CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Ipilimumab (Yervoy®)

Version: 1.0

EFFECTIVE DATE: 1/1/2025

NantHealth® | Eviti®

Please note the following:

Ipilimumab (Yervoy®)

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.

Ipilimumab (Yervoy): Discussion

Ipilimumab is a monoclonal antibody that binds to cytotoxic T-lymphocyte antigen-4 (CTLA-4) and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. CTLA-4 is a negative regulator of T-cell activity, an immune-inhibitory molecule expressed in activated T-cells and in suppressor T regulatory cells. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response.[1,2]

Ipilimumab is approved by the Food and Drug Administration (FDA) for the following cancer types: melanoma, renal cell, colorectal, hepatocellular, non-small cell lung, pleural mesothelioma, and esophageal.

Significant adverse reactions that can be associated with ipilimumab include fatal immune mediated reactions, embryo fetal toxicity, and severe infusion related toxicities.[1]

The National Comprehensive Cancer Network (NCCN) endorses ipilimumab for the following cancer types: Merkel cell, uveal, esophageal and esophagogastric junction, pancreatic adenocarcinoma, ampullary adenocarcinoma, gastric, chondrosarcoma, chordoma, Ewing sarcoma, osteosarcoma, colon, appendiceal adenocarcinoma, rectal, kidney, well-differentiated grade 3 neuroendocrine, extrapulmonary poorly differentiated neuroendocrine large or small cell and mixed neuroendocrine-non-neuroendocrine neoplasm, limited brain metastases, extensive brain metastases, non-small cell lung, hepatocellular carcinoma, cutaneous, Kaposi sarcoma, peritoneal, pleural, soft tissue sarcoma, intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, head and neck, gallbladder, and small bowel adenocarcinoma.[3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24]

Ipilimumab: Definitions

- **CD80/CD86** - Proteins found on antigen-presenting cells that interact with CD28 and CTLA-4 on T cells to regulate immune responses. CD80 is expressed more slowly, while CD86 is more abundant and increases rapidly upon activation.[25]
- **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.

Ipilimumab: Policy

Note: Coverage of ipilimumab 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.

Ipilimumab will be considered for coverage when the following criteria are met:

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. Single agent or in combination with nivolumab for M1 disseminated disease if anti-PD-L1 or anti-PD-1 therapy is contraindicated or disease has progressed on anti-PD-L1 or anti-PD-1 monotherapy.[3]

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 for unresectable or metastatic disease.[1]

Uveal

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 nivolumab for metastatic or unresectable disease.[4]

Cutaneous

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

For **FDA** required criteria coverage:

3. Adjuvant treatment of patients with pathologic involvement of regional lymph nodes of more than 1 mm, who have undergone complete resection, including total lymphadenectomy[1]; OR

For **NCCN** required criteria coverage:

4. Neoadjuvant systemic therapy in combination with nivolumab for one of the following:
   a) Primary treatment for stage III disease with clinically positive, resectable nodal disease
   b) Initial and/or subsequent-line of treatment for limited resectable stage III disease with clinical satellite/in-transit metastases
   c) Initial and/or subsequent-line of treatment for limited resectable local satellite/in-transit recurrence
   d) For resectable disease limited to nodal recurrence; OR
5. Single agent adjuvant systemic therapy option (if prior exposure to anti-PD-1 therapy) for one of the following:
   a) Local satellite/in-transit recurrence if no evidence of disease (NED) after complete excision to clear margins or consider if NED after initial treatment with local or regional therapy
   b) Resectable disease limited to nodal recurrence following excision of the recurrence and therapeutic lymph node dissection
   c) 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
6. First-line systemic therapy for metastatic or unresectable disease for one of the following in combination with:
   a) Nivolumab
   b) Pembrolizumab at a low dose; OR
7. Second-line or subsequent-line systemic therapy for metastatic or unresectable disease after disease progression, intolerance, and/or projected risk of progression with BRAF-targeted therapy for one of the following:
   a) In combination with nivolumab if not previously used or for disease progression on single agent anti-PD-1 therapy
   b) At a low dose, in combination with pembrolizumab for disease progression following single agent anti-PD-1 therapy
   c) Single agent (if not previously used alone or in combination with anti-PD-1 therapy)
   d) In combination with intralesional injection of talimogene laherparepvec (for low burden of disease and injectable lesions)

e) Re-induction therapy (as a single agent or in combination with anti-PD-1 therapy) if prior use 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.[5]

Note: Systemic therapy is preferred for unresectable or widely disseminated distant metastatic disease which includes stage III unresectable/borderline resectable disease with clinically positive nodes 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.

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. First-line treatment in combination with nivolumab for unresectable advanced or metastatic squamous cell carcinoma[1]; OR

For **NCCN** required criteria coverage:

4. Induction systemic therapy for relieving dysphagia in select patients with or without microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors (independent of PD-L1 status) who are medically fit and planned for an esophagectomy with cT2, N0 (high-risk lesions: lymphovascular invasion, ≥ 3cm, poorly differentiated), cT1b-cT2, N+ or cT3-cT4a, any N disease in combination with nivolumab; OR
5. Neoadjuvant or perioperative immunotherapy in combination with nivolumab as primary treatment for adenocarcinoma if a 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
6. 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 for one of the following:
   a) First-line therapy in combination with nivolumab for squamous cell carcinoma (if no prior tumor progression while on therapy with a checkpoint inhibitor)
   b) First-line therapy for MSI-H or dMMR tumors (independent of PD-L1 status) in combination with nivolumab (if no prior tumor progression while on therapy with a checkpoint inhibitor)
   c) Second-line or subsequent-line therapy for MSI-H or dMMR tumors in combination with nivolumab (if no prior tumor progression while on therapy with a checkpoint inhibitor).[6]

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-line therapy in combination with nivolumab if no prior immunotherapy and if 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 a ECOG PS 0-1 with good biliary drainage and adequate nutritional intake)
   b) Intermediate PS (ECOG 2); OR
4. In combination with nivolumab if there is no prior immunotherapy and if the tumor mutational burden is high (TMB-H) [≥ 10 mut/Mb], for patients with a good performance status (ECOG PS 0-1) or an intermediate performance status (ECOG 2) 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.[7]

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 nivolumab in patients with intestinal type disease if MSI-H or dMMR for one of the following:
   a) Unresectable localized disease
   b) Stage IV resected
   c) Metastatic disease at initial presentation; OR
4. For disease progression in combination with nivolumab if no prior immunotherapy and if MSI-H or dMMR.[8]

Gastric 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. In combination with nivolumab for patients with early-stage gastric adenocarcinoma with MSI-H or dMMR tumors (independent of PD-L1 status) with endoscopic features suggestive of deep submucosal invasion including converging folds, irregular surface

pattern, and ulceration in a large gastric mass with favorable histology and completed an endoscopic resection; OR

4. Neoadjuvant or perioperative immunotherapy with nivolumab for MSI-H or dMMR tumors as primary
treatment prior to surgery for potentially resectable locoregional disease (cT2 or higher, any N) if medically fit for surgery; OR
5. Primary treatment in combination with nivolumab for patients with MSI-H or dMMR tumors (independent of PD-L1 status) who are medically fit for surgery but with unresectable locoregional disease; OR
6. 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 in combination with nivolumab (if no prior tumor progression while on therapy with a checkpoint inhibitor); OR
7. 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 nivolumab for MSI-H or dMMR tumors (if no prior tumor progression while on therapy with a checkpoint inhibitor).[9]

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 nivolumab for unresectable or metastatic disease that has progressed following prior treatment and has no satisfactory alternative treatment options for tumor mutational burden-high (TMB-H) tumors with 10 or more mutations per megabase.[10]

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. MSI-H or dMMR metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab[1]; OR

For **NCCN** required criteria coverage:

4. At least 18 years of age; AND
5. In combination with nivolumab (dMMR/MSI-H only) for neoadjuvant therapy for clinical T4b disease; OR
6. In combination with nivolumab (dMMR/MSI-H or polymerase epsilon/delta [POLE/POLD1] mutation) for one of the following:
   a) Neoadjuvant therapy for resectable synchronous liver or lung metastases (if no previous treatment with a checkpoint inhibitor)
   b) Initial treatment for resectable metachronous metastases if no previous immunotherapy.[11]

Appendiceal 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. Systemic therapy for advanced or metastatic disease dMMR, MSI-H or POLE/POLD1 mutation in combination with nivolumab if a candidate for immunotherapy and no prior immunotherapy received.[11]

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. MSI-H or dMMR metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab[1]; OR

For **NCCN** required criteria coverage:

4. At least 18 years of age; AND
5. In combination with nivolumab in patients dMMR/MSI-H or POLE/POLD1 mutation if candidate for immunotherapy and no prior immunotherapy received for one of the following as primary treatment:
   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. Therapy in combination with nivolumab for patients dMMR/MSI-H or POLE/POLD1 mutation for one of the following:

a) Neoadjuvant treatment for resectable synchronous liver or lung metastases and no previous treatment with a checkpoint inhibitor
b) Initial treatment for resectable metachronous metastases and no previous immunotherapy.[12]

Kidney 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. First-line treatment in combination with nivolumab for intermediate or poor risk advanced renal cell carcinoma[1]; OR

For **NCCN** required criteria coverage:

4. In combination with nivolumab 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-line therapy if immuno-oncology therapy naive
   c) Subsequent-line therapy if prior history of immuno-oncology therapy; OR
5. For stage IV or relapsed disease in combination with nivolumab for 4 cycles followed by single agent nivolumab as systemic therapy for non-clear cell histology.[13]

Note: If treatment is first-line therapy and stage IV, then M1 or unresectable T4, M0 only.

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. For locally advanced or metastatic disease with unfavorable biology (relatively high Ki-67 [≥55%], rapid growth rate, negative SSTR-based PET imaging) in combination with nivolumab.

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

For **NCCN** required criteria coverage:

4. Subsequent-line of therapy for treatment in combination with nivolumab if progression on first-line chemotherapy for metastatic disease.[14]

Central Nervous System

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 nivolumab or as a single agent treatment 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.

Extensive Brain Metastases

For **NCCN** required criteria coverage:

4. In combination with nivolumab or as a single agent in 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.[15]

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. First-line treatment in combination with nivolumab for metastatic cancer expressing PD-L1 (≥1%) with no EGFR or ALK genomic tumor aberrations; OR
4. First-line treatment, in combination with nivolumab and two cycles of platinum doublet chemotherapy for metastatic or recurrent cancer with no EGFR or ALK genomic tumor aberrations[1]; OR

For **NCCN** required criteria coverage:

5. 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 performance status 0-2 in combination with one of the following:
   a) Nivolumab (for PDL1 ≥50%; other recommended for PDL1 ≥1-49%)
   b) Nivolumab, pemetrexed and either carboplatin or cisplatin for nonsquamous cell histology
   c) Nivolumab, paclitaxel and carboplatin for squamous cell histology; OR
6. Continuation maintenance therapy in combination with nivolumab 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 performance status 0-2 who achieve a response or stable disease following first-line therapy if nivolumab + ipilimumab +/- chemotherapy given; OR
7. For recurrent, advanced, or metastatic disease with a performance status (PS) 0-1 and no contraindications to PD-1 or PD-L1 inhibitors in combination with one of the following:
   a) Nivolumab
   b) Nivolumab, pemetrexed and either carboplatin or cisplatin for nonsquamous cell histology
   c) Nivolumab, 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-line of therapy for BRAF V600E mutation positive tumors
   4. First-line or subsequent-line of therapy for NTRK1/2/3 gene fusion positive tumors
   5. First-line or subsequent-line of therapy for MET exon 14 skipping mutation positive tumors
   6. First-line or subsequent-line of therapy for RET rearrangement positive tumors
   7. First-line therapy for ERBB2 (HER2) mutation positive tumors
   8. Subsequent-line of therapy for EGFR exon 19 deletion or exon 21 L858R tumors and prior erlotinib +/- (ramucirumab or bevacizumab), afatinib, gefitinib, osimertinib, amivantamab-vmjw + lazertinib, or dacomitinib therapy
   9. Subsequent-line of therapy for EGFR S768I, L861Q, and/or G719X mutation positive tumors and prior afatinib, osimertinib, erlotinib, gefitinib, or dacomitinib therapy
   10. Subsequent-line of therapy for ALK rearrangement positive tumors and prior crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib therapy
   11. Subsequent-line of therapy for ROS1 rearrangement positive tumors and prior crizotinib, entrectinib, repotrectinib, ceritinib, or lorlatinib therapy.[16]

Note:

1. Complete genotyping for EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, and ERBB2 (HER2), via biopsy or plasma testing. If a clinically actionable marker is found, it is reasonable to start therapy based on the identified marker. 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 or current use of immunosuppressive agents, and some oncogenic drivers (i.e., EGFR exon 19 deletion or exon 21 L858R, ALK rearrangements) have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors.

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. Treatment of patients previously treated with sorafenib, in combination with nivolumab[1]; OR

For **NCCN** required criteria coverage:

4. Subsequent-line of systemic therapy in combination with nivolumab if progression on or after systemic therapy in those who have not been previously treated with a checkpoint inhibitor (unless following atezolizumab plus bevacizumab) for 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.[17]

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. In combination with nivolumab 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.[18]

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 nivolumab 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 (epithelioid histology; absence of any high-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 given
   c) Medically inoperable disease; complete cytoreduction not achievable, or presence of any 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)]; OR
4. Subsequent-line of systemic therapy in combination with nivolumab if chemotherapy administered first-line.[19]

Note: May also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma.

Pleural

For **FDA** required criteria coverage:

1. First-line treatment in combination with nivolumab for unresectable disease; OR

For **NCCN** required criteria coverage:

2. Induction systemic therapy in combination with nivolumab prior to surgical exploration for clinical stage I disease and epithelioid histology; OR
3. In combination with nivolumab as first-line systemic therapy for one of the following:
   a) Stage I disease and epithelioid histology as initial treatment
   b) Stage II-IV disease and epithelioid histology, sarcomatoid or biphasic histology (any stage), or if medically inoperable as initial treatment
   c) Stage I disease and epithelioid histology following surgical exploration (if induction systemic therapy not given); OR
4. Subsequent-line of systemic therapy in combination with nivolumab if chemotherapy administered first-line.[20]

Note: May also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma.

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. In combination with nivolumab as a 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 and metastatic disease with disseminated metastases.[21]

Note: If atypical lipomatous tumor/well differentiated liposarcoma (ALT/WDLPS) of the extremity, abdominal wall, or trunk, if a disease that was initially diagnosed as ALT/WDLPS shows evidence of de-differentiation, treat as other soft tissue sarcomas.

Retroperitoneal/Intra-Abdominal

For **NCCN** required criteria coverage:

1. In combination with nivolumab 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
2. In combination with nivolumab for the treatment of patients with unresectable or (TMB-H) [≥10 mut/Mb] tumors regardless of soft tissue sarcoma sub-type, which have progressed following prior treatment and who have no satisfactory alternative treatment options in 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.[21]

Note: Treat WDLPS (retroperitoneum, para-testicular) with or without evidence of de-differentiation as other soft tissue sarcomas.

Rhabdomyosarcoma

For **NCCN** required criteria coverage:

1. In combination with nivolumab for advanced/metastatic pleomorphic rhabdomyosarcoma as subsequent line of therapy (including for unresectable or metastatic TMB-H) [≥10 mut/Mb] tumors, which have progressed following prior treatment and who have no satisfactory alternative treatment options).[21]

Angiosarcoma

For **NCCN** required criteria coverage:

1. In combination with nivolumab.[21]

Biliary Tract Cancers

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

Gallbladder Cancer

For **NCCN** required criteria coverage:

3. Neoadjuvant systemic therapy in combination with nivolumab for resectable locoregionally advanced disease that is TMB-H and presents for one of the following:
   a) Incidental finding of suspicious mass during surgery where hepatobiliary surgery expertise is unavailable
   b) Incidental finding on pathologic review (cystic duct node positive)
   c) Mass on imaging
   d) Jaundice; OR
4. Primary treatment in combination with nivolumab for unresectable or resected gross residual (R2) disease, or metastatic disease that is TMB-H; OR
5. Subsequent-line of treatment in combination with nivolumab for progression on or after systemic treatment for unresectable or resected gross residual (R2) disease, or metastatic disease that is (TMB-H) in those who have not been previously treated with a checkpoint inhibitor.

Note: For patients whose disease is refractory to standard therapies or for whom no standard treatment options are available.

Intrahepatic/Extrahepatic Cholangiocarcinoma

For **NCCN** required criteria coverage:

1. Primary treatment in combination with nivolumab for unresectable or resected gross residual (R2) disease, or metastatic disease that is tumor mutational burden high (TMB-H); OR
2. Subsequent-line treatment (in combination with nivolumab) for progression on or after systemic therapy for unresectable or resected gross residual (R2) disease, or metastatic disease that is (TMB-H) in those who have not been previously treated with a checkpoint inhibitor.[22]

Note: This is for patients whose disease is refractory to standard therapies or for whom no standard treatment options are available.

Head and Neck 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. First-line systemic therapy as an option in patients with non-nasopharyngeal cancer 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 radiation therapy (RT)
   d) Unresectable second primary with prior RT
   e) Unresectable persistent disease with prior RT; OR
4. In combination with nivolumab if combined positive score (CPS) ≥ 20; OR
5. In combination systemic therapy in non-nasopharyngeal cancer for resectable locoregional recurrence or persistent disease without prior radiation therapy (RT) given with nivolumab if combined positive score (CPS) ≥ 20 (first-line only).[23]

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. In combination with nivolumab as primary treatment for locally unresectable or medically inoperable disease (dMMR/MSI-H); OR
4. In combination with nivolumab for advanced or metastatic disease (dMMR/MSI-H) or (POLE/POLD1) mutation with ultra-hypermutated phenotype [e.g., tumor mutational burden (TMB) > 50 mut/Mb]), if no previous treatment with a checkpoint inhibitor, for any line of therapy.[24]

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

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

Ipilimumab: References

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Ipilimumab: 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
C15.9	Esophageal and esophagogastric junction cancers
C16.9	Gastric cancer
C17.9	Small bowel adenocarcinoma
C18.9	Colon cancer
C20.0	Rectal cancer
C22.0	Hepatocellular carcinoma
C23.0	Gallbladder cancer

C24.0	Biliary tract cancers
C24.1	Ampullary adenocarcinoma
C25.9	Pancreatic adenocarcinoma
C32.9	Head and neck cancer
C34.9	Non-small cell lung cancer
C4A.9	Merkel cell carcinoma
C41.9	Bone cancer
C43.9	Cutaneous melanoma
C45.9	Mesothelioma
C46.9	Kaposi sarcoma
C49.9	Soft tissue sarcoma
C64.9	Kidney cancer
C69.3	Uveal melanoma
C71.9	Central nervous system cancers
C74.9	Neuroendocrine and adrenal tumors
J9228	Ipilimumab

Ipilimumab: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	1/1/2025
2	Policy Review Dates:	
3	Policy Revision Dates:	
4	Department Owner:	Medical Affairs
5	NH Advisory Committee:	1/24/2025
6	Revision Changes:	