CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Nivolumab (Opdivo®)

Version: 2.0

EFFECTIVE DATE: 1/1/2025

NantHealth® | Eviti®

Please note the following:

Nivolumab (Opdivo®)

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

Note: For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Nivolumab (Opdivo): Discussion

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. Binding of the PD-1 ligands to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. This action obstructs the signal that impedes the activation of T-cells against cancerous cells.[1,2]

Nivolumab is associated with side effects including immune-mediated pneumonitis, colitis, hepatitis, nephritis, renal dysfunction, hypothyroidism, hyperthyroidism, and embryofetal toxicity. Other clinically important adverse reactions are ventricular arrhythmias, iridocyclitis, increased amylase, dizziness, peripheral neuropathy, sensory neuropathy, exfoliative dermatitis, erythema multiforme, vitiligo, and psoriasis.

Nivolumab is approved by the Food and Drug Administration (FDA) for the following cancer types: classical Hodgkin lymphoma, colorectal, esophageal, gastric, gastroesophageal, head and neck, hepatocellular, melanoma, non-small cell lung cancer, pleural mesothelioma, renal cell, and urothelial.[2]

The National Comprehensive Cancer Network (NCCN) endorses nivolumab for the following cancer types: ampullary, anal, B-cell lymphomas, biliary tract, bladder, bone, central nervous system, cervical, chronic lymphocytic leukemia/small lymphocytic lymphoma, colon, esophageal/esophagogastric junction, gastric, gestational trophoblastic neoplasia, head and neck, hepatocellular, Hodgkin lymphoma, Kaposi sarcoma, kidney, melanoma, Merkel cell, mesothelioma, neuroendocrine and adrenal, non-small cell lung cancer, pancreatic, pediatric aggressive mature B-cell lymphomas, pediatric central nervous system, pediatric Hodgkin lymphoma, rectal, squamous cell skin cancer, small bowel adenocarcinoma, small cell lung cancer, soft tissue sarcoma, T-cell lymphoma, thyroid, uterine, vaginal, and vulvar.[3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41]

Nivolumab: Definitions

- **Deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H)** - When the microsatellite DNA segments in cancer cells show changes (mutations), this indicates that the tumor cells are deficient in the repair of the mismatch errors. These cancers have microsatellite instability (also called MSI-High, MSI-H, or mismatch repair deficiency, dMMR).
- **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.
- **National Comprehensive Cancer Network (NCCN)** - An alliance of more than 30 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.
- **Programmed cell death protein 1 (PD-1)/Programmed cell death-ligand 1 (PD-L1)** - The binding of PD-L1 to PD-1 keeps T cells from killing tumor cells 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.[42]

Nivolumab: Policy

Note: Coverage of nivolumab will be provided for an FDA-approved indication or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation or when all criteria are met.

Nivolumab will be considered for coverage 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. First-line therapy in combination with ipilimumab in patients with intestinal type disease if MSI-H or dMMR for metastatic disease; OR
4. In combination with ipilimumab for disease progression if no prior immunotherapy was received and if MSI-H or dMMR.[3]

Anal Carcinoma

Squamous Cell 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 before proceeding to an abdominoperineal resection for locally recurrent, progressive disease; OR
4. Second-line and subsequent therapy as a single agent for metastatic disease if no prior immunotherapy was received.[4]

B-Cell Lymphomas - Diffuse Large B-Cell

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

For **NCCN** required criteria coverage:

3. With or without brentuximab vedotin (BV) for relapsed or refractory primary mediastinal disease

Note: Responses from BV have been seen in patients with a low level of CD30 positivity, which is acceptable for the use of BV-based regimens.[5]

Biliary Tract Cancers

Intrahepatic Cholangiocarcinoma/Extrahepatic Cholangiocarcinoma

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

For **NCCN** required criteria coverage:

3. Primary treatment in combination with ipilimumab for unresectable or resected gross residual (R2) disease, or metastatic disease that is tumor mutational burden-high (TMB-H); OR
4. Subsequent treatment for progression on or after systemic therapy for unresectable or resected gross residual (R2) disease, or metastatic disease as a single agent in those who have not been previously treated with a checkpoint inhibitor; OR
5. Subsequent treatment in combination with ipilimumab for progression on or after systemic therapy for unresectable or resected gross residual (R2) disease, or metastatic disease that TMB-H in those who have not been previously treated with a checkpoint inhibitor

   Note: For those with disease refractory to standard therapies or who have no standard treatment options available; OR

Gallbladder Cancer

6. Neoadjuvant systemic therapy in combination with ipilimumab for resectable locoregionally advanced disease that is tumor mutational burden-high (TMB-H) and presents as one of the following:
   a) Incidental finding of suspicious mass during surgery when hepatobiliary surgery expertise unavailable

b) Incidental finding on pathologic review (cystic duct node positive)
c) Mass on imaging
d) Jaundice; OR

7. Primary treatment in combination with ipilimumab for unresectable or resected gross residual (R2) disease, or metastatic disease that is TMB-H; OR
8. Subsequent treatment for progression on or after systemic therapy for unresectable or resected gross residual (R2) disease, or metastatic disease as a single agent in those who have not been previously treated with a checkpoint inhibitor; OR
9. Subsequent treatment in combination with ipilimumab for progression on or after systemic therapy for unresectable or resected gross residual (R2) disease, or metastatic disease that TMB-H in those who have not been previously treated with a checkpoint inhibitor.

Note: The above indication is for those with disease refractory to standard therapies or who have no standard treatment options available.[6]

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. Adjuvant therapy 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
4. First-line systemic therapy in combination with cisplatin and gemcitabine followed by nivolumab maintenance therapy in cisplatin eligible patients for one of the following:
   a) Stage II (cT2, N0) disease or stage IIIA (cT3, N0; cT4a, N0; cT1-T4a, N1) disease if a tumor is present following reassessment of tumor status 2-3 months after primary treatment with bladder preserving concurrent chemoradiotherapy and maximal 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 or TURBT
   c) Stage IIIB (cT1-T4a, N2,3) disease as downstaging systemic therapy
   d) Stage IIIB (cT1-T4a, N2,3) disease following partial response or progression after primary treatment with concurrent chemoradiotherapy
   e) Stage IVA (cT4b, any N, M0; any T, any N, M1a) disease
   f) Stage IVA (cT4b, any N, M0) disease as consolidation systemic therapy if no tumor is present following a reassessment of tumor status 2-3 months after primary treatment with concurrent chemoradiotherapy
   g) Stage IVA (cT4b, any N, M0) disease if tumor present following a reassessment of tumor status 2-3 months after primary treatment with concurrent chemoradiotherapy

h) Metastatic stage IVB (any T, any N, M1b) disease
i) Muscle invasive local recurrence or persistent disease in a preserved bladder treated with curative intent
j) Metastatic or local recurrence post cystectomy treated with curative intent; OR

5. Second-line systemic therapy post-platinum or other chemotherapy as a single agent 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 partial response or progression after primary treatment with downstaging systemic therapy or concurrent chemoradiotherapy
   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 the 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 Genitourinary (GU) Tract Tumors

For **NCCN** required criteria coverage:

6. 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
7. Metastatic disease for one of the following:
   a) First-line systemic therapy in combination with cisplatin and gemcitabine in cisplatin eligible patients followed by nivolumab maintenance therapy
   b) Second-line systemic therapy as a single agent post-platinum or other chemotherapy; OR

Urothelial Carcinoma

For **FDA** required criteria coverage:

8. Adjuvant treatment for patients who are at high risk of recurrence after undergoing radical resection; OR
9. First-line treatment for unresectable or metastatic disease in combination with cisplatin and gemcitabine; OR
10. Locally advanced or metastatic disease with progression for one of the following cases:
    a) During or following platinum-containing chemotherapy
    b) Within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy[2]; 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 for one of the following:
    a) First-line systemic therapy in combination with cisplatin and gemcitabine in cisplatin eligible patients followed by nivolumab maintenance therapy
    b) Second-line systemic therapy as a single agent for post-platinum or other chemotherapy; OR

Primary Carcinoma of the Urethra

For **NCCN** required criteria coverage:

13. Adjuvant treatment for pathologic stage T3-4 or N1-2 disease in the male bulbar urethra for one of the following:
    a) If platinum-based neoadjuvant chemotherapy was not given and pT3, pT4a, pN+
    b) If platinum-based neoadjuvant chemotherapy was given and ypT2-ypT4a or ypN+; OR
14. Primary treatment for clinical stage T3-4, cN1-2 disease or cN1-2 palpable inguinal lymph nodes as first-line systemic therapy in combination with cisplatin and gemcitabine in cisplatin eligible patients followed by nivolumab maintenance therapy; OR
15. Recurrent or metastatic disease for one of the following:
    a) First-line systemic therapy in combination with cisplatin and gemcitabine in cisplatin eligible patients followed by nivolumab maintenance therapy
    b) Second-line systemic therapy as a single agent post-platinum or other chemotherapy.[7]

Bone Cancer – Chondrosarcoma/Chordoma/Ewing Sarcoma/Osteosarcoma

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

For **NCCN** required criteria coverage:

3. In combination with ipilimumab for unresectable or metastatic disease that has progressed following prior treatment and has no satisfactory alternative treatment options for TMB-H tumors with 10 or more mutations per megabase.

   Note: Other primary round cell tumors of the bone (e.g., CIC/DUX4, BCOR/CCNB3) can be treated like Ewing sarcoma.[8]

Central Nervous System Cancers

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. In combination with ipilimumab or a single agent treatment for limited brain metastases in BRAF non-specific melanoma for one of the following:
   a) Initial treatment in select cases (e.g., small asymptomatic brain metastases)
   b) Recurrent brain metastases
   c) Relapsed disease with either stable systemic disease or reasonable systemic treatment options; OR
4. Single agent treatment for limited brain metastases in 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)
   b) Recurrent brain metastases
   c) Relapsed disease with either stable systemic disease or reasonable systemic treatment options; OR

Extensive Brain Metastases

For **NCCN** required criteria coverage:

5. In combination with ipilimumab or a single agent treatment for BRAF non-specific melanoma for one of the following:
   a) Primary treatment in select cases (e.g., small asymptomatic brain metastases)
   b) Recurrent disease with stable systemic disease or reasonable systemic treatment options; OR
6. Single agent treatment for PD-L1 positive (Tumor Proportion Score TPS ≥1%) from non-small cell lung cancer for one of the following:
   a) Primary treatment in select cases (e.g., small asymptomatic brain metastases)
   b) Recurrent stable systemic disease or reasonable systemic treatment options; OR

Leptomeningeal Metastases

For **NCCN** required criteria coverage:

7. Intrathecal and intravenous treatment for leptomeningeal metastases from melanoma for one of the following:
   a) Primary treatment for patients with good risk status (KPS ≥60, no major neurologic deficits, minimal systemic disease, and reasonable systemic treatment options, if needed)
   b) Maintenance treatment in patients with negative cerebrospinal fluid (CSF) cytology or in clinically stable patients with persistently positive CSF cytology.[9]

Cervical 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. Second-line or subsequent therapy as a single agent if PD-L1 positive (combined positive score [CPS] ≥1) for one of the following:
   a) Locoregional recurrence
   b) Stage IVB or recurrence with distant metastases.[10]

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. Single agent or in combination with ibrutinib for histologic (Richter) transformation to diffuse large B-cell lymphoma (clonally related or unknown clonal status) in patients with del(17p)/TP53 mutation or who are chemotherapy refractory or unable to receive chemoimmunotherapy.[11]

Colon Cancer

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

For **FDA** required criteria coverage:

2. At least 12 years of age; AND
3. Single agent or in combination with ipilimumab for patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic disease that has progressed after treatment with fluoropyrimidine, oxaliplatin, and irinotecan[2]; OR

For **NCCN** required criteria coverage:

4. At least 18 years of age; AND
5. Single agent or in combination with ipilimumab (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation with ultra-hypermutated phenotype [e.g., TMB >50 mut/Mb] 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) Synchronous unresectable metastases
   d) Unresectable metachronous metastases; OR
6. Single agent or in combination with ipilimumab for dMMR/MSI only 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
   c) Initial treatment for resectable metachronous metastases, if no previous immunotherapy; OR

7. Systemic therapy for advanced or metastatic disease dMMR/MSI-H or POLE/POLD1 mutation with ultra-hypermutated phenotype (e.g., TMB >50 mut/Mb) in combination with ipilimumab if the patient is a candidate for immunotherapy and if checkpoint inhibitor monotherapy was previously received; OR

Appendiceal Adenocarcinoma

For **NCCN** required criteria coverage:

8. Advanced or metastatic disease dMMR/MSI-H or POLE/POLD1 mutation with ultra-hypermutated phenotype (e.g., TMB >50 mut/Mb), as a single agent or in combination with ipilimumab, if a candidate for immunotherapy and no prior immunotherapy was received; OR
9. Advanced or metastatic disease dMMR/MSI-H or POLE/POLD1 mutation with ultra-hypermutated phenotype (e.g., TMB >50 mut/Mb) in combination with ipilimumab if patient is a candidate for immunotherapy and if checkpoint inhibitor monotherapy was previously received.[12]

Esophageal and Esophagogastric Junction 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. Completely resected and residual pathologic disease who have received neoadjuvant chemoradiotherapy (CRT); OR
4. First-line treatment in combination with fluoropyrimidine- and platinum-containing chemotherapy for unresectable advanced or metastatic squamous cell; OR
5. First-line treatment in combination with ipilimumab for unresectable advanced or metastatic squamous cell; OR
6. Unresectable advanced, recurrent, or metastatic squamous cell after prior treatment with fluoropyrimidine and platinum-based chemotherapy; OR
7. In combination with fluoropyrimidine and platinum-containing chemotherapy for advanced or metastatic adenocarcinoma[2]; OR

For **NCCN** required criteria coverage:

8. Induction systemic therapy in combination with cisplatin or oxaliplatin and capecitabine or fluorouracil for relieving dysphagia in select patients 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; OR
9. Induction systemic therapy for relieving dysphagia in select patients with MSI-H or 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 in combination with one of the following:
   a) Ipilimumab
   b) Oxaliplatin and capecitabine or fluorouracil; OR

10. Induction systemic therapy for relieving dysphagia in select patients 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 ipilimumab; OR
11. Neoadjuvant or perioperative immunotherapy in combination with ipilimumab as primary treatment for adenocarcinoma if the tumor is MSI-H or dMMR and the patient is medically fit for surgery with cT2, N0 (high-risk lesions: lymphovascular invasion, ≥ 3cm, poorly differentiated), cT1b-cT2, N+ or cT3-cT4a, any N disease; OR
12. Perioperative immunotherapy as a single agent for patients with adenocarcinoma and MSI-H or dMMR tumors as postoperative management following R0 resection in patients who have received preoperative therapy with nivolumab and ipilimumab; OR
13. Postoperative therapy for patients who have received preoperative chemoradiation and R0 resection and residual disease (yp T positive and/or N positive); OR
14. Palliative therapy for HER2 overexpression negative patients with PD-L1 CPS ≥ 1 who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease and a Karnofsky performance score ≥60% or an ECOG (PS) ≤2 as first-line therapy in combination with oxaliplatin and fluorouracil or capecitabine for adenocarcinoma (if no prior tumor progression while on therapy with a checkpoint inhibitor); OR
15. 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 in combination with fluorouracil or capecitabine and cisplatin or oxaliplatin for squamous cell carcinoma (if no prior tumor progression while on therapy with a checkpoint inhibitor); OR
16. 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 in combination with ipilimumab for squamous cell carcinoma (if no prior checkpoint inhibitor or no tumor progression while on therapy with a checkpoint inhibitor); OR
17. Palliative therapy for patients with MSI-H or dMMR tumors (independent of PD-L1 status) who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease and a Karnofsky performance score ≥60% or an ECOG (PS) ≤2 (if no prior tumor progression while on therapy with a checkpoint inhibitor) for first-line therapy in combination with one of the following:
    a) Ipilimumab
    b) Oxaliplatin and fluorouracil or capecitabine; OR
18. Palliative therapy for patients with MSI-H or dMMR tumors who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease and a Karnofsky performance score ≥60% or an ECOG (PS) ≤2 as second-line or subsequent therapy in combination with ipilimumab, if no prior tumor progression while on treatment with a checkpoint inhibitor; OR
19. 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 preferred second-line or subsequent therapy (if no prior tumor progression while on therapy with a checkpoint inhibitor).[13]

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 fluoropyrimidine and platinum-containing chemotherapy for advanced or metastatic adenocarcinoma[2]; OR

For **NCCN** required criteria coverage:

4. Neoadjuvant or perioperative immunotherapy in combination with ipilimumab for patients with MSI-H or dMMR tumors as primary treatment before surgery for potentially resectable locoregional disease (cT2 or higher, any N) if medically fit for surgery; OR
5. Perioperative immunotherapy as a single agent for patients with MSI-H or dMMR tumors as postoperative management following R0 resection in patients who have received preoperative therapy with nivolumab and ipilimumab; OR
6. Primary treatment in combination with oxaliplatin and fluorouracil or capecitabine for patients who are medically fit for surgery but with surgically unresectable locoregional HER2 overexpression negative disease and PD-L1 CPS ≥ 1; OR
7. Primary treatment for patients with MSI-H or dMMR tumors (independent of PD-L1 status) who are medically fit for surgery but with surgically unresectable locoregional disease in combination with one of the following:
   a) Ipilimumab
   b) Oxaliplatin and fluorouracil or capecitabine; OR
8. Palliative therapy in combination with oxaliplatin and fluorouracil or capecitabine 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 a Karnofsky performance score ≥60% or an ECOG performance score ≤2 as first-line therapy if no prior checkpoint inhibitor therapy was given or no tumor progression while on therapy with a checkpoint inhibitor; OR
9. Palliative therapy for patients with MSI-H or 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 first-line therapy (if no prior tumor progression while on therapy with a checkpoint inhibitor) in combination with one of the following:
   a) Ipilimumab
   b) Oxaliplatin and fluorouracil or capecitabine; OR
10. 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 a Karnofsky performance score ≥60% or an ECOG performance score ≤2 as second-line or subsequent therapy in combination with ipilimumab for MSI-H or dMMR tumors, if no prior tumor progression while on therapy with a checkpoint inhibitor).[14]

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 or in combination with ipilimumab for multiagent chemotherapy-resistant disease for one of the following:
   a) High-risk
   b) Recurrent or progressive intermediate trophoblastic tumor (placental site or epithelioid).[15]

Head and Neck 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. Recurrent or metastatic squamous cell carcinoma with disease progression on or after a platinum-based therapy[2]; OR

Nasopharynx

For **NCCN** required criteria coverage:

4. First-line systemic therapy in combination with cisplatin and gemcitabine for T1-4, N0-3, M1 and a PS 0-2 for one of the following:
   a) Oligometastatic disease
   b) Widely metastatic disease; OR
5. Subsequent-line systemic therapy, if not previously used, in combination with cisplatin and gemcitabine for T1-4, N0-3, M1 and a PS 0-2 for one of the following:
   a) Oligometastatic disease
   b) Widely metastatic disease; OR
6. Subsequent single agent systemic therapy, if previously treated, recurrent or metastatic non-keratinizing disease for T1-4, N0-3, M1 for one of the following:
   a) Oligometastatic disease
   b) Widely metastatic disease; OR

Very Advanced Head and Neck Cancer

Non-Nasopharyngeal Cancer

For **NCCN** required criteria coverage:

7. Systemic therapy as a first-line option and a performance status PS 0-1 for one of the following:
   a) Metastatic (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
   f) In combination with ipilimumab if a combined positive score (CPS) ≥ 20; OR
8. Systemic therapy as a first-line or subsequent-line option in combination with cetuximab and a PS 0-1 for one of the following:
   a) Metastatic (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; OR

9. Used as combination systemic therapy for resectable locoregional recurrence or persistent disease without prior RT given with one of the following:
   a) Cetuximab
   b) Ipilimumab if there is a combined positive score (CPS) ≥ 20 (first-line only); OR
10. Systemic therapy as an alternate single agent subsequent-line option, if not previously used, if disease progression on or after platinum therapy for 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 and unresectable locoregional recurrence with prior RT, unresectable second primary with prior RT, unresectable persistent disease with prior RT, or recurrent/persistent disease with distant metastases; OR

Nasopharyngeal Cancer

For **NCCN** required criteria coverage:

11. Systemic therapy as an alternate single agent subsequent-line option if previously treated, recurrent, or metastatic non-keratinizing, and a PS 0-3 for unresectable locoregional recurrence with prior radiation therapy (RT), unresectable second primary with prior RT, unresectable persistent disease with prior RT, or recurrent/persistent disease with distant metastases; OR
12. Systemic therapy as a first-line or subsequent-line option with a PS 0-1 for unresectable locoregional recurrence with prior radiation therapy (RT), unresectable second primary with prior RT, unresectable persistent disease with prior RT, or 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

Mucosal Melanoma

For **NCCN** required criteria coverage:

13. Adjuvant systemic therapy as a single agent with postoperative radiation for T3-4a, N0-1 mucosal melanoma of the sinus cavity, nasal cavity, oral cavity, oropharynx, larynx, or hypopharynx.

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. Previously treated with sorafenib in combination with ipilimumab[2]; OR

For **NCCN** required criteria coverage:

4. Subsequent-line systemic therapy as a single agent for those who have not been previously treated with a checkpoint inhibitor or in combination with ipilimumab (in those who have not been previously treated with a checkpoint inhibitor unless following atezolizumab plus bevacizumab) if progression on or after systemic therapy in those who 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

   Note: There is a lack of data for subsequent use of single-agent immunotherapy in those who have previously been treated with a checkpoint inhibitor.[17]

Hodgkin Lymphoma

Classical Hodgkin Lymphoma (CHL)

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

For **FDA** required criteria coverage:

2. At least 18 years of age; AND
3. Relapsed or progressed after one of the following:
   a) Autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin
   b) Three or more lines of systemic therapy that includes autologous HSCT[2]; OR

For **NCCN** required criteria coverage:

4. At least 18 of years age to 60 years of age; AND
5. Primary treatment in combination with AVD (doxorubicin, vinblastine, dacarbazine) for one of the following:
   a) Stage I/II unfavorable disease (B symptoms or bulky mediastinal disease or >10 cm adenopathy)
   b) Stage III-IV disease; OR
6. Second-line systemic therapy for primary refractory disease or suspected relapse and candidate for high-dose therapy and autologous stem cell rescue (HDT/ASCR) in combination with brentuximab vedotin, or in combination with ICE (ifosfamide, carboplatin, etoposide); OR
7. 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 brentuximab vedotin
   b) ICE (ifosfamide, carboplatin, etoposide)
   c) Single agent palliative therapy; OR

8. 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 prior CPI or brentuximab vedotin exposure and progression after <3 months of a CPI or BV-containing regimen for one of the following:
   a) In combination with brentuximab vedotin
   b) In combination with ICE (ifosfamide, carboplatin, etoposide)
   c) Single agent palliative therapy; OR
9. Subsequent systemic therapy (if not previously used) in combination with one of the following:
   a) Brentuximab vedotin
   b) ICE (ifosfamide, carboplatin, etoposide)

   The above regimens are used for primary refractory disease or suspected relapse for one of the following:
   1. Within 3 months and candidate for high-dose therapy and autologous stem cell rescue (HDT/ASCR) (only if Deauville 4 or 5 following restaging with FDG-PET/CT)
   2. After ≥3 months and candidate for HDT/ASCR
   3. Not a candidate for HDT/ASCR; OR

10. Single agent palliative therapy for subsequent treatment (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); OR
11. Single agent for post-allogeneic hematopoietic cell transplant; OR

Management of CHL in Adults Age >60 or Adults with Poor Performance Status or Substantial Comorbidities

For **NCCN** required criteria coverage:

12. Primary treatment for patients >60 years of age who are a candidate for anthracycline in combination with one of the following:
    a) AVD (doxorubicin, vinblastine, dacarbazine) x 4 cycles + ISRT for stage I-II unfavorable disease
    b) AVD (doxorubicin, vinblastine, dacarbazine) x 6 cycles for stage III-IV disease; OR
13. Primary treatment for patients any age and not a candidate for anthracycline in combination with one of the following:
    a) Brentuximab vedotin + ISRT
    b) Single agent + ISRT (if no contraindications to brentuximab vedotin).[18]

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. Single agent or in combination with ipilimumab as subsequent systemic therapy for relapsed or refractory advanced cutaneous, oral, visceral, or nodal disease that has progressed on or

not responded to first-line systemic therapy and progressed on alternate first-line systemic therapy.

Note: Immune checkpoint inhibitors (ICIs) should not be used in patients with multicentric Castleman disease (MCD) or Kaposi's sarcoma herpesvirus (KSHV)-associated inflammatory cytokine syndrome (KICS) due to the risk of a flare of these conditions. If the patient has a history of KSHV-associated diseases, ICIs should be used with caution and consideration with more frequent monitoring for signs and symptoms of KICS or MCD.[19]

Kidney 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 therapy for stage IV or relapsed disease for one of the following:
   a) Subsequent therapy for clear cell histology if immuno-oncology therapy is naive
   b) Systemic therapy for non-clear cell histology; OR
4. In combination with ipilimumab for 4 cycles followed by single agent nivolumab 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 naive
   c) Subsequent therapy if prior history includes immuno-oncology therapy; OR
5. In combination with cabozantinib for stage IV or relapsed disease with clear cell histology for one of the following:
   a) First-line
   b) Subsequent therapy if immuno-oncology therapy naive
   c) Subsequent therapy if prior history includes immuno-oncology therapy; OR
6. In combination with cabozantinib for stage IV or relapsed disease with non-clear cell histology; OR
7. In combination with ipilimumab for stage IV or relapsed disease for 4 cycles followed by single agent nivolumab as single therapy for non-clear cell histology

   Note: If first-line therapy and stage IV, then M1 or unresectable T4, M0 only[20]; OR

Renal Cell Carcinoma

For **FDA** required criteria coverage:

8. First-line treatment in combination with ipilimumab for intermediate or poor risk advanced disease; OR
9. First-line treatment in combination with cabozantinib for advanced disease; OR
10. Advanced disease patients who have received prior anti-angiogenic therapy[2]; OR

Hereditary Renal Cell Carcinoma

For **NCCN** required criteria coverage:

11. In combination with cabozantinib for non-clear cell histology including hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated renal cell carcinoma (RCC).[20]

Melanoma

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

For **FDA** required criteria coverage:

2. At least 12 years of age; AND
3. Single agent or in combination with ipilimumab for unresectable or metastatic disease; OR
4. Adjuvant treatment for completely resected stage IIB, stage IIC, stage III, or stage IV disease[2]; OR

Uveal

For **NCCN** required criteria coverage:

5. At least 18 years of age; AND
6. Metastatic or unresectable disease for one of the following:
   a) Single agent
   b) In combination with ipilumumab[21]; OR

Cutaneous

For **NCCN** required criteria coverage:

7. At least 18 years of age; AND
8. Adjuvant systemic therapy 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
9. Single agent for adjuvant systemic therapy for one of the following:
   a) Clinical stage IIIB/C/D disease following a wide excision alone or wide excision with negative SLN biopsy after microscopic satellites are found in the biopsy specimen from the primary lesion
   b) Clinical stage IIIB/C/D disease if SLN negative or if SLN biopsy is not performed after microscopic satellites are found in a wide excision specimen
   c) Resected stage III sentinel node positive disease (based on risk of recurrence), during radiographic surveillance or after the completion of a lymph node dissection (CLND)
   d) Stage III disease with clinically positive node(s) following the wide excision of the primary tumor with the therapeutic lymph node dissection (TLND)
   e) Stage III disease with clinical satellite/in-transit metastases if there is no evidence of disease (NED) after complete excision to clear margins or consider if there is 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 the excision of the recurrence with TLND
h) 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

10. Neoadjuvant systemic therapy option in combination with ipilimumab or as a single agent for one of the following:
    a) Primary treatment for stage III disease with 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
11. Adjuvant systemic therapy option in combination with ipilimumab if no evidence of disease following metastasis-directed therapy (complete resection, stereotactic ablative therapy, or T-VEC/intralesional therapy) or systemic therapy followed by resection for oligometastatic disease; OR
12. First-line systemic therapy as a single agent or in combination with ipilimumab for metastatic or unresectable disease; OR
13. Second-line or subsequent systemic therapy option for metastatic or unresectable disease for progression, intolerance and/or projected risk of progression with BRAF-targeted therapy for one of the following:
    a) Single agent (if not previously used) or in combination with ipilimumab
    b) Re-induction therapy (as a single agent or in combination with ipilimumab), if prior anti-PD-1 immunotherapy 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.

    Note: Systemic therapy is preferred for unresectable or widely disseminated distant metastatic disease which includes stage III unresectable/borderline resectable disease with clinically positive node(s) or clinical satellite/in-transit metastases, or as well as unresectable/borderline resectable local satellite/in-transit recurrence, unresectable nodal recurrence, and widely disseminated distant metastatic disease.[22]

Merkel Cell 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. Neoadjuvant treatment as a single agent for one of the following:
    a) Surgical candidates after a multidisciplinary consultation if diagnosed with primary clinical N0 locally advanced disease where curative surgery and curative radiation therapy were originally deemed not feasible
    b) Primary clinical N+, M0 regional disease with biopsy positive draining nodal basin; OR
4. Treatment as a single agent for one of the following:

a) Primary N+, M0 regional disease with biopsy positive draining nodal basin if curative surgery and curative radiation therapy (RT) are not feasible
b) Recurrent N+ regional disease if curative surgery and curative RT are not feasible
c) M1 disseminated disease; OR

5. Treatment in combination with ipilimumab for one of the following:
   a) Primary N+, M0 regional disease with biopsy positive draining nodal basin if curative surgery and curative radiation therapy (RT) are not feasible
   b) Recurrent N+ regional disease if curative surgery and curative RT are not feasible
   c) M1 disseminated disease.[23]

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

   Note:

   1. May also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma
   2. Best supportive care is recommended for patients presenting with a PS=3-4
   3. Low-risk features: epithelioid histology; absence of any high-risk features
   4. High-risk features: biphasic/sarcomatoid histology, nodal metastasis, Ki-67 >9%, thrombocytosis, a PS=2, bicavitary disease, high disease burden/incomplete cytoreduction (peritoneal cancer index [PCI] >17, completeness of cytoreduction [cc] score >1);OR

4. Subsequent systemic therapy if chemotherapy was administered first-line for one of the following:
   a) Single agent
   b) In combination with ipilimumab

Note:

1. May also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma.
2. Best supportive care is recommended for patients presenting with a PS of 3-4[24]; OR

Pleural

For **FDA** required criteria coverage:

5. First-line treatment in combination with ipilimumab for unresectable disease[2]; OR

For **NCCN** required criteria coverage:

6. Induction systemic therapy in combination with ipilimumab before surgical exploration for clinical stage I disease and epithelioid histology; OR
7. In combination with ipilimumab as first-line systemic therapy for one of the following:
   a) Clinical stage I disease and epithelioid histology as initial treatment
   b) Clinical stage II-IV disease and epithelioid histology, sarcomatoid or biphasic histology (any stage), or if medically inoperable as initial treatment
   c) Clinical stage I disease and epithelioid histology following surgical exploration (if induction systemic therapy was not given)

   Note: For the above 2 indications, the best supportive care is recommended for patients presenting with a PS 3-4; OR

8. Subsequent systemic therapy if chemotherapy was administered first-line for one of the following:
   a) Single agent
   b) In combination with ipilimumab

   Note: It may also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma.[25]

Neuroendocrine and Adrenal Tumors

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

Well-Differentiated Grade 3 Neuroendocrine Tumors

For **NCCN** required criteria coverage:

3. Locally advanced, metastatic disease with unfavorable biology (relatively high Ki-67 [≥55%], rapid growth rate, negative SSTR-based PET imaging) in combination with ipilimumab; OR

Extrapulmonary Poorly Differentiated: Neuroendocrine Carcinoma/Large or Small Cell Carcinoma/Mixed Neuroendocrine-Non-Neuroendocrine Neoplasm

For **NCCN** required criteria coverage:

4. Subsequent therapy for treatment in combination with ipilimumab if progression on first-line chemotherapy for metastatic disease.[26]

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. Neoadjuvant treatment in combination with platinum-doublet chemotherapy for resectable tumors ≥4 cm or node positive; OR
4. Neoadjuvant treatment, in combination with platinum-doublet chemotherapy, followed by single agent nivolumab as adjuvant treatment after surgery, for patients with resectable tumors ≥4 cm or node positive disease and no known EGFR mutations or ALK rearrangements; OR
5. First-line treatment in combination with ipilimumab for metastatic disease expressing PD-L1 (≥1%), with no EGFR or ALK genomic tumor aberrations; OR
6. First-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, for patients with metastatic or recurrent disease with no EGFR or ALK genomic tumor aberrations; OR
7. Metastatic disease with progression on or after platinum-based chemotherapy for patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivulomab[2]; OR

For **NCCN** required criteria coverage:

8. Neoadjuvant systemic therapy for resectable (tumors ≥4 cm or node positive) disease (if candidates for immune checkpoint inhibitors and no known EGFR mutations or ALK rearrangements) in combination with one of the following:
   a) Paclitaxel and carboplatin
   b) Pemetrexed and cisplatin or carboplatin for those who are not candidates for cisplatin-based therapy (nonsquamous cell histology)
   c) Gemcitabine and cisplatin or carboplatin for those who are not candidates for cisplatin-based therapy (squamous cell histology)
   d) Paclitaxel and cisplatin

   The above regimens are used for one of the following:

   1. 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
   2. Clinical presentation of chest wall, trachea/carina, mediastinum, or diaphragm; T3 invasion, N0-1; resectable T4 invasion, N0-1 disease
   3. Clinical presentation of resectable stage IIIA (T4 [size], N0-1)

4. Operable T2a-3, N0 or T1-3, N1 nodes positive, M0 findings on mediastinal biopsy
5. T1-3, N2 nodes positive, M0 findings on mediastinal biopsy
6. Clinical presentation of separate pulmonary nodule(s), same lobe (T3, N0-1), or ipsilateral non-primary lobe (T4, N0-1); OR

Note:

1. Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents. Some oncogenic drivers (e.g., EGFR exon 19 deletion or exon 21 L858R; ALK, RET, or ROS1 rearrangements) are associated with less benefit from PD-1/PD-L1 inhibitors
2. Selected patients with N2 disease (fit, single station non-bulky N2, requiring only lobectomy) may be considered for systemic therapy followed by surgery; OR

9. Single agent systemic therapy for those with completely resected tumors ≥ 4 cm or node positive NSCLC stages IB-IIIA, IIIB (T3-4, N2) who have received previous neoadjuvant nivolumab plus chemotherapy (and no known EGFR mutations or ALK rearrangements); OR
10. For recurrent, advanced, or metastatic disease as first-line therapy 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 PS 0-2 in combination for one of the following:
    a) Ipilimumab
    b) Ipilimumab, pemetrexed, and either carboplatin or cisplatin for non-squamous cell histology
    c) Ipilimumab, paclitaxel, and carboplatin for squamous cell histology; OR
11. Continuation maintenance therapy in combination with ipilimumab for recurrent, advanced, or metastatic disease for PD-L1 expression positive (≥1%) or 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 in patients with a PS 0-2 who achieved a response or stable disease following first-line therapy if nivolumab + ipilimumab +/- chemotherapy was given; OR
12. For recurrent, advanced, or metastatic disease with a PS 0-2, 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) Ipilimumab
    b) Ipilimumab, pemetrexed, and either carboplatin or cisplatin for nonsquamous cell histology
    c) Ipilimumab, paclitaxel, and carboplatin for squamous cell histology

    The above regimens are used for one of the following:

    1. Initial systemic therapy for PD-L1 <1% and negative for actionable molecular biomarkers (may be KRAS G12C mutation positive)
    2. First-line therapy for EGFR exon 20 insertion mutation positive tumors
    3. First-line or subsequent therapy for BRAF V600E mutation positive tumors
    4. First-line or subsequent therapy for NTRK1/2/3 gene fusion positive tumors
    5. First-line or subsequent therapy for MET exon 14 skipping mutation positive tumors
    6. First-line therapy for ERBB2 (HER2) mutation positive tumors

7. First-line therapy for NRG1 gene fusion positive tumors
8. Subsequent therapy for EGFR S768I, L861Q, and/or G719X mutation positive tumors and prior afatinib, osimertinib, erlotinib, gefitinib, or dacomitinib therapy; OR

13. Single agent as subsequent therapy for recurrent, advanced, or metastatic disease with a PS 0-2 if no contraindications to PD-1 or PD-L1 inhibitors and no prior progression on a PD-1/PD-L1 inhibitor.

Note:

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 (i.e., 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.[27]

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. Subsequent therapy in combination with ipilimumab if no prior immunotherapy was received and if TMB-H [≥ 10 mut/Mb] for locally advanced or metastatic disease and disease progression for one of the following:
   a) A good performance status (PS) defined as an ECOG PS 0-1 with good biliary drainage and adequate nutritional intake
   b) An intermediate PS (ECOG 2); OR
4. In combination with ipilimumab is used if there is no prior immunotherapy was received, if TMB-H is ≥ 10 mut/Mb is present for one of the following:
   a) A good PS 0-1
   b) An intermediate PS 2 for one of the following:
      i. Local recurrence in the pancreatic operative bed after resection
      ii. Recurrent metastatic disease with or without local recurrence after resection.
      iii. As alternate systemic therapy not previously used.[28]

Pediatric Aggressive Mature B-Cell Lymphomas - Primary Mediastinal Large B-Cell Lymphoma

1. Less than 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; OR
4. Consolidation/additional therapy in combination with brentuximab vedotin, if a partial response is achieved after therapy for relapsed or refractory disease.[29]

Pediatric Central Nervous System Cancers

Pediatric Diffuse High-Grade Gliomas

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 hyper-mutant tumor in pediatric diffuse high-grade glioma for one of the following:
   a) Post standard brain radiation therapy (SBRT) with or without concurrent temozolomide in patients ≥3 years old
   b) Patients <3 years old

   Note: The above indication does not include diffuse midline glioma, H3 K27-altered or pontine location; OR

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

Note: The above indication does not include oligodendroglioma, IDH-mutant and 1p/19q co-deleted, or astrocytoma IDH-mutant.[30]

Pediatric Hodgkin Lymphoma

Classical Hodgkin Lymphoma

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

For **NCCN** required criteria coverage:

2. Primary treatment for intermediate risk disease in combination with AVD (doxorubicin, vinblastine, dacarbazine) for patients 12 years of age or greater with stage III or IV disease; OR
3. Primary treatment for high-risk disease in combination with AVD for patients 12 years of age or greater with stage III or IV disease; OR
4. Re-induction therapy or subsequent therapy (if not previously used) in combination with brentuximab vedotin for relapsed or refractory disease as a consideration in patients with heavily pretreated disease (with platinum or anthracycline-based chemotherapy) or if a decrease in cardiac function is observed; OR
5. Re-induction therapy in combination with brentuximab vedotin and involved site radiation therapy (ISRT) (only in highly favorable patients) for relapsed or refractory disease as a consideration in patients with heavily pretreated disease (with platinum or anthracycline-based chemotherapy) or if a decrease in cardiac function is observed

Note: Recommended for those who may avoid autologous stem cell rescue (ASCR): initial stage other than IIIB or IVB, no prior exposure to RT, duration of CR1 >1 year, absence of extranodal disease, or B symptoms at relapse; OR

6. Subsequent therapy (if not previously used) as a single agent for relapsed or refractory disease in patients with heavily pretreated disease (with platinum or anthracycline-based chemotherapy) or if a decrease in cardiac function is observed.[31]

Rectal Cancer

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

For **FDA** required criteria coverage:

2. At least 12 years of age; AND
3. As a single agent or in combination with ipilimumab for patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic disease that has progressed after treatment with fluoropyrimidine, oxaliplatin, and irinotecan[2]; OR

For **NCCN** required criteria coverage:

4. At least 18 years of age; AND
5. Primary treatment as single agent or in combination with ipilimumab in patients with deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) or polymerase epsilon/delta (POLE/POLD1) mutation with ultra-hypermutated phenotype (e.g., TMB >50 mut/Mb), if a candidate for immunotherapy and no prior immunotherapy was received for one of the following:
   a) Synchronous abdominal/peritoneal metastases that are nonobstructing, or following local therapy for patients with existing or imminent obstruction
   b) Synchronous unresectable metastases
   c) Potentially resectable or unresectable isolated pelvic/anastomotic recurrence
   d) Unresectable metachronous metastases; OR
6. Systemic therapy for advanced or metastatic disease dMMR/MSI-H or POLE/POLD1 mutation with ultra-hypermutated phenotype (e.g., TMB >50 mut/Mb) in combination with ipilimumab if a patient is a candidate for immunotherapy and if checkpoint inhibitor monotherapy was previously received; OR
7. Single agent for patients with dMMR/MSI-H or polymerase epsilon/delta [POLE/POLD1] mutation with ultra-hypermutated phenotype (e.g., TMB >50 mut/Mb) with no previous treatment and a checkpoint inhibitor as neoadjuvant/definitive immunotherapy for T3, N any; T1-2, N1-2; T4, N any; or locally unresectable or medically inoperable disease; OR
8. Single agent or in combination with ipilimumab for patients with dMMR/MSI-H or POLE/POLD1 mutation with ultra-hypermutated phenotype (e.g., TMB >50 mut/Mb) for one of the following:
   a) Neoadjuvant for resectable synchronous liver only and/or lung only metastases, if no previous treatment with a checkpoint inhibitor
   b) Initial treatment for resectable metachronous metastases and no previous immunotherapy.[32]

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 therapy for locally advanced disease for one of the following:
   a) Primary treatment if curative surgery and curative radiation therapy (RT) are not feasible
   b) Additional treatment if positive surgical margins and curative surgery and curative RT are not feasible; OR
4. Single agent therapy for one of the following:
   a) Regional disease that is unresectable, inoperable, or incompletely resected if curative radiation therapy (RT) is not feasible
   b) Satellitosis/in-transit metastasis that is unresectable or incompletely resected
   c) Regional recurrence or distant metastatic disease.[33]

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 or in combination with ipilimumab 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 [e.g., tumor mutational burden (TMB) > 50 mut/Mb]); OR
4. Single agent or in combination with ipilimumab for advanced or metastatic disease dMMR/MSI-H or POLE/POLD1 mutation with ultra-hypermutated phenotype (e.g., TMB >50 mut/Mb), if no previous treatment with a checkpoint inhibitor, for any line of therapy

   Note: The combination of nivolumab with ipilimumab may be considered as subsequent therapy if checkpoint inhibitor monotherapy was previously received.[34]

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 there has been a chemotherapy-free interval of ≤6 months with a performance status 0-2 for one of the following:
   a) Relapse following complete or partial response or stable disease with primary treatment
   b) Primary progressive disease.[35]

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 treatment as a single agent or in combination with ipilimumab as 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. Single agent or in combination with ipilimumab as palliative treatment for patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] tumors regardless of soft tissue sarcoma sub-type, that have progressed following prior treatment and who have no satisfactory alternative treatment options as subsequent lines of therapy for advanced/metastatic disease with disseminated metastases

   Note: If an atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLPS) in the extremity, abdominal wall, or trunk shows evidence of de-differentiation, it should be treated as other soft tissue sarcomas; OR

Retroperitoneal/Intra-Abdominal

For **NCCN** required criteria coverage:

5. Single agent or in combination with ipilimumab 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 or in combination with ipilimumab for the treatment of patients with unresectable or metastatic TMB-H (≥10 mut/Mb) tumors regardless of soft tissue sarcoma sub-type, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options 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 or in combination with ipilimumab for advanced/metastatic pleomorphic disease as subsequent-line of therapy (including for unresectable or metastatic TMB-H) [≥10 mut/Mb] tumors, that have progressed following prior treatment and who have no satisfactory alternative treatment options; OR

Angiosarcoma

For **NCCN** required criteria coverage:

8. In combination with ipilimumab.[36]

T-Cell Lymphomas - Extranodal Natural Killer Cells

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 or refractory disease following additional therapy with an alternate combination chemotherapy regimen (asparaginase-based) not previously used, if a clinical trial is unavailable.[37]

Thyroid Carcinoma - Anaplastic 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 stage IVC (metastatic) disease for one of the following:
   a) Aggressive first-line therapy
   b) Second-line therapy.[38]

Uterine Neoplasms

Endometrial 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. Second-line or subsequent therapy as a single agent for recurrent MSI-H or 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 EBRT and with or without brachytherapy for locoregional recurrence in patients with no prior RT to the 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 the site of recurrence.[39]

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. Second-line or subsequent therapy as a single agent if PD-L1 positive (combined positive score [CPS] ≥1) for one of the following:
   a) Locoregional recurrence
   b) Stage IVB or recurrent distant metastases.[40]

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. Second-line or subsequent-line of therapy for advanced or recurrent/metastatic disease as a single agent for HPV-related tumors.[41]

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

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Nivolumab: 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	Neuroendocrine tumors
C11	Nasopharynx

C15.9	Esophageal and esophagogastric junction/esophageal adenocarcinoma
C16.9	Gastric cancer
C17.9	Small bowel adenocarcinoma
C18.1	Appendiceal adenocarcinoma
C18.9	Colon cancer
C20.0	Rectal cancer
C21.1	Anal carcinoma
C22.0	Hepatocellular carcinoma
C22.1	Intrahepatic cholangiocarcinoma
C23.0	Gallbladder cancer
C24.0	Extrahepatic cholangiocarcinoma
C24.1	Ampullary adenocarcinoma
C24.9	Biliary tract cancers
C25.0	Pancreatic adenocarcinoma
C34.1	Small cell lung cancer
C34.9	Non-small cell lung cancer
C43.0	Cutaneous melanoma
C41.0	Osteosarcoma
C41.1	Chondrosarcoma
C41.2	Chordoma
C41.4	Ewing sarcoma
C43.9	Mucosal melanoma

C44.92	Squamous cell skin cancer
C45.0	Pleural mesothelioma
C45.1	Peritoneal mesothelioma
C46.9	Kaposi sarcoma
C48.2	Retroperitoneal/intra-abdominal soft tissue sarcoma
C49.0	Rhabdomyosarcoma/angiosarcoma
C49.9	Extremity/body wall, head/neck
C51.9	Vulvar cancer
C52.0	Vaginal cancer
C53.9	Cervical cancer
C54.1	Endometrial carcinoma
C58.0	Gestational trophoblastic neoplasia
C64.0	Kidney cancer
C67.0	Bladder cancer
C67.5	Urothelial carcinoma of the prostate
C67.9	Urothelial carcinoma
C68.0	Primary carcinoma of the urethra
C68.9	Upper genitourinary tract tumors
C69.4	Uveal melanoma
C71.0	Pediatric central nervous system cancers
C71.9	Pediatric diffuse high-grade gliomas
C73.0	Thyroid carcinoma – oncocytic carcinoma

C74.0	Adrenal tumors
C76.0	Head and neck cancers
C79.31	Limited brain metastases/extensive brain metastases
C79.49	Leptomeningeal metastases
C81.9	Pediatric Hodgkin lymphoma/Hodgkin lymphoma/classic Hodgkin lymphoma
C83.0	Small lymphocytic lymphoma
C83.3	Diffuse large B-cell lymphomas
C83.7	Pediatric aggressive mature B-cell
C85.2	Primary mediastinal large B-cell lymphoma
C91.1	Chronic lymphocytic leukemia
C91.5	T-cell lymphoma

Nivolumab: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	1/1/2025
2	Policy Review Dates:	3/14/2025
3	Policy Revision Dates:	3/10/2025, 3/14/2025
4	Department Owner:	Medical Affairs
5	NH Advisory Committee:	2/10/2025, 3/20/2025
6	Revision Changes:	3/14/2025 - One indication added for colon, appendiceal adenocarcinoma, gastric, non-small cell lung, and rectal cancer. One gastric indication was removed, and two were removed under head and neck.