isolated metastases
    b) Disseminated metastases with or without sequential palliative EBRT
    c) With sequential EBRT and with or without brachytherapy for locoregional recurrence in patients with no prior RT to site of recurrence, or previous vaginal brachytherapy only
    d) After surgical exploration, with sequential EBRT for locoregional recurrence in patients with disease confined to the vagina or paravaginal soft tissue, or in pelvic or para-aortic lymph nodes
    e) After surgical exploration, with or without sequential EBRT for locoregional recurrence in patients with upper abdominal or peritoneal disease
    f) With or without sequential palliative EBRT or brachytherapy for locoregional recurrence in patients who have received prior EBRT to site of recurrence; OR
11. First-line therapy or second-line or subsequent therapy as clinically appropriate if not used previously as a single agent for recurrent unresectable or metastatic tumor mutational burden-high (TMB-H) ≥10 mutations/megabase [mut/Mb] tumors that have progressed

following prior treatment and with no satisfactory alternative treatment options, or for recurrent microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors for one of the following:
a) Isolated metastases
b) Disseminated metastases with or without sequential palliative external beam radiation therapy (EBRT)
c) With sequential external beam radiation therapy (EBRT) and with or without brachytherapy for locoregional recurrence in patients with no prior RT to site of recurrence, or previous vaginal brachytherapy only
d) After surgical exploration, with sequential EBRT for locoregional recurrence in patients with disease confined to the vagina or paravaginal soft tissue, or in pelvic or para-aortic lymph nodes
e) After surgical exploration, with or without sequential EBRT for locoregional recurrence in patients with upper abdominal or peritoneal disease
f) With or without sequential palliative EBRT or brachytherapy for locoregional recurrence in patients who have received prior EBRT to site of recurrence; OR

Uterine Sarcoma

For **NCCN** required criteria coverage:

12. Single-agent for second-line or subsequent therapy (if not previously used) for patients with unresectable or metastatic TMB-H ≥10 mut/Mb tumors that have progressed following prior treatment and with no satisfactory alternative treatment options.[47]

Vaginal Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. First-line, second-line, or subsequent therapy as clinically appropriate (if not used previously as first-line) in combination with cisplatin or carboplatin, paclitaxel, and with or without bevacizumab for PD-L1 positive tumors (combined positive score [CPS] ≥1) for one of the following:
   a) Locoregional recurrence if prior intracavitary brachytherapy only, or prior EBRT with or without brachytherapy and noncentral disease
   b) Stage IVB or recurrent distant metastases: OR
4. Second-line or subsequent therapy as a single agent if PD-L1 positive (combined positive score [CPS] ≥1) or if microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors for one of the following:
   a) Locoregional recurrence
   b) Stage IVB or recurrent distant metastases; OR
5. Second-line or subsequent treatment for patients with unresectable or metastatic tumor mutational burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) tumors, that have progressed following prior treatment and with no satisfactory alternative treatment options.[48]

Vulvar Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. First-line therapy for advanced or recurrent/metastatic disease (or second-line or subsequent therapy as clinically appropriate if not used previously) in combination with paclitaxel and cisplatin or carboplatin with or without bevacizumab and continued for maintenance therapy, for one of the following:
   a) Additional treatment following primary therapy with concurrent chemoradiation for locally advanced unresectable disease or initially unresectable nodes, regardless of stage that is clinically suspicious for residual tumor at the primary site and/or nodes at least three months after completion of treatment and remains unresectable
   b) Additional treatment following primary therapy with concurrent chemoradiation for locally advanced disease or initially unresectable nodes, regardless of stage, that is clinically suspicious for residual tumor at the primary site and/or nodes at least three months after completion of treatment and with positive margins for invasive disease following resection
   c) Primary treatment for metastatic disease beyond the pelvis (stage IVB)
   d) Confirmed isolated inguinofemoral/pelvic lymph node recurrence if prior external beam radiation therapy (EBRT)
   e) Confirmed recurrence with distant metastasis or prior pelvic EBRT

   Note: Bevacizumab and pembrolizumab may be continued as a maintenance therapy; OR

4. Second-line or subsequent therapy for advanced or recurrent/metastatic disease as a single agent for one of the following:
   a) Tumor mutational burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) tumors that have progressed following prior treatment and with no satisfactory alternative treatment options
   b) Disease progression on or after chemotherapy in patients whose tumors express PD-L1 (Combined Positive Score ≥1)
   c) Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors.[49]

Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

Coding (CPT®, ICD-10, and HCPCS)

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

Code	Description
C4A	Merkel cell carcinoma
C7A	Malignant neuroendocrine tumors
C06	Malignant neoplasm of other and unspecified parts of mouth
C15	Malignant neoplasm of esophagus
C16	Malignant neoplasm of stomach
C17	Malignant neoplasm of small intestine
C21.0	Malignant neoplasm of anus, unspecified
C22.1	Intrahepatic bile duct carcinoma
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C23	Malignant neoplasm of gallbladder
C24.0	Malignant neoplasm of extrahepatic bile duct
C24.1	Malignant neoplasm of ampulla of Vater
C25.9	Malignant neoplasm of pancreas, unspecified
C34.9	Malignant neoplasm of unspecified part of bronchus or lung
C37	Malignant neoplasm of thymus
C41	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
C43.9	Malignant melanoma of skin, unspecified
C44.9	Other and unspecified malignant neoplasm of skin, unspecified
C45.9	Mesothelioma, unspecified
C46.9	Kaposi's sarcoma, unspecified
C49.9	Malignant neoplasm of connective and soft tissue, unspecified

C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C51.9	Malignant neoplasm of vulva, unspecified
C52	Malignant neoplasm of vagina
C53.9	Malignant neoplasm of cervix uteri, unspecified
C56.9	Malignant neoplasm of unspecified ovary
C60.9	Malignant neoplasm of penis, unspecified
C61	Malignant neoplasm of prostate
C62	Malignant neoplasm of testis
C64.9	Malignant neoplasm of unspecified kidney, except renal pelvis
C67.9	Malignant neoplasm of bladder, unspecified
C69.60	Malignant neoplasm of unspecified orbit
C71.9	Malignant neoplasm of brain, unspecified
C73	Malignant neoplasm of thyroid gland
C80.0	Disseminated malignant neoplasm, unspecified
C81.10	Nodular sclerosis Hodgkin lymphoma, unspecified site
C81.99	Hodgkin lymphoma, unspecified, extranodal and solid organ sites
C83.3	Diffuse large B-cell lymphoma
C84.00	Mycosis fungoides, unspecified site
C84.9	Mature T/NK-cell lymphomas, unspecified
C85.20	Mediastinal (thymic) large B-cell lymphoma, unspecified site
C86.6	Primary cutaneous CD30-positive T-cell proliferations
J9271	Injection, pembrolizumab

Revision and Review History

No.	Description	Date
1	Original Effective Date:	11/30/2025
2	Policy Annual Review Dates:	
3	Department Owner:	Medical Affairs
4	NH Advisory Committee Approval Dates:	11/30/2025
5	Revision Changes:	

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