CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Nivolumab and Hyaluronidase-nvhy

(Opdivo Qvantig™)

Version: 1.0

EFFECTIVE DATE: 2/1/2025

NantHealth® | Eviti®

Please note the following:

Nivolumab and Hyaluronidase-nvhy (Opdivo Qvantig®)

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 and Hyaluronidase-nvhy (Opdivo Qvantig): Discussion

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. This action releases the PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. The binding of PD-1 ligands (PD-L1 and PD-L2) to the PD-1 receptor on T cells inhibits T-cell proliferation and cytokine production. In some tumors, the upregulation of PD-1 ligands can inhibit active T-cell immune surveillance of tumors through this pathway.

Hyaluronan is a polysaccharide found in the extracellular matrix of the subcutaneous tissue. It is depolymerized by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the interstitial matrix, hyaluronan has a half-life of approximately 0.5 days. Hyaluronidase increases the permeability of the subcutaneous tissue by temporarily depolymerizing hyaluronan.

Nivolumab and hyaluronidase-nvhy is associated with adverse reactions which include severe and fatal immune-mediated reactions, complications of allogeneic hematopoietic stem cell transplantation, embryo-fetal toxicity, and increased mortality in patients with multiple myeloma when nivolumab is added to a thalidomide analog and dexamethasone.

Nivolumab and hyaluronidase-nvhy is approved by the Food and Drug Administration (FDA) for following cancer types: colorectal, esophageal, gastroesophageal, gastric, head and neck, hepatocellular, melanoma, non-small cell, renal cell, and urothelial.[1]

The National Comprehensive Cancer Network (NCCN) endorses nivolumab and hyaluronidase-nvhy for the following cancer types: anal, biliary tract, cervical, central nervous system, colon, gallbladder, gestational, hepatocellular, hereditary renal cell, Kaposi sarcoma, kidney, melanoma, mesothelioma, non-small cell, rectal, small bowel, small cell lung, squamous cell, thyroid, uterine, vaginal, and vulvar.

Nivolumab and Hyaluronidase-nvhy: Definitions

- **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 in a timely manner.
- **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.

Nivolumab and Hyaluronidase-nvhy: Policy

Note: Coverage of Nivolumab and hyaluronidase-nvhy 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 and Hyaluronidase-nvhy will be considered for coverage when the following criteria are met:

Anal Carcinoma

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

For **NCCN** required criteria coverage:

3. Single agent 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.[2]

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 tumor is present following reassessment of tumor status 2-3 months after primary treatment with bladder preserving concurrent chemoradiotherapy and a maximal transurethral resection of bladder tumor (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 a TURBT
   c) Stage IIIB (cT1-T4a, N2,3) disease as downstaging systemic therapy
   d) Stage IIIB (cT1-T4a, N2,3) disease following a 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 there is 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 is 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 a 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 disease is stable 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 was not given and pT3, pT4, or pN+

b) Platinum-based neoadjuvant chemotherapy was 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; 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 was 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.

Note: May be substituted for intravenous nivolumab but it is not indicated in combination with ipilimumab.[3]

Biliary Tract Cancers

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

Gallbladder Cancer/Intrahepatic Cholangiocarcinoma/Extrahepatic Cholangiocarcinoma

For **NCCN** required criteria coverage:

3. 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.

Note: May be substituted for intravenous nivolumab but it is not indicated in combination with ipilimumab.[4]

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. Single agent second-line or subsequent therapy 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.[5]

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. 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; OR
4. Single agent treatment in PD-L1 positive (tumor proportion score [TPS] ≥1%) in 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. Single agent treatment 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; OR
6. Single agent treatment in PD-L1 positive (TPS ≥1%) in non-small cell lung cancer 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

Leptomeningeal Metastases

For **NCCN** required criteria coverage:

7. Intrathecal and intravenous treatment hyroifrom melanoma for one of the following:
   a) Primary treatment for patients with a good risk status (Karnofsky performance score [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.

Note: May be substituted for intravenous nivolumab but it is not indicated in combination with ipilimumab.[6]

Colon Cancer

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

For **FDA** required criteria coverage:

3. MSI-H or dMMR metastatic disease that has progressed after treatment with fluoropyrimidine, oxaliplatin, and irinotecan, as monotherapy or as monotherapy following combination treatment with intravenous nivolumab and ipilimumab[1]; OR

For **NCCN** required criteria coverage:

4. Single agent for deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) or polymerase epsilon/delta (POLE/POLD1) mutation and a candidate for immunotherapy and if no prior immunotherapy was 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

5. Single agent 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 for resectable synchronous liver and/or lung metastases, if no previous treatment with a checkpoint inhibitor was given
   b) Initial treatment for resectable metachronous metastases, if no previous immunotherapy was given; OR
6. Single agent as neoadjuvant therapy in clinical T4b or bulky nodal disease

   Note: May be substituted for intravenous nivolumab but it is not indicated in combination with ipilimumab[7]; OR

   Appendiceal Adenocarcinoma

   For **NCCN** required criteria coverage:

   7. Single agent for advanced or metastatic disease (dMMR/MSI-H or POLE/POLD1 mutation with ultra-hypermutated phenotype [e.g., TMB >50 mut/Mb]), if a candidate for immunotherapy and no prior immunotherapy was received.

      Note: Not indicated in combination with ipilimumab for the treatment of MSI-H or dMMR metastatic disease.[7]

Esophageal 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 chemoradiotherapy for completely resected patients with residual pathologic disease; OR
4. First-line treatment in combination with fluoropyrimidine and platinum-containing chemotherapy for unresectable, advanced or metastatic disease; OR
5. Unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine and platinum-based chemotherapy.

Note: Not indicated in combination with ipilimumab for treating unresectable advanced or metastatic disease patients.[8]

Gastric Cancer and Gastroesophageal Junction Cancer

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

For **FDA** required criteria coverage:

3. Neoadjuvant chemoradiotherapy for completely resected patients with gastroesophageal junction cancer with residual pathologic disease; OR
4. In combination with fluoropyrimidine and platinum-containing chemotherapy for advanced or metastatic disease.[1]

Gestational Trophoblastic Neoplasia

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

For **NCCN** required criteria coverage:

3. Single-agent therapy, for patients who are multiagent chemotherapy-resistant, for one of the following:
   a) High risk disease
   b) Recurrent or progressive intermediate trophoblastic tumor (placental site trophoblastic tumor or epithelioid trophoblastic tumor).[9]

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 disease with progression on or after platinum-based therapy[1]; 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-line 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 or subsequent line option and a PS 0-1 in combination with cetuximab 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
8. Combination systemic therapy for resectable locoregional recurrence or persistent disease without prior RT when given with cetuximab; OR

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

9. Systemic therapy as an alternate single agent subsequent-line option, if not previously used, if there is disease progression on or after platinum therapy for one of the following:
   a) A PS 0-3 and persistent or progressive metastatic disease (M1) at initial presentation following first-line therapy
   b) A PS 3 and unresectable locoregional recurrence without prior RT or unresectable persistent disease without prior RT
   c) A 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:

10. First-line or subsequent-line therapy if 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; OR
11. Systemic therapy as an alternate single agent subsequent-line option if previously treated, recurrent, or metastatic non-keratinizing disease, 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

Mucosal Melanoma

For **NCCN** required criteria coverage:

12. As a single agent for adjuvant systemic therapy with postoperative radiation for T3-4a, N0-1 disease of the sinus cavity, nasal cavity, oral cavity, oropharynx, larynx, or hypopharynx.

Note: May be substituted for intravenous nivolumab but it is not indicated in combination with ipilimumab.[10]

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 and following combination treatment with intravenous nivolumab and ipilimumab; OR

For **NCCN** required criteria coverage:

4. Single agent subsequent line therapy for those who have not been previously treated with a checkpoint inhibitor if there is progression on or after systemic treatment 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.

   Note:
   1. A lack of data exists for subsequent use of single-agent immunotherapy in those who have previously been treated with a checkpoint inhibitor.
   2. May be substituted for intravenous nivolumab but it is not indicated in combination with ipilimumab.[11]

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 naive
   b) Systemic therapy for non-clear cell histology; OR
4. Used in combination with cabozantinib 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. Stage IV or relapsed disease in combination with cabozantinib as systemic therapy for non-clear cell histology.

   Note:
   1. If first-line therapy and stage IV, then M1 or unresectable T4, M0 only
   2. May be substituted for intravenous nivolumab but it is not indicated in combination with ipilimumab[12]; OR

Renal Cell Carcinoma

For **FDA** required criteria coverage:

6. First-line treatment following combination therapy with intravenous nivolumab and ipilimumab for intermediate or poor risk advanced disease; OR
7. First-line treatment in combination with cabozantinib for advanced disease; OR
8. For advanced disease for patients who have received prior anti-angiogenic therapy.

   Note: May be substituted for intravenous nivolumab but it is not indicated in combination with ipilimumab.[1]

Hereditary Renal Cell Carcinoma

For **NCCN** required criteria coverage:

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

   Note: May be substituted for intravenous nivolumab but it is not indicated in combination with ipilimumab.[12]

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 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:
   1. Immune checkpoint inhibitors should not be used in patients with multicentric Castleman disease (MCD) or KSHV–associated inflammatory cytokine syndrome (KICS) due to risk of flare of these conditions. If the patient has a history of KSHV-associated diseases, ICIs should be used with caution and consideration of more frequent monitoring for signs and symptoms of KICS or MCD.
   2. May be substituted for intravenous nivolumab but it is not indicated in combination with ipilimumab.[13]

Melanoma

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

For **FDA** required criteria coverage:

3. Unresectable or metastatic disease; OR

4. Unresectable or metastatic disease following combination treatment with intravenous nivolumab and ipilimumab; OR
5. Adjuvant treatment for patients with completely resected IIB, IIC, III, or IV disease; OR

Note: May be substituted for intravenous nivolumab but it is not indicated in combination with ipilimumab [1]; OR

Cutaneous

For **NCCN** required criteria coverage:

6. Adjuvant systemic therapy as a single agent for stage IIB/IIC disease following the wide excision alone or the wide excision with negative sentinel lymph node (SLN) biopsy; OR
7. Adjuvant systemic therapy as a single agent for one of the following:
   a) Clinical stage IIIB/C/D disease following the wide excision alone or the 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 a SLN biopsy is not performed after microscopic satellites are found in the wide excision specimen
   c) Resected stage III sentinel node positive disease (based on the risk of recurrence), during radiographic surveillance or after the completion of a lymph node dissection
   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 talimogene laherparepvec [T-VEC]/intralesional therapy), or systemic therapy followed by resection for oligometastatic disease; OR
8. Neoadjuvant systemic therapy 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
9. First-line systemic therapy as a single agent for metastatic or unresectable disease
10. Second-line or subsequent systemic therapy 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
    b) Re-induction therapy as a single agent, 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:
1. 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 as well as unresectable/borderline resectable local satellite/in-transit recurrence, unresectable nodal recurrence, and widely disseminated distant metastatic disease
2. May be substituted for intravenous nivolumab but it is not indicated in combination with ipilimumab[14]; OR

Uveal

For **NCCN** required criteria coverage:

11. Single agent therapy for metastatic or unresectable disease.[15]

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 (RT) were originally deemed not feasible
   b) Primary clinical N+, M0 regional disease with biopsy positive draining nodal basin; OR
4. Single agent treatment for one of the following:
   a) Primary N+, M0 regional disease with biopsy positive draining nodal basin if curative surgery and curative RT are not feasible
   b) Recurrent N+ regional disease if curative surgery and curative RT are not feasible
   c) M1 disseminated disease.

Note: May be substituted for intravenous nivolumab but it is not indicated in combination with ipilimumab.[16]

Mesothelioma

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

Peritoneal

3. Single-agent subsequent therapy, if chemotherapy was administered as first-line treatment[17]; OR

Pleural

4. Single-agent subsequent therapy, if chemotherapy was administered as first-line treatment.[18]

   Note:
   1. May also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma.
   2. May be substituted for intravenous nivolumab but it is not indicated in combination with ipilimumab.[17,18]

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 nivolumab and hyaluronidase-nvhy monotherapy as adjuvant treatment after surgery for resectable tumors ≥4 cm or node positive and no known EGFR mutations or ALK rearrangements; OR
5. Metastatic disease and progression on or after platinum-based chemotherapy

   Note: Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA approved therapy for these aberrations prior to receiving nivolumab and hyaluronidase-nvhy[1]; OR

For **NCCN** required criteria coverage:

6. Neoadjuvant systemic therapy for resectable (tumors ≥4 cm or node positive) disease (if a candidate 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 for nonsquamous cell histology
   c) Gemcitabine and cisplatin or carboplatin for those who are not candidates for cisplatin-based therapy for 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).

Note: Selected patients with N2 disease (fit, single station non-bulky N2, requiring only lobectomy) may be considered for systemic therapy followed by surgery; OR

7. Single agent systemic therapy for those with completely resected tumors ≥ 4 cm or node positive NSCLC stages IB-IIIA, IIIB [T3-4, N2] who received previous neoadjuvant nivolumab plus chemotherapy (and no known EGFR mutations or ALK rearrangements); OR
8. 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. 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 of a benefit from PD-1/PD-L1 inhibitors.
2. May be substituted for intravenous nivolumab but it is not indicated in combination with ipilimumab.[19]

Rectal Cancer

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

For **FDA** required criteria coverage:

3. MSI-H or dMMR metastatic disease that has progressed after treatment with fluoropyrimidine, oxaliplatin, and irinotecan, as monotherapy or as monotherapy following combination treatment with intravenous nivolumab and ipilimumab[1]; OR

For **NCCN** required criteria coverage:

4. Single agent as primary treatment for 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
5. Single agent for patients with dMMR/MSI-H or POLE/POLD1 mutation with ultra-hypermutated phenotype [e.g., TMB >50 mut/Mb]) with no previous treatment with a

checkpoint inhibitor as neoadjuvant/definitive immunotherapy for T3, N any; T1-2, N1-2; T4, N any; or locally unresectable or medically inoperable disease; OR

6. Single agent 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.

Note: May be substituted for intravenous nivolumab but it is not indicated in combination with ipilimumab.[20]

Small Bowel Adenocarcinoma

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

For **NCCN** required criteria coverage:

3. Single agent as primary treatment for locally unresectable or medically inoperable disease (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation with ultra-hypermutated phenotype [e.g., tumor mutational burden (TMB) > 50 mut/Mb]); OR
4. Single agent for advanced or metastatic disease (deficient mismatch repair/microsatellite instability-high [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:
   1. The combination of nivolumab with ipilimumab may be considered as subsequent therapy if checkpoint inhibitor monotherapy was previously received.
   2. May be substituted for intravenous nivolumab but it is not indicated in combination with ipilimumab.[21]

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.

Note: May be substituted for intravenous nivolumab but it is not indicated in combination with ipilimumab.[22]

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 RT is not feasible
   b) Satellitosis/in-transit metastasis that is unresectable or incompletely resected
   c) Regional recurrence or distant metastatic disease.

Note: May be substituted for intravenous nivolumab but it is not indicated in combination with ipilimumab.[23]

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.

Note: May be substituted for intravenous nivolumab but it is not indicated in combination with ipilimumab.[24]

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. Single agent second-line or subsequent therapy for recurrent microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors for one of the following:
   a) Isolated metastases
   b) Disseminated metastases with or without sequential palliative external beam radiation therapy (EBRT)

c) Sequential EBRT 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, 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.[25]

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. Single agent second-line or subsequent therapy if PD-L1 positive (combined positive score [CPS] ≥1) for one of the following:
   a) Locoregional recurrence
   b) Stage IVB or recurrent distant metastases.[26]

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. Single agent second-line or subsequent therapy for advanced or recurrent/metastatic disease for HPV-related tumors.[27]

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

Nivolumab and Hyaluronidase-nvhy: References

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Nivolumab and Hyaluronidase-nvhy: 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.9	Merkel cell carcinoma
C15.9	Esophageal adenocarcinoma
C16.0	Gastroesophageal junction cancer
C16.9	Gastric cancer
C17.9	Small bowel adenocarcinoma
C18.9	Colon cancer
C20.0	Rectal cancer

C21.1	Anal cancer
C22.0	Hepatocellular carcinoma
C22.1	Intrahepatic cholangiocarcinoma
C23.0	Gallbladder cancer
C24.0	Extrahepatic cholangiocarcinoma
C24.9	Biliary tract cancers
C34.1	Small cell lung cancer
C34.9	Non-small cell lung cancer
C43.9	Melanoma
C46.9	Kaposi sarcoma
C51	Vulvar cancer
C52	Vaginal cancer
C53.9	Cervical cancer
C54.1	Endometrial carcinoma
C64.0	Kidney cancer
C64.9	Renal cell carcinoma
C67.9	Urothelial carcinoma
C72.9	Limited brain metastases
C73.0	Thyroid carcinoma
C76.0	Head and neck
C79.31	Extensive brain metastases
C79.49	Leptomeningeal metastases

D39.2	Gestational trophoblastic neoplasia
J9999	Nivolumab and hyaluronidase-nvhy

Nivolumab and Hyaluronidase-nvhy: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	2/1/2025
2	Policy Review Dates:	
3	Policy Revision Dates:	
4	Department Owner:	Medical Affairs
5	NH Advisory Committee:	2/25/2025
6	Revision Changes:	