Medical Policy

Utilization Management and Clinical Medical Policy

Policy Name:	Policy Number:	Scope:	Origination Date:	Effective Date:
Nivolumab (Opdivo®) and Nivolumab and hyaluronidase-nvhy (Opdivo Qvantig®)	MP-RX-FP-66-23	☒ **MMM MA** ☒ **MMM MultiHealth**	11/30/2023 **Last Review Date:** 03/24/2026	03/24/2026 **Frequently Revision:** Annual

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B DRUG

Service Description

This document addresses the use of nivolumab (Opdivo®), a programmed death receptor-1 (PD-1) blocking monoclonal antibody approved by the Food and Drug Administration (FDA) for the treatment of various cancers.

Background Information

This document addresses the use of Opdivo, a programmed death receptor-1 (PD-1) blocking monoclonal antibody. The following are the FDA indications or NCCN compendia uses for Opdivo.

Ampullary Adenocarcinoma

NCCN provides Category 2A recommendations supporting immune checkpoint inhibitor–based therapy (single agent or in combination with ipilimumab) for select appendiceal malignancies (appendiceal adenocarcinoma, goblet cell adenocarcinoma, and undifferentiated carcinoma NOS) with dMMR/MSI-H or POLE/POLD1 ultra-hypermutated phenotype (e.g., TMB >50 mut/Mb). NCCN supports use as neoadjuvant systemic therapy in checkpoint inhibitor–naïve patients with biopsy-proven recurrence of high-risk disease without prior cytoreductive surgery and for peritoneal-only metastatic disease, as well as for recurrent/progressive disease including extraperitoneal disease. NCCN also notes nivolumab plus ipilimumab may be considered as subsequent therapy if checkpoint inhibitor monotherapy was previously received.

Anal Carcinoma

The NCCN Compendia and Clinical Practice Guideline (CPG) in 2018 provided 2A recommendations for the use of Opdivo as a single agent for second-line or subsequent treatment of metastatic squamous cell carcinoma of the anal canal if neither nivolumab or pembrolizumab was previously received. The recommendation is based on the results of an ongoing single arm phase 2, multi-center trial. Of the 37 enrolled participants, 2 received a complete response and 7 received partial response with overall response rate of 24% (95% CI, 15-33) (Morris 2017).

NCCN states that Opdivo Qvantig subcutaneous injection may be substituted for IV Opdivo. Opdivo Qvantig has different dosing and administration instructions compared to IV Opdivo.

Appendiceal Adenocarcinoma

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Appendiceal adenocarcinoma is a rare gastrointestinal malignancy arising from the epithelial lining of the appendix. It includes several histologic subtypes such as intestinal-type adenocarcinoma, goblet cell adenocarcinoma, and poorly differentiated or undifferentiated carcinoma. These tumors often present at an advanced stage and may spread within the peritoneal cavity, sometimes mimicking other intra-abdominal cancers. Because of its rarity, treatment recommendations are frequently extrapolated from colorectal cancer data, but the NCCN now provides specific guidance for appendiceal tumors, particularly for biomarker-defined subgroups. Tumors that are deficient in mismatch repair (dMMR) or microsatellite instability–high (MSI-H), or that harbor POLE/POLD1 mutations with an ultra-hypermutated phenotype, may be candidates for immune checkpoint inhibitor therapy.

The NCCN Clinical Practice Guidelines include nivolumab (Opdivo) as a Category 2A recommendation for select patients with biomarker-positive appendiceal adenocarcinoma, either as a single agent or in combination with ipilimumab, in specific neoadjuvant and recurrent or metastatic treatment settings.

Biliary Tract Cancers

The NCCN CPG provides a 2A recommendation in combination with Yervoy for progression on or after systemic therapy in unresectable/resected gross residual or metastatic disease that is Tumor Mutation Burden-High (TMB-H). NCCN also provides a Category 2A recommendation for use as neoadjuvant systemic therapy for resectable locoregionally advanced disease in patients without jaundice. Additionally, NCCN provides a Category 2B recommendation for use in the neoadjuvant setting for patients with jaundice, as well as for use as primary treatment for unresectable disease, resected gross residual (R2) disease, or metastatic disease that is TMB-H.

According to NCCN guidelines, Opdivo Qvantig is not approved for concurrent use with IV Yervoy; however, NCCN states for Opdivo monotherapy, Opdivo Qvantig subcutaneous injection may be substituted for IV Opdivo. Opdivo Qvantig has different dosing and administration instructions compared to IV Opdivo.

Bone Cancer

NCCN provides a Category 2A recommendation for nivolumab in combination with ipilimumab for unresectable or metastatic bone cancer (including chondrosarcoma, chordoma, Ewing sarcoma, mesenchymal chondrosarcoma, and osteosarcoma) that has progressed following prior treatment and has no satisfactory alternative treatment options for tumor mutational burden-high (TMB-H) tumors (≥10 mutations per megabase) (useful in certain circumstances). NCCN also provides a Category 2A recommendation for dedifferentiated chondrosarcoma, either as a single agent or in combination with sunitinib. In the most recent guidelines (Version 1.2026), hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab for all recommended uses not combined with ipilimumab.

Central Nervous System Cancers

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NCCN also provides a 2A recommendation for the use of Opdivo in combination with Yervoy for central nervous system cancers in the treatment of symptomatic patients with newly diagnosed or recurrent brain metastases secondary to melanoma and stable systemic disease or reasonable systemic treatment options. However, while the evidence for asymptomatic patients was promising, the study results for patients with symptomatic disease showed little to no intracranial response (Long 2017, 2018, Tawbi 2017).

Opdivo Qvantig is not approved for concurrent use with IV Yervoy; however, NCCN states for Opdivo monotherapy, Opdivo Qvantig subcutaneous injection may be substituted for IV Opdivo. Opdivo Qvantig has different dosing and administration instructions compared to IV Opdivo.

Cervical Cancer

NCCN also provides 2A recommendation for Opdivo for cervical cancer for second-line or subsequent therapy as a single agent if PD-L1 positive in recurrent or metastatic disease. It also has a 2A recommendation when used in combination with ipilimumab in patients with persistent, recurrent, or metastatic small cell neuroendocrine carcinoma of the cervix (NECC) or patients with locoregional recurrence or stage IVB or recurrence with distant metastases.

NCCN states that Opdivo Qvantig subcutaneous injection may be substituted for IV Opdivo. Opdivo Qvantig has different dosing and administration instructions compared to IV Opdivo.

Colorectal Cancer

NCCN Clinical Practice Guidelines provide multiple Category 2A recommendations supporting the use of immune checkpoint inhibitor–based therapy for colorectal cancer in patients with deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) disease or POLE/POLD1 mutation with an ultra-hypermutated phenotype (e.g., TMB >50 mutations/Mb). NCCN supports use as single agent or in combination with ipilimumab for immunotherapy-eligible patients with no prior immunotherapy in several settings, including locally unresectable/medically inoperable disease, synchronous abdominal/peritoneal metastases (nonobstructing or following local therapy if obstruction is present or imminent), synchronous unresectable metastases, and unresectable metachronous metastases. NCCN also supports use as neoadjuvant therapy (preferred) for clinical T4b or bulky nodal disease, for resectable synchronous liver/lung metastases (checkpoint inhibitor–naïve), and as initial treatment for resectable metachronous metastases in patients with no prior immunotherapy. In addition, NCCN supports nivolumab in combination with ipilimumab as systemic therapy for advanced/metastatic disease in immunotherapy-eligible patients when checkpoint inhibitor monotherapy was previously received.

FDA labeling supports nivolumab plus ipilimumab for unresectable or metastatic MSI-H/dMMR colorectal cancer in adults and pediatric patients ≥12 years, and nivolumab monotherapy for MSI-H/dMMR metastatic colorectal cancer following progression on fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

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According to NCCN, Opdivo Qvantig may be substituted for intravenous nivolumab. Limitation of use: nivolumab and hyaluronidase-nvhy is not indicated in combination with ipilimumab (yervoy).

Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia

NCCN provides a Category 2A recommendation for the use of a non-chemoimmunotherapy (immune checkpoint inhibitor)-based regimen, as a single agent or in combination with ibrutinib, for Richter transformation to diffuse large B-cell lymphoma (DLBCL) in select patients with CLL/SLL. This recommendation includes use as additional therapy for patients with untreated CLL or clonally unrelated disease at initial diagnosis who have partial response, refractory disease, or progression while receiving chemoimmunotherapy (CIT), as well as use as first-line therapy for Richter transformation in patients with previously treated CLL and clonally related disease (or clonal relation unknown). NCCN also supports continuation therapy following complete response until progression, or use as additional therapy not previously used in patients with partial response, refractory disease, or progression while on CIT or non-CIT regimens.

Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer

According to the ACS, there will be an estimated 95,520 new cases of colon cancer and 39,910 new cases of rectal cancer diagnosed in 2017. It is expected that 50,620 persons will die from colon and rectal cancer combined in 2017.

Opdivo, as a single agent, is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine-, oxaliplatin-, and/or irinotecan-based chemotherapy.

Opdivo Qvantig as a single agent is indicated in adult patients with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as monotherapy or as monotherapy following combination treatment with intravenous nivolumab and ipilimumab.

Opdivo, in combination with ipilimumab, is indicated for the treatment of adults and pediatric patients 12 years and older with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan based chemotherapy.

Opdivo Qvantig is not approved for concurrent use with IV Yervoy; however, NCCN states for Opdivo monotherapy, Opdivo Qvantig subcutaneous injection may be substituted for IV Opdivo. Opdivo Qvantig has different dosing and administration instructions compared to IV Opdivo.

The safety and effectiveness of OPDIVO QVANTIG have not been established in pediatric patients.

Esophageal Squamous Cell Carcinoma (ESCC)

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Esophageal cancers can be classified as squamous cell carcinoma (SCC) or adenocarcinoma. Unlike adenocarcinoma, SCC is usually localized near the tracheal bifurcation and associated with poorer prognosis.

The FDA has indicated Opdivo for the following:

- for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in adult patients who have received neoadjuvant chemoradiotherapy (CRT).
- in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).
- in combination with ipilimumab, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).
- for the treatment of adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

NCCN also provides multiple 1 and 2A recommendations for use in Esophageal and Esophagogastric Junction Cancers. The recommendations are for use in relieving dysphagia in those medically fit and planned for esophagectomy, as primary and maintenance treatment for MSI-H/dMMR individuals for neoadjuvant or perioperative immunotherapy, and use as palliative therapy when patients are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease as first-line therapy or second-line therapy/subsequent therapy if individual has a Karnofsky performance score ≥60% or ECOG performance score ≤2.

Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

Opdivo is indicated for use in patients with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy (CRT).

Opdivo is indicated for use in advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy.

NCCN compendia also provides a NCCN 1 recommendation for Opdivo as preferred postoperative therapy for patients who have received preoperative chemoradiation and R0 resection and residual disease (yp T positive and/or N positive).

NCCN compendia also provides a NCCN 1 recommendation for use as primary treatment in those with surgically unresectable locoregional HER2 negative disease in combination with oxaliplatin and fluorouracil or capecitabine.

Opdivo (nivolumab) is recommended as primary treatment for medically fit patients with surgically unresectable locoregional HER2 overexpression negative disease in combination with Oxaliplatin and fluorouracil or capecitabine (PD-L1 CPS≥5).

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Gestational Trophoblastic Neoplasia (GTN)

NCCN provides a Category 2A recommendation for Opdivo (nivolumab) for gestational trophoblastic neoplasia as therapy useful in certain circumstances, including single-agent therapy (preferred when used as a single agent) or in combination with ipilimumab for multiagent chemotherapy-resistant high-risk disease, and for recurrent or progressive intermediate trophoblastic tumors (placental site trophoblastic tumor [PSTT] or epithelioid trophoblastic tumor [ETT]). However, there is insufficient published evidence to support the use of Opdivo for these conditions. This use is largely extrapolated as a PD-1/PD-L1 class effect based on available pembrolizumab data (Ghorani E et al., 2017).

NCCN states for Opdivo monotherapy, Opdivo Qvantig subcutaneous injection may be substituted for IV Opdivo. Opdivo Qvantig has different dosing and administration instructions compared to IV Opdivo.

Head and Neck Cancer

NCCN provides a category 2A recommendation for the use of Opdivo (nivolumab) in combination with cetuximab in non-nasopharyngeal, advanced head and neck squamous cell carcinoma (SCCHN) for resectable locoregional recurrence or persistent disease in patients without prior radiation therapy. This recommendation is supported by the Chung 2022 trial, an open-label, single-arm, phase 2 study. The trial reported a median overall survival (OS) of 11.4 months in patients with prior treatment and 20.2 months in patients without prior treatment.

NCCN also provides a category 2A recommendation for the use of Opdivo in combination with cisplatin and gemcitabine in nasopharyngeal carcinoma as first-line or subsequent systemic therapy for T1–T4, N0–N3, M1 disease, including both oligometastatic and widely metastatic presentations. This recommendation is currently based on extrapolated data from two clinical studies using non–FDA-approved PD-1 inhibitors. No direct study evidence is currently available for the use of nivolumab in this setting.

NCCN states for Opdivo monotherapy, Opdivo Qvantig subcutaneous injection may be substituted for IV Opdivo. Opdivo Qvantig has different dosing and administration instructions compared to IV Opdivo.

Squamous Cell Carcinoma of the Head and Neck

Head and neck cancers account for nearly 3 percent (approximately 62,000 cases) of all cancers in the US, and an estimated 13,000 deaths, with nearly 90% form the squamous cell variety.

Opdivo is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

NCCN states for Opdivo monotherapy, Opdivo Qvantig subcutaneous injection may be substituted for IV Opdivo. Opdivo Qvantig has different dosing and administration instructions compared to IV Opdivo.

Malignant Pleural and Peritoneal Mesothelioma

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Opdivo in combination with ipilimumab is FDA approved for use as first line therapy for unresectable malignant pleural mesothelioma (MPM), a highly aggressive cancer with poor prognosis and limited treatment options.

NCCN compendia also includes a category 2A recommendation for off-label use of nivolumab as monotherapy or in combination with Yervoy (ipilimumab) in the treatment of malignant pleural and peritoneal mesothelioma (MPM) as subsequent therapy.

Opdivo Qvantig is not approved for concurrent use with IV Yervoy; however, NCCN states for Opdivo monotherapy, Opdivo Qvantig subcutaneous injection may be substituted for IV Opdivo. Opdivo Qvantig has different dosing and administration instructions compared to IV Opdivo.

Hepatocellular Carcinoma (HCC)

HCC is the most common form of liver cancer with about 40,710 new cases of liver and intrahepatic bile duct cancer diagnosed in 2017 and nearly 28,920 deaths from the disease annually in the US.

The NCCN Guidelines provide Category 2A recommendations supporting the use of Opdivo (nivolumab) for select patients with advanced hepatocellular carcinoma (HCC). Opdivo is recommended as first-line systemic therapy in combination with ipilimumab for individuals with liver-confined, unresectable disease who are ineligible for transplant, or those with extrahepatic/metastatic disease who are ineligible for resection, transplant, or locoregional therapy. NCCN also provides a Category 2A recommendation for Opdivo as subsequent-line systemic therapy, either as single-agent therapy for individuals not previously treated with a checkpoint inhibitor (useful in certain circumstances), or in combination with ipilimumab in appropriate patients without prior exposure to anti–CTLA-4–based combinations, following progression on or after systemic therapy.

Opdivo Qvantig is not approved for concurrent use with IV Yervoy; however, NCCN states for Opdivo monotherapy, Opdivo Qvantig subcutaneous injection may be substituted for IV Opdivo. Opdivo Qvantig has different dosing and administration instructions compared to IV Opdivo.

Classical Hodgkin Lymphoma

Hodgkin lymphoma is a malignant lymphoma originating from B lymphocytes, characterized by the presence of Reed-Sternberg cells. It typically presents in young adults (ages 15–40) and in a second peak among older adults over age 55. In developed countries, classical Hodgkin lymphoma (cHL) accounts for approximately 95% of all Hodgkin lymphomas (ACS, 2017).

Opdivo (nivolumab) is a programmed death-1 (PD-1) immune checkpoint inhibitor indicated for the treatment of adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after:

- Autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
- Three or more lines of systemic therapy that includes autologous HSCT.

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The NCCN Clinical Practice Guidelines in Oncology for B-cell Lymphomas include nivolumab (Opdivo) with a Category 2A recommendation in several clinical scenarios for patients with cHL, including:

- Primary treatment in combination with AVD for stage III–IV disease or stage I–II unfavorable disease in adults of varying ages based on fitness for anthracyclines;
- First-line therapy in patients who are ineligible for anthracyclines, either in combination with brentuximab vedotin or as monotherapy;
- Second-line systemic therapy in relapsed or refractory cHL, both in transplant-eligible and ineligible settings, used in combination with brentuximab vedotin or ICE;
- Subsequent therapy after second-line failure, particularly in patients with Deauville score 4–5 or not candidates for high-dose therapy/autologous transplant;
- Later-line single-agent use in individuals with disease refractory to three or more lines of systemic therapy;
- Post-allogeneic transplant use as single-agent therapy.

Opdivo Qvantig is not referenced in NCCN guidelines for the treatment of classical Hodgkin lymphoma.

Malignant Pleural and Peritoneal Mesothelioma

Opdivo in combination with ipilimumab is FDA approved for use as first line therapy for unresectable malignant pleural mesothelioma (MPM), a highly aggressive cancer with poor prognosis and limited treatment options.

Opdivo Qvantig is not approved for concurrent use with IV Yervoy; however, NCCN states for Opdivo monotherapy, Opdivo Qvantig subcutaneous injection may be substituted for IV Opdivo. Opdivo Qvantig has different dosing and administration instructions compared to IV Opdivo.

Metastatic Melanoma with Brain Metastases

The NCCN Compendia and Clinical Practice Guideline (CPG) for central nervous system cancers offers a category 2A recommendation for nivolumab in combination with Yervoy (ipilimumab) in the treatment of asymptomatic patients with newly diagnosed or recurrent brain metastases secondary to melanoma and stable systemic disease or reasonable systemic treatment options (Long 2017, 2018, Tawbi 2017).

Opdivo Qvantig is not approved for concurrent use with IV Yervoy.

Adjuvant Treatment of Melanoma

The FDA has approved nivolumab (Opdivo) for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

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Cutaneous Melanoma

The NCCN Compendia and Clinical Practice Guideline (CPG) in cutaneous melanoma offers NCCN recommendations for nivolumab as preferred systemic therapy, option as a single agent for initial treatment of limited resectable in Stage III disease with clinical satellite/in-transit metastases (NCCN1) or local satellite/in-transit recurrence (NCCN 2A)

Unresectable or Metastatic Melanoma

The American Cancer Society (ACS) estimated that approximately 87,110 cases of melanoma (also referred to as malignant melanoma) will be diagnosed in the United States in 2017 (ACS, 2017).

The FDA has approved nivolumab (Opdivo) in combination with ipilimumab (Yervoy) for the treatment of those with unresectable or metastatic melanoma BRAF V600 wild-type.

The FDA has approved nivolumab (Opdivo) as a single agent or in combination with ipilimumab for the treatment of those with unresectable or metastatic melanoma.

Opdivo Qvantig is not approved for concurrent use with IV Yervoy; however, NCCN states for Opdivo monotherapy, Opdivo Qvantig subcutaneous injection may be substituted for IV Opdivo. Opdivo Qvantig has different dosing and administration instructions compared to IV Opdivo.

Uveal Melanoma

The NCCN panel recommendation for use of Yervoy (ipilimumab) as a single agent is based on retrospective case series that evaluated nivolumab as a treatment option of uveal melanoma. The recommendation for combination therapy is based on unpublished data from a phase II multicenter, single arm, and open-label study of nivolumab in combination with ipilimumab as first line in adults with metastatic uveal melanoma (NCT02626962).

Opdivo Qvantig is not approved for concurrent use with IV Yervoy; however, NCCN states for Opdivo monotherapy, Opdivo Qvantig subcutaneous injection may be substituted for IV Opdivo. Opdivo Qvantig has different dosing and administration instructions compared to IV Opdivo.

Merkel Cell Carcinoma

Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine skin cancer that primarily affects older adults and immunocompromised individuals. It carries a high risk of local recurrence and distant metastasis.

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The NCCN Clinical Practice Guidelines include nivolumab (Opdivo) with a Category 2A recommendation in multiple treatment settings. Nivolumab may be used as a neoadjuvant (pre-operative) systemic therapy, as a single agent, in surgical candidates diagnosed with primary clinical N0 locally advanced disease or primary N+, M0 regional disease with biopsy-positive draining nodal basin, particularly when curative surgery and curative radiation therapy were initially not feasible. Additionally, nivolumab is recommended as preferred treatmentfor patients with primary or recurrent N+, M0 regional disease, in-transit nodal disease, or M1 disseminated disease, in cases where curative surgery and radiation are not appropriate. In these settings, nivolumab may be used either as a single agent or in combination with ipilimumab (Yervoy®). These recommendations reflect accumulating clinical evidence demonstrating that PD-1/PD-L1 blockade offers improved durable response rates compared to traditional cytotoxic therapies in relapsed or advanced MCC.

Metastatic Non-Small Cell Lung Cancer

Lung cancer remains the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of all lung cancer cases. In the United States alone, tens of thousands of new NSCLC diagnoses occur annually, often at advanced stages where curative treatment is no longer feasible.

Opdivo (nivolumab) is FDA approved and NCCN-recommended for use across multiple stages and molecular subtypes of NSCLC, including as part of neoadjuvant, adjuvant, first-line, and subsequent therapy regimens.

Neoadjuvant Setting

Nivolumab is FDA approved for use in combination with platinum-doublet chemotherapy as neoadjuvant systemic therapy in adult patients with resectable NSCLC (tumors ≥4 cm or node-positive). NCCN supports this approach for patients with stage IB–IIIA and select stage IIIB disease (T2–T3, N2b; T4, N2) deemed resectable after surgical evaluation, provided there are no known EGFR mutations or ALK gene fusions and the patient is eligible for checkpoint inhibition. Supported chemotherapy backbones include paclitaxel/carboplatin, pemetrexed/platinum (nonsquamous), gemcitabine/platinum (squamous), and docetaxel/cisplatin.

Adjuvant and Post-Adjuvant Setting

NCCN also recommends single-agent adjuvant Opdivo for patients who have completed neoadjuvant chemoimmunotherapy and surgery, especially in the setting of margin-positive (R1/R2) resection followed by adjuvant chemoradiation, and who remain candidates for continued immunotherapy.

First-Line Therapy (Advanced/Metastatic NSCLC)

Nivolumab is FDA approved for use in combination with ipilimumab, with or without platinum-doublet chemotherapy, as first-line therapy in patients with recurrent, advanced, or metastatic NSCLC who have:

- PD-L1 expression ≥1%, and

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- No EGFR, ALK, or ROS1 genomic aberrations.

NCCN extends its Category 2A recommendation for this regimen to tumors with PD-L1 <1% in patients who are negative for actionable molecular markers, such as EGFR exon 19 deletion/L858R, ALK, RET, ROS1, MET exon 14 skipping, BRAF V600E, NTRK, ERBB2 (HER2), and NRG1 fusions.

Biomarker Consideration

Before initiating systemic therapy, comprehensive biomarker testing is essential. Per NCCN, testing should include EGFR, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, ERBB2 (HER2), and NRG1. If initial tissue biopsy is insufficient, plasma-based testing or repeat biopsy is advised. If driver mutation status is unknown but testing is pending, immunotherapy may be withheld until results are available.

Continuation Maintenance Therapy

Nivolumab in combination with ipilimumab is also recommended as continuation maintenance therapy in patients who respond or achieve stable disease following initial induction with nivolumab + ipilimumab ± chemotherapy, regardless of PD-L1 expression status.

Subsequent Therapy

Nivolumab is FDA approved and NCCN recommended as subsequent systemic therapy for patients with advanced or metastatic NSCLC who have progressed on or after platinum-based chemotherapy, provided they have not previously received PD-1/PD-L1 inhibitor therapy, and have no contraindications or known actionable mutations (e.g., EGFR exon 19/L858R, ALK, RET, ROS1).

Additionally, NCCN supports subsequent use of nivolumab + ipilimumab, with or without chemotherapy, in patients with specific mutations such as:

- EGFR S768I, L861Q, and/or G719X, following failure of EGFR tyrosine kinase inhibitors (e.g., afatinib, osimertinib);
- BRAF V600E, NTRK, MET exon 14, ERBB2 (HER2), or NRG1 fusions, as first-line or subsequent therapy depending on mutation type and prior treatment history.

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Metastatic NSCLC with Brain Metastases

The NCCN Compendia and Clinical Practice Guideline (CPG) for central nervous system cancers offers a category 2A recommendation for nivolumab as single agent in individuals with brain metastases secondary to NSCLC who are PD-L1 positive (Gauvain 2019, Rizvi 2015, Goldman 2016).

NCCN states for Opdivo monotherapy, Opdivo Qvantig subcutaneous injection may be substituted for IV Opdivo. Opdivo Qvantig has different dosing and administration instructions compared to IV Opdivo.

Advanced Renal Cell Carcinoma

Renal cell carcinoma (RCC) represents a significant proportion of kidney cancers, with clear cell histology being the most common subtype. In the United States, tens of thousands of RCC cases are diagnosed each year, and a substantial percentage present with or progress to advanced or metastatic disease.

Opdivo (nivolumab) has multiple treatment roles in advanced RCC across first-line, subsequent, and histology-specific settings:

- Single-agent therapy: Nivolumab is recommended as single-agent systemic therapy for patients with stage IV or relapsed advanced RCC who are immune checkpoint inhibitor–naïve, particularly in those with clear cell histology (NCCN Category 2A). It is also recognized as a systemic therapy option in non-clear cell histology in appropriate clinical contexts.
- Combination immunotherapy: Nivolumab in combination with ipilimumab (a CTLA-4 immune checkpoint inhibitor) is recommended for adults with stage IV or relapsed clear cell RCC, used for four cycles followed by single-agent nivolumab. This regimen is preferred as first-line therapy for eligible patients with metastatic disease and continues to be an option as subsequent therapy in both immune checkpoint inhibitor–naïve and select previously treated patients (NCCN Category 1 for first-line, Category 2A for others).
- Combination targeted therapy: Nivolumab in combination with the tyrosine kinase inhibitor cabozantinib is recommended for stage IV or relapsed disease with clear cell histology as first-line therapy (preferred) and also as subsequent therapy depending on prior immuno-oncology exposure. For non-clear cell RCC, the combination of nivolumab with cabozantinib is recommended as preferred systemic therapy for stage IV or relapsed disease (NCCN Category 2A).
- Biomarker and histology considerations: Treatment selection in RCC is guided by histologic subtype (clear cell vs. non-clear cell) and clinical context (first-line vs. subsequent therapy). NCCN guidelines emphasize the relevance of prior therapies, including prior immune checkpoint inhibitors, in determining optimal sequencing of nivolumab-based regimens.

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Opdivo Qvantig is not approved for concurrent use with IV Yervoy; however, NCCN states for Opdivo monotherapy, Opdivo Qvantig subcutaneous injection may be substituted for IV Opdivo. Opdivo Qvantig has different dosing and administration instructions compared to IV Opdivo.

Small Bowel Adenocarcinoma (SBA)

Small bowel cancer is relatively rare compared to other cancers of the gastrointestinal tract, accounting for about 3% of cancers in this system. Due to the rarity of SBA, historically, treatment for SBA mimicked those for colorectal cancer. In 2019, NCCN developed the first guidelines in the U.S., and the second in the world, to address small bowel adenocarcinomas.

NCCN Compendia and Clinical Practice Guidelines (CPG) for SBA include a category 2A recommendation for the use of nivolumab (Opdivo) as a single agent or in combination with ipilimumab in multiple treatment settings, when the tumor exhibits one of the following biomarkextranodalers:

- Deficient mismatch repair (dMMR),
- Microsatellite instability-high (MSI-H), or
- Polymerase epsilon/delta (POLE/POLD1) mutation with ultra-hypermutated phenotype (e.g., tumor mutational burden >50 mutations/megabase).

Nivolumab may be used as monotherapy or in combination with ipilimumab in the following clinical settings:

- Neoadjuvant therapy for resectable SBA that is T4 or has a bulky primary tumor,
- Primary treatment for locally unresectable or medically inoperable disease, or
- Therapy for advanced or metastatic disease, for any line of treatment if no prior checkpoint inhibitor has been used.

Additionally, the combination of nivolumab and ipilimumab may be used as subsequent therapy following prior treatment with a checkpoint inhibitor monotherapy (e.g., PD-1 or PD-L1 agent).

Opdivo Qvantig is not approved for concurrent use with IV Yervoy; however, NCCN states for Opdivo monotherapy, Opdivo Qvantig subcutaneous injection may be substituted for IV Opdivo. Opdivo Qvantig has different dosing and administration instructions compared to IV Opdivo.

T-cell Lymphomas

NCCN provides a 2A recommendation for use of Opdivo as single agent for individuals relapsed or refractory T-cell lymphoma following additional therapy with an alternate combination chemotherapy regimen (asparaginase-

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based) not previously used, if a clinical trial is not available. The recommendation was based on a case report of 3 patients (Chan 2018). Therefore, at this time, there is insufficient evidence to support its use in this situation.

Opdivo Qvantig is not referenced in NCCN guidelines for T-Cell Lymphoma.

Urothelial Carcinoma

Urothelial carcinoma is the most common type of bladder cancer. According to the American Cancer Society (ACS), bladder cancer affects tens of thousands of individuals annually in the United States, with higher incidence in men. The majority of urothelial carcinomas originate in the bladder but can also arise in the upper genitourinary tract, urethra, and prostate.

Opdivo (nivolumab) is FDA-approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) who:

A. Have disease progression during or following platinum-containing chemotherapy.
B. Have disease progression within 12 months of receiving neoadjuvant or adjuvant platinum-based chemotherapy.
C. Are at high risk of recurrence after undergoing radical resection (adjuvant setting).
D. Are being treated in combination with cisplatin and gemcitabine as first-line systemic therapy for unresectable or metastatic UC.

NCCN Recommendations (1 and 2A)

- Bladder Cancer: NCCN Clinical Practice Guidelines include a Category 1 recommendation for nivolumab in combination with cisplatin and gemcitabine as first-line treatment for patients with unresectable or metastatic bladder cancer, followed by nivolumab maintenance therapy.
- Upper Genitourinary Tract Tumors (Renal Pelvis/Ureter): NCCN provides a 2A recommendation for adjuvant nivolumab in individuals with pathologic stage T2–T4 or nodal disease (N+) urothelial carcinoma of the renal pelvis or ureter, after platinum-based neoadjuvant chemotherapy.
- Urothelial Carcinoma of the Prostate: Nivolumab has a Category 2A recommendation as adjuvant therapy for tumors with stromal invasion (pT3, pT4a, or pN+) when platinum-based neoadjuvant chemotherapy was not given.
- Primary Carcinoma of the Urethra:
  NCCN gives a 2A recommendation for use of nivolumab in:
  - Adjuvant therapy for pathologic stage T3–T4 or cN1–2 disease in the bulbar urethra.
  - First-line systemic therapy in combination with cisplatin and gemcitabine, followed by nivolumab maintenance.

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- Second-line systemic therapy with cisplatin and gemcitabine after prior immunotherapy (with or without enfortumab vedotin-ejfv) and no prior chemotherapy—if no satisfactory alternatives exist.

These NCCN recommendations broaden the scope of Opdivo use across various urothelial carcinoma subtypes, allowing for its use in adjuvant, first-line, and subsequent-line settings, with histologic and clinical context considered. Where applicable, Opdivo Qvantig (subcutaneous formulation) may be used in place of IV Opdivo, except when used in combination with ipilimumab.

Uterine Sarcoma

Uterine cancers include endometrial carcinomas and uterine sarcomas, with endometrial carcinoma being the most common histologic subtype. The NCCN Clinical Practice Guidelines provide Category 2A recommendations for the use of nivolumab (Opdivo) as monotherapy or in combination with ipilimumab in select patients with recurrent or metastatic disease, based on tumor biomarker status.

For endometrial carcinoma, including endometrioid, serous, clear cell, carcinosarcoma, and undifferentiated/dedifferentiated histologies, Opdivo is recommended as second-line or subsequent therapy in the following settings:

- As monotherapy for tumors that are microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) and have not previously received checkpoint inhibitor therapy.
- In combination with ipilimumab for tumor mutational burden-high (TMB-H) (≥10 mutations/megabase) tumors, if the individual has no satisfactory alternative treatment options and has not received prior immunotherapy.

These uses apply across various patterns of recurrence, including isolated or disseminated metastases, with or without concurrent radiation therapy, and in patients with or without prior radiation or surgical treatment.

For uterine sarcoma histologies, including leiomyosarcoma, endometrial stromal sarcoma, adenosarcoma, PEComa, and undifferentiated sarcoma, NCCN provides a Category 2A recommendation for Opdivo in combination with ipilimumabin individuals with TMB-H tumors, if not previously treated with checkpoint inhibitors and no alternative treatment options exist.

These recommendations are based on early-phase studies and biomarker-driven extrapolation. NCCN notes that this approach may be considered useful in certain circumstances.

NCCN states for Opdivo monotherapy, Opdivo Qvantig subcutaneous injection may be substituted for IV Opdivo. Opdivo Qvantig has different dosing and administration instructions compared to IV Opdivo.

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Vulvar Cancer

NCCN provides a 2A recommendation for use of Opdivo as useful in certain circumstances as single agent for second-line or subsequent treatment of HPV-related advanced, recurrent, or metastatic squamous cell vulvar cancer. This recommendation was based on a small (n=24) phase I/II trial, of which 5 had vaginal/vulvar cancer). The authors concluded that use of Opdivo is this situation is promising and warrants additional investigation (Naumann 2019).

NCCN states for Opdivo monotherapy, Opdivo Qvantig subcutaneous injection may be substituted for IV Opdivo. Opdivo Qvantig has different dosing and administration instructions compared to IV Opdivo.

Abbreviations

Abbreviation	Name
ALK	Anaplastic Lymphoma Kinase
cHL	Classical Hodgkin Lymphoma
CPC	Circulating Plasma Cells
CRC	Colorectal Cancer
cSCC	Cutaneous Squamous Cell Carcinoma
dMMR	Mismatch Repair Deficient Cancer
ECOG	Eastern Cooperative Oncology Group (ECOG) Performance Status
EGFR	Epidermal Growth Factor Receptor
ESCC	Esophageal cell Carcinoma
GEJ	Gastroesophageal Junction
HCC	Hepatocellular Carcinoma
HNSCC	Head and Neck Squamous Cell Cancer
MCC	Merkel Cell Carcinoma
MSI-H	Microsatellite Instability-High Cancer
NSCLC	Non-Small Cell Lung Cancer
PD-1	Programmed Death Receptor-1 (PD-1)
PMBCL	Primary Mediastinal Large B-Cell Lymphoma
pMMR	Mismatch Repair Proficient Cancer
RCC	Renal Cell Carcinoma
SCCHN	Squamous Cell Carcinoma of the Head and Neck

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TMB-H	Tumor Mutational Burden-High Cancer
TNBC	Triple-Negative Breast Cancer
TPS	Tumor Proportion Score

Definitions and Measures

- Adjuvant therapy: Treatment given after the primary treatment to increase the chances of a cure; may include chemotherapy, radiation, hormone or biological therapy.
- Anal cancer: Cancer originating in the tissues of the anus; the anus is the opening of the rectum (last part of the large intestine) to the outside of the body.
- BRAF: The oncogene which directions production of a protein in the regulating MAP kinase/ERKs signaling pathway, which affects cell division, differentiation, and secretion.
- Colon cancer: Cancer originating in the tissues of the colon (the longest part of the large intestine). Most colon cancers are adenocarcinomas that begin in cells that make and release mucus and other fluids.
- Colorectal cancer: Cancer originating in the colon (the longest part of the large intestine) or the rectum (the last several inches of the large intestine before the anus).
- ECOG or Eastern Cooperative Oncology Group Performance Status: A scale and criteria used by doctors and researchers to assess how an individual's disease is progressing, assess how the disease affects the daily living abilities of the individual, and determine appropriate treatment and prognosis. This scale may also be referred to as the WHO (World Health Organization) or Zubrod score which is based on the following scale:
    - 0 = Fully active, able to carry on all pre-disease performance without restriction.
    - 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work.
    - 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
    - 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
    - 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
    - 5 = Dead
- Immune checkpoint inhibitor: A type of drug that blocks certain proteins made by some types of immune system cells, such as T cells, and some cancer cells. When these proteins are blocked, the "brakes" on the immune system are released and T cells are able to kill cancer cells better. Examples of checkpoint proteins found on T cells or cancer cells include programmed death (PD)-1, PD-ligand 1 (PD-L1), and cytotoxic T-lymphocyte–associated antigen (CTLA)-4/B7-1/B7-2.

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- Karnofsky Performance Status: A scale and criteria used by doctors and researchers to assess an individual's prognosis, measure changes in their function and abilities, and determine their ability to tolerate therapies. The lower the score (from 0- 100), the worse the likelihood of survival.
    - 100 = Normal, no complaints
    - 90 = Able to carry on normal activities
    - 80 = Normal activity with effort
    - 70 = Care for self. Unable to carry on normal activity or to do active work
    - 60 = Requires occasional assistance, but able to care for most of his needs
    - 50 = Requires considerable assistance and frequent medical care
    - 40 = Disabled. Requires special care and assistance
    - 30 = Severely disabled. Hospitalization indicated though death nonimminent
    - 20 = Very sick. Hospitalization necessary. Active supportive treatment necessary
    - 10 = Moribund
    - 0 = Dead
- Line of Therapy:
    - First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
    - Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
    - Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second-line therapy) are not effective or there is disease progression.
- Melanoma: A type of cancer that begins in the melanocytes. Melanoma is also referred to as malignant melanoma and cutaneous melanoma.
- Merkel cell carcinoma: A rare, aggressive skin cancer.
- Metastasis: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.
- Monoclonal antibody: A protein developed in the laboratory that can locate and bind to specific substances in the body and on the surface of cancer cells.
- Mutation: A permanent, transmissible change in genetic material.
- Neoadjuvant therapy: Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy.

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- Non-small cell lung cancer: A group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of non-small cell lung cancer are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma.
- Non-Hodgkin Lymphoma (NHL): A group of malignant solid tumors or lymphoid tissues.
- Primary treatment: The first treatment given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation. Also called first-line therapy, induction therapy, and primary therapy.
- Programmed death (PD)-1 proteins: PD-1 proteins are found on T-cells and attach to PD ligands (PD-L1) found on normal (and cancer) cells (see immune checkpoint inhibitor above). Normally, this process keeps T-cells from attacking other cells in the body. However, this can also prevent T-cells from attacking cancer cells in the body. Examples of FDA approved anti-PD- 1 agents include Keytruda (pembrolizumab), Opdivo (nivolumab), and Libtayo (cemiplimab).
- Programmed death ligand (PD-L)-1: The ligands found on normal (and cancer) cells to which the PD-1 proteins attach (see immune checkpoint inhibitor above). Cancer cells can have large amounts of PD-L1 on their surface, which helps them to avoid immune attacks. Examples of FDA approved anti-PD-L1 agents include Bavencio (avelumab), Tecentriq (atezolizumab), and Imfinzi (durvalumab).
- Progression free survival (PFS): The length of time during and after treatment that an individual lives but does not get worse (usually measured by the size of a tumor or amount of cancer in the body).
- Progressive Disease (PD): Cancer that is growing, spreading, or getting worse.
- Rectal cancer: Cancer originating in tissues of the rectum (the last several inches of the large intestine closest to the anus). Refractory Disease: Illness or disease that does not respond to treatment.
- Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.
- Small bowel adenocarcinoma: Cancer originating in the small intestine (i.e., duodenum, jejunum, and ileum). Unresectable: Unable to be removed with surgery.
- Urothelial carcinoma: A type of bladder cancer which occurs in the urinary tract system.

<u>Important Biomarkers</u>

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Indication	Molecular Testing	Cut Point
NSCLC		
In early-stage NSCLC when used as neoadjuvant and adjuvant	EGFR or ALK	No EGFR exon 19 deletions or exon 21 L858R mutations or ALK rearrangements
In Metastatic NSCLC when used as first-line treatment in combination with ipilimumab	PD-L1	% PD-L1 expression ≥1%
	EGFR or ALK	No EGFR exon 19 deletions or exon 21 L858R mutations or ALK rearrangements
In Metastatic NSCLC when used as first-line treatment in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy	EGFR or ALK	No EGFR exon 19 deletions or exon 21 L858R mutations or ALK rearrangements
MSI-H/dMMR Cancers		
MSI-H/dMMR Colorectal Cancer	MSI-H* or dMMR*	Presence

* A deficient MMR (dMMR) system results in the persistence of DNA mismatches in microsatellites that may then be incorporated into the genetic code as mutations. A dMMR system can be hereditary or sporadic in nature. Tumors that have a dMMR system can develop MSI, which is the expansion or reduction in the length of repetitive sequences in tumor DNA compared with normal DNA. MSI/MMR can be identified by Immunohistochemistry (IHC, to detect the presence or absence of MMR protein expression; and Next Generation Sequencing (NGS, a gene sequencing technique used to identify genetic mutations or variants).

Approved Indications

A. See Background section above.

Other Uses

A. See Background section above.

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Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J9299	Injection, Nivolumab, 1 mg [Opdivo]
J9289	Injection, Nivolumab and hyaluronidase-nvhy [Opdivo Qvantig]

ICD-10	Description
C00.0-C06.9	Malignant neoplasm of parts of lip and oral cavity
C09.0-C13.9	Malignant neoplasm of tonsil, pharynx, pyriform sinus
C14.0-C14.8	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx
C15.3-C15.9	Malignant neoplasm of esophagus
C16.0-C16.9	Malignant neoplasm of stomach
C17.0-C17.9	Malignant neoplasm of small intestine
C18.0-C18.9	Malignant neoplasm of colon
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.0-C21.8	Malignant neoplasm of anus and anal canal
C22.0	Liver cell carcinoma
C22.1	Intrahepatic bile duct carcinoma
C22.8	Malignant neoplasm of liver, primary, unspecified as to typ
C22.9	Malignant neoplasm of liver, not specified as primary or seconda
C23.0	Malignant neoplasm of nasal cavity
C24.0-C24.9	Malignant neoplasm of other and unspecified parts of biliary tract
C30.0	Malignant neoplasm of nasal cavity
C31.0-C31.1	Malignant neoplasm of accessory sinuses
C32.0-C32.9	Malignant neoplasm of larynx
C33	Malignant neoplasm of trachea
C34.00-C34.92	Malignant neoplasm of bronchus and lung
C38.4	Malignant neoplasm of pleura

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ICD-10	Description
C40.10-C40.92	Malignant neoplasm of bone and articular cartilage of limbs
C41.0-C41.9	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
C43.0-C43.9	Malignant melanoma of skin
C44.02	Squamous cell carcinoma of skin of lip
C44.320	Squamous cell carcinoma of skin of unspecified parts of face
C4A.0-C4A.9	Merkel cell carcinoma
C44.42	Squamous cell carcinoma of skin of scalp and neck
C45.0-C45.9	Mesothelioma
C46.0-C46.9	Kaposi's sarcoma
C48.0-C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C49.0-C49.9	Malignant neoplasm of other connective and soft tissue
C51.0-C51.9	Malignant neoplasm of vulva
C52	Malignant neoplasm of vagina
C53.0-C53.9	Malignant neoplasm of cervix uteri
C54.0-C54.9	Malignant neoplasm of corpus uteri
C58	Malignant neoplasm of placenta
C61	Malignant neoplasm of prostate [specified as urothelial carcinoma]
C64.1-C65.9	Malignant neoplasm of kidney, renal pelvis
C66.1-C66.9	Malignant neoplasm of ureter [specified as urothelial carcinoma]
C67.0-C67.9	Malignant neoplasm of bladder [specified as urothelial carcinoma]
C68.0	Malignant neoplasm of urethra [specified as urothelial carcinoma]
C69.30-C69.32	Malignant neoplasm of choroid
C69.40-C69.42	Malignant neoplasm of ciliary body
C71.0-C71.9	Malignant neoplasm of brain
C72.0	Malignant neoplasm of spinal cord
C72.1	Malignant neoplasm of cauda equina
C72.9	Malignant neoplasm of central nervous system, unspecified
C73	Malignant neoplasm of thyroid gland
C76.0	Malignant neoplasm of head, face and neck
C77.0	Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck
C78.00-C78.02	Secondary malignant neoplasm of lung
C79.31	Secondary malignant neoplasm of brain
C81.10-C81.99	Hodgkin lymphoma (classical)
C83.00-C83.09	Small cell B-cell lymphoma
C83.30-C83.38	Diffuse large B-cell lymphoma

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ICD-10	Description
C83.398	Diffuse large B-cell lymphoma of other extranodal and solid organ sites
C84.90-C84.99	Mature T/NK-cell lymphomas, unspecified
C84.Z0-C84.Z9	Other mature T/NK-cell lymphomas
C85.20-C85.29	Mediastinal (thymic) large B-cell lymphoma
C86.00	Extranodal NK/T-cell lymphoma, nasal type not having achieved remission
C91.10-C91.12	Chronic lymphocytic leukemia of B-cell type
D37.3	Neoplasm of uncertain behavior of appendix
D37.8-D37.9	Neoplasm of uncertain behavior of other specified digestive organs
Z85.00-Z85.01	Personal history of malignant neoplasm of unspecified digestive organ
Z85.038	Personal history of other malignant neoplasm of large intestine
Z85.09	Personal history of malignant neoplasm of other digestive organs
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
Z85.51	Personal history of malignant neoplasm of bladder
Z85.528	Personal history of other malignant neoplasm of kidney
Z85.53	Personal history of malignant neoplasm of renal pelvis
Z85.71	Personal history of Hodgkin lymphoma
Z85.820	Personal history of malignant melanoma of skin
Z85.821	Personal history of Merkel cell carcinoma

Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Nivolumab (Opdivo®)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

Note: Nivolumab (Opdivo®) and nivolumab and hyaluronidase-nvhy (Opdivo Qvantig®) are not used interchangeably for each indication. Nivolumab and hyaluronidase-nvhy (Opdivo Qvantig®) is not approved for concurrent use with IV ipilimumab (Yervoy®).

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NCCN guidelines states for nivolumab (Opdivo®) monotherapy, nivolumab and hyaluronidase-nvhy (Opdivo Qvantig®) subcutaneous injection may be substituted for IV nivolumab (Opdivo®). Nivolumab and hyaluronidase-nvhy (Opdivo Qvantig®) different dosing and administration instructions compared to IV nivolumab (Opdivo®).

i. Individual has a diagnosis of Ampullary Adenocarcinoma (NCCN 2A):**AND**
   - A. Using in one of the following ways:
     1. As first-line therapy for metastatic intestinal type disease; **OR**
     2. For disease progression; **AND**
   - B. Individual has deficient mismatch repair or microsatellite instability-high [dMMR or MSI-H] disease; **AND**
   - C. Individual is using in combination with ipilimumab; **AND**
     1. Individual has an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2;
   - D. Individual is using as a single agent; **AND**
     1. Individual has an Eastern Cooperative Oncology Group (ECOG) performance status of 3;
   - E. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
   - F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

ii. Individual has a diagnosis of Appendiceal Adenocarcinoma, including: Appendiceal Adenocarcinoma, Goblet Cell Adenocarcinoma, or Undifferentiated Carcinoma (not otherwise specified) (NCCN 2A); **AND**
   - A. Individual is using therapy as a single agent or in combination with ipilimumab; AND
   - B. Individual has ONE of the following biomarkers (NCCN 2A):
     1. Deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H); **OR**
     2. Polymerase epsilon/delta (POLE/POLD1) mutation with ultra-hypermutated phenotype (e.g., tumor mutational burden [TMB] >50 mutations/Mb);

   AND
   - C. Individual meets ONE of the following treatment settings (NCCN 2A):
     1. Neoadjuvant systemic therapy (NCCN 2A); **AND**
        - a. Biopsy-proven recurrence of high-risk disease (with or without prior cytoreductive surgery); **OR**
        - b. Metastatic peritoneal-only disease (either as neoadjuvant therapy or after inadequate response to prior neoadjuvant therapy);

     OR

2. Therapy for recurrent, progressive or metastatic disease

AND

D. Individual has not previously received treatment with a checkpoint inhibitor; **OR**

E. Individual previously received checkpoint inhibitor monotherapy and is now using nivolumab in combination with ipilimumab as subsequent therapy (monotherapy not allowed in this setting); **AND**

F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

iii. Individual has a diagnosis of Anal carcinoma (NCCN 2A); **AND**

A. Individual is using as second-line and subsequent therapy; **AND**

B. Individual is using in metastatic disease; **AND**

C. Individual is using as a single agent; **AND**

D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**

E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

iv. Individual is using for the treatment of Bone cancer, including osteosarcoma, Ewing Sarcoma, chondrosarcoma, and chordoma (NCCN 2A); **AND**

A. Individual is using in combination with ipilimumab for unresectable or metastatic disease (excluding mesenchymal chondrosarcoma); **AND**

1. Individual has failed and progression on prior treatment; **AND**
2. Individual has no satisfactory alternative treatment options for tissue tumor mutation burden-high (TMB-H) tumors with 10 or more mutations per megabase;

OR

B. Individual is using as single agent or in combination with suntinib (NCCN 2A); **AND**

C. Individual has dedifferentiated chondrosarcoma;

AND

D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**

E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

v. Individual has a diagnosis of Biliary Tract Cancers (NCCN 2A); **AND**

A. Individual is using in combination with ipilimumab; **AND**

B. Individual has tumor mutational burden-high (TMB-H) disease; **AND**

C. Meets one of the following:

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1. Individual is using for progression on or after systemic treatment for unresectable or resected gross residual (R2) disease, or metastatic disease; **OR**
2. Individual is using as neoadjuvant systemic therapy for resectable locoregionally advanced disease and does not have jaundice;

AND

D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**

E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

vi. Individual has a diagnosis of Cervical Cancer (NCCN 2A); **AND**

A. Individual is using as a single agent; **AND**

1. Individual is using for second-line or subsequent therapy; **AND**
2. Individual has CPS ≥ 1 for local/regional recurrence or stage IVB or recurrence with distant metastases;

OR

B. Individual is using in combination with ipilimumab; **AND**

1. Individual is using for second-line or subsequent therapy; **AND**
2. Individual has persistent, recurrent, or metastatic small cell neuroendocrine carcinoma of the cervix (NECC); **OR**
3. Individual has locoregional recurrence or stage IVB or recurrence with distant metastases;

AND

C. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**

D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

vii. Individual has a diagnosis of Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia (CLL/SLL) (NCCN 2A); **AND**

A. Individual is using as a single agent or in combination with ibrutinib; **AND**

B. Individual is using for histologic (Richter) transformation to diffuse large B-cell lymphoma; **AND**

C. Meets one of the following (per NCCN):

1. Untreated CLL or clonally unrelated disease at initial diagnosis, and requested therapy is being used as additional therapy for partial response, refractory disease, or progression while on chemoimmunotherapy (CIT) regimens; **OR**

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2. Previously treated CLL with clonally related disease or clonal relation unknown, and requested therapy is being used as first-line treatment for Richter transformation; **OR**
3. Previously treated CLL with clonally related disease or clonal relation unknown, and requested therapy is being used as:
    a. Continuation therapy for complete response until progression; **OR**
    b. Additional therapy (not previously used) for partial response, refractory disease, or progression while on treatment with CIT or non-CIT regimens;

AND

D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

viii. Individual has a diagnosis of Colorectal Cancer (Label, NCCN 2A); **AND**

A. Individual is using nivolumab as monotherapy or in combination with ipilimumab; **AND**
B. Individual has one of the following biomarkers (NCCN 2A):
    1. Deficient mismatch repair (dMMR) or microsatellite instability-high (MSI-H); **OR**
    2. POLE/POLD1 mutation with ultra-hypermutated phenotype (e.g., TMB >50 mutations/Mb); **AND**
    3. Individual is using therapy in **one** of the following settings:
        a. Unresectable, metastatic, or recurrent disease (synchronous or metachronous); **OR**
        b. Neoadjuvant therapy for T4b tumors, bulky nodal disease, or resectable liver/lung metastases; **OR**
        c. Primary treatment of non-obstructing abdominal/peritoneal metastases, or following local therapy for obstruction; **OR**
        d. Subsequent therapy after prior checkpoint inhibitor monotherapy (only when used in combination with ipilimumab; o monotherapy allowed); **OR**
        e. Label-based use following progression on fluoropyrimidine, oxaliplatin, and irinotecan;

    AND

    4. Individual has not received anti–PD-1, anti–PD-L1, or anti–CTLA-4 therapy in the same clinical setting (unless specifically allowed as in B.3.d); **AND**
    5. Individual is not receiving treatment for an autoimmune condition or chronic systemic immunosuppression.

OR

ix. Individual has a diagnosis of Esophageal and Esophagogastric Junction cancer (NCCN 1, 2A); **AND**

A. Individual is using for induction systemic therapy; **AND**
B. Individual is using to relieve dysphagia; **AND**
C. Individual is medically fit and planned for esophagectomy; **AND**
D. Meets one of the following:
    1. Individual has microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors (independent of PD-L1 status) (NCCN 2A); **OR**
    2. Tumor has expression of PD-L1 CPS ≥ 1 (NCCN 1);
E. Meets one of the following:
    1. Individual is using in combination with platinum-containing chemotherapy and capecitabine or fluorouracil (NCCN 1); **AND**
    2. Individual is using in combination with ipilimumab; **AND**

AND

F. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
G. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

x. Individual has a diagnosis of Gastric, Esophageal and Esophagogastric Junction Adenocarcinoma and has microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumor (NCCN, 2A); **AND**

A. One of the following:
    1. Individual Is using in combination with ipilimumab for primary treatment of adenocarcinoma as neoadjuvant or perioperative immunotherapy; **OR**
    2. Individual is using as a single agent for adenocarcinoma as postoperative management following completely resected disease in those who received preoperative therapy with nivolumab + ipilimumab;

OR

B. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xi. Individual has a diagnosis of Gastric, Esophageal or Esophagogastric Junction (EGJ Cancer and is using nivolumab as palliative therapy (NCCN 1 and 2A)

A. Individual is not a surgical candidate OR has unresectable locally advanced, recurrent, or metastatic disease, including peritoneal-only metastatic disease and/or positive cytology when applicable; **AND**

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B. Individual has Karnofsky performance score ≥60% OR ECOG performance score 0-2; **AND**
C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant; **AND**
D. Individual meets **ONE** of the regimen-specific criteria below:
    1. Adenocarcinoma (HER2 negative) of the gastric, esophageal, or EGJ region – Used as preferred first line therapy with oxaliplatin + 5FU/capecitabine:
        a. Individual has HER2 negative disease; **AND**
        b. Individual has PD-L1 CPS ≥1 (NCCN 1 if CPS ≥5); **AND**
        c. Individual is using nivolumab in combination with
            i. oxaliplatin + fluorouracil
            ii. oxaliplatin + capecitabina; **AND**
        d. Individual has no prior checkpoint inhibitor therapy OR no tumor progression while on therapy with a checkpoint inhibitor

    OR

    2. Esophageal squamous cell carcinoma (ESCC) – Preferred first line therapy in combination with fluorouracil/capecitabine and cisplatin/oxaliplatin or with Ipilimumab (Label, NCCN 2A):
        a. Individual has esophageal squamous cell carcinoma (ESCC); **AND**
        b. Individual has PD-L1 CPS ≥1; **AND**
            i. Individual is using novolumab in combination with fluorouracil or capecitabine AND cisplatin or oxaliplatin; **OR**
            ii. Indiviudal Is using nivolumab with ipilimumab;

        AND
        c. Individual has no prior checkpoint inhibitor therapy OR no tumor progression while on therapy with a checkpoint inhibitor

    OR

    3. Esophageal squamous cell carcinoma (ESCC) – Preferred second line therapy (Label, NCCN1)
        a. Individual has esophageal squamous cell carcinoma (ESCC); **AND**
        b. Individual is using nivolumab single therapy as preferred second-line or subsequent therapy; **AND**
        c. Individual has no prior checkpoint inhibitor therapy OR no tumor progression while on therapy with a checkpoint inhibitor.

    OR

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4. Esophageal, Gastric, or EGJ adenocarcinoma or esophageal squamous cell carcinoma– microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors - preferred first line (PD-L1 independent) (NCCN 2A):
    a. Individual has a diagnosis of adenocarcinoma or ESCC of the gastric, esophageal, or EGJ region; **AND**
    b. Individual has microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors; **AND**
    c. Individual is using novolumab:
        i. As preferred first-line therapy in ONE of the following ways:
            1. in combination with ipilimumab; **OR**
            2. in combination with oxaliplatin + fluorouracil/capecitabine;

        OR

        ii. As second-line or subsequent therapy in combination with ipilimumab; **OR**
        iii. As a single therapy after completing nivolumab with ipilimumab palliative treatment**;**

    AND

    d. Individual has no prior checkpoint inhibitor therapy OR no tumor progression while on therapy with a checkpoint inhibitor.

OR

xii. Individual has a diagnosis of completely resected Esophageal or Esophagogastric Junction Cancer (Label, NCCN 1); **AND**

A. Individual is using as single agent for residual pathologic disease; **AND**
B. Individual has received neoadjuvant chemoradiotherapy (CRT); **AND**
C. Individual has a current ECOG performance status of 0-2; **AND**
D. Individual has not received treatment with another anti-PD-1, anti-PD-L1 agent, or other checkpoint inhibitor;
AND
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xiii. Individual has a diagnosis of Gastric Cancer (adenocarcinoma) (NCCN 1, 2A)

A. Individual is using nivolumab as primary treatment (preferred) in any of the following regimens:

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1. In combination with oxaliplatin and fluorouracil or capecitabine; **AND**
   a. Individual meets one of the following biomarker criteria:
      i. HER2 negative disease AND PD-L1 CPS ≥ 1 (NCCN 1 if PD-L1 CPS ≥ 5); **OR**
      ii. microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumor (independent of PD-L1 Status);

OR

2. In combination with ipilimumab; **AND**
   a. Individual has microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumor (independent of PD-L status);

AND

B. Individual is medically fit for surgery; **AND**
C. Individual has surgically unresectable locoregional disease; **AND**
D. Individual has a current ECOG performance status of 0–2; **AND**
E. Individual has not received treatment with another anti-PD-1, anti-PD-L1 agent, or other checkpoint inhibitor; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant.

OR

xiv. Individual has a diagnosis of multi-agent chemotherapy-resistant gestational trophoblastic neoplasia (NCCN 2A); **AND**

A. Individual has high-risk disease; **OR**
B. Individual has recurrent or progressive intermediate trophoblastic tumor;

AND

C. Individual is using as single-agent therapy or in combination with ipilimumab; **AND**
D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xv. Individual has a diagnosis of advanced hepatocellular Carcinoma and the following criteria are met (Label, NCCN 2A):

A. Individual is using in one of the following ways:
   1. Individual is using as subsequent-line systemic therapy after progression on or after prior systemic therapy; **AND**

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a. Individual has not previously been treated with ipilimumab; **AND**
b. Individual has not been previously treated with anti-CTLA4-based combinations (CTLA-4 examples include ipilimumab, tramelimumab); **AND**
c. Individual is using nivolumab wither as a single agent or in combination with ipilimumab;

OR

2. Individual is using as first line systemic therapy for unresectable or metastatic disease; **AND**
    a. Individual is using nivolumab in combination with ipilimumab

AND

B. Individual has a current ECOG performance status of 0-2; **AND**
C. Individual has not received treatment with another anti-PD-1 or anti-PD-1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xvi. Individual has a diagnosis of Classic Hodgkin Lymphoma (CHL) and the following criteria are met (NCCN 2A unless otherwise specified); AND

A. Individual is using as primary (First-line) treatment; **AND**
    1. Individual is using Opdivo in one (1) of the following ways:
        a. Adults age 18–60 years
            i. Opdivo is used in combination with AVD (doxorubicin, vinblastine, dacarbazine) for primary treatment and one of the following applies:
                1. Individual has stage III–IV disease (NCCN Category 1; preferred); **OR**
                2. Individual has stage I–II unfavorable disease with one or more of the following risk features:
                    a. B symptoms; **OR**
                    b. Bulky mediastinal disease; **OR**
                    c. >10 cm adenopathy; **OR**
                    d. ≥4 nodal sites; **OR**
                    e. ESR ≥50 mm/hr

OR

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b. Adults age >60 years (or adults unfit for intensive treatment)and candidate for anthracycline
   i. Opdivo is used in combination with AVD (doxorubicin, vinblastine, dacarbazine) and one of the following applies:
      1. Stage III–IV disease (NCCN Category 1; preferred) in combination with AVD x 6 cycles + ISRT; **OR**
      2. Stage I–II unfavorable disease in combination with AVD x 4 cycles + ISRT.

OR

c. Adults any age not a candidate for anthracycline
   i. Opdivo is used as primary treatment in one (1) of the following ways:
      1. In combination with brentuximab vedotin with or without ISRT; **OR**
      2. As a single agent, with or without ISRT, if contraindications to brentuximab vedotin.

OR

B. Individual is using as second-line systemic therapy (primary refractory or relapsed disease); **AND**
   1. Individual is an adult aged 18–60 years; **AND**
   2. Individual is using Opdivo for primary refractory disease or relapse (within any time frame) as second-line systemic therapy in one (1) of the following ways:
      a. Individual is a candidate for HDT/ASCR (high-dose therapy and autologous stem cell rescue) and Opdivo is used in combination with one of the following regimens:
         i. Brentuximab vedotin + Opdivo (preferred if no prior checkpoint inhibitor exposure); **OR**
         ii. ICE + Opdivo (ifosfamide, carboplatin, etoposide) (preferred if no prior checkpoint inhibitor exposure).

      OR

      b. Individual is not a candidate for HDT/ASCR (high-dose therapy and autologous stem cell rescue) and meets one of the following Checkpoint Inhibitor-related criteria:
         i. No prior checkpoint inhibitor, OR progression after ≥3 months of a checkpoint inhibitor-containing regimen; **OR**
         ii. Prior checkpoint inhibitor or brentuximab exposure AND progression after <3 months of these regimens;

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AND

iii. Opdivo is used in one (1) of the following ways:
1. In combination with brentuximab vedotin; **OR**
2. In combination with ICE; **OR**
3. As a single-agent palliative therapy option.

OR

3. Second-line systemic therapy WITH radiation (special scenario); **AND**
   a. Individual is not a candidate for HDT/ASCR and is receiving second-line systemic therapy with radiation therapy, where the individual previously received abbreviated chemotherapy (3–4 cycles) without radiotherapy, **AND**
   b. Opdivo is used in combination with:
      i. Brentuximab vedotin (preferred if no prior checkpoint inhibitor exposure); **OR**
      ii. ICE (ifosfamide, carboplatin, etoposide) (preferred if no prior checkpoint inhibitor exposure).

OR

C. Individual is using as subsequent systemic therapy in combination with Brentuximab Vedotin OR ICE (ifosfamide, carboplatin, etoposide); **AND**
   1. Opdivo has not been used previously; **AND**
   2. Individual has primary refractory disease or biopsy-proven relapse:
      a. Individual has Deauville 4 or 5 following restaging with FDG-PET/CT; **AND**
         i. Individual is candidate for high-dose therapy and autologous stem cell rescue (HDT/ASCR)

         OR

         ii. Individual is not a candidate for HDT/ASCR; **AND**
         iii. Individual received second-line systemic therapy plus radiation therapy (RT) for previously abbreviated chemotherapy without RT

OR

D. Individual is using as subsequent systemic therapy for refractory disease or relapse as a single agent palliative therapy; **AND**
   1. Individual is not a candidate for high-dose therapy and autologous stem cell rescue (HDT/ASCR).

OR

E. Individual has disease that is refractory to at least three (3) prior lines of subsequent therapy; **AND**
   1. Opdivo is used as single-agent palliative therapy.

OR

F. Individual is receiving Opdivo as a single agent post-allogeneic hematopoietic cell transplant

OR

xvii. The individual has a diagnosis of Pediatric Classic Hodgkin Lymphoma (CHL) (NCCN Category 1 or 2A); AND

A. The individual is using Opdivo in one (1) of the following ways:
   1. Individual is using as a single agent for relapsed or refractory disease (considered in patients with heavily pretreated disease [e.g., prior exposure to platinum- or anthracycline-based chemotherapy] or with decreased cardiac function) (there is no pediatric data available for this regimen);

   OR

   2. Individual is using in combination with brentuximab vedotin, with or without bendamustine, with or without involved-site radiation therapy (ISRT), including:
      a. Preferred re-induction or subsequent therapy in patients with heavily pretreated disease (e.g., prior exposure to platinum- or anthracycline-based chemotherapy) or with decreased cardiac function; **OR**
      b. Highly favorable relapsed patients as an alternative to autologous stem cell rescue (ASCR), such as those with initial stage other than IIIB or IVB, no prior radiation therapy, complete remission 1 (CR1) duration >1 year, absence of extranodal disease, or absence of B symptoms at relapse;

   OR

   3. Individual is using for relapsed or refractory disease in combination with ICE (ifosfamide, carboplatin, etoposide) regimen (may be useful in select cases; there is no pediatric data available for this regimen);

   OR

   4. Individual is using as primary treatment in combination with AVD (doxorubicin, vinblastine, dacarbazine) for stage III–IV disease in individuals aged 12 years or older (NCCN Category 1);

AND

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B. The individual has not received prior treatment with another anti–PD-1 or anti–PD-L1 agent;
AND
C. The individual is not receiving systemic therapy for an autoimmune disease or chronic condition requiring immunosuppression.

OR

xviii. Individual has a diagnosis of Endometrial Carcinoma (NCCN 2A); AND

A. Histology is one of the following:
1. Endometrioid adenocarcinoma; **OR**
2. Serous carcinoma; **OR**
3. Clear cell carcinoma; **OR**
4. Carcinosarcoma; **OR**
5. Undifferentiated or dedifferentiated carcinoma;

AND

B. Individual is using as second line or subsequent therapy for recurrent or metastatic disease; AND
1. Nivolumab is being used as single therapy and the tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); **OR**
2. Nivolumab is being used with ipilimumab and the tumor is mutational burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]); **AND**

C. Individual has not received another anti–PD-1 or anti–PD-L1 agent; AND
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring systemic immunosuppressant

OR

xix. Individual has a diagnosis of Uterine Sarcoma (NCCN 2A); AND

A. Histology is one of the following:
1. Leiomyosarcoma (LMS); **OR**
2. Endometrial stromal sarcoma (ESS); **OR**
3. Adenosarcoma; **OR**
4. PEComa; **OR**
5. Undifferentiated uterine sarcoma (UUS);

AND

B. Tumor is tumor mutational burden-high (TMB-H) (≥10 mutations/megabase), as determined by an FDA-approved test; **AND**

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C. Individual is using nivolumab in combination with ipilimumab as second-line or subsequent systemic therapy; **AND**
D. Disease has progressed following prior therapy and no satisfactory alternative treatment options are available; **AND**
E. Individual has not received another anti–PD-1 or anti–PD-L1 agent; AND
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring systemic immunosuppressant.

OR

xx. Individual has a diagnosis of relapsed/refractory advanced classic Kaposi Sarcoma and the following criteria are met (NCCN 2A):

A. Individual is using as a single agent or in combination with ipilimumab (Yervoy); **AND**
B. Individual is using as subsequent systemic therapy; **AND**
C. Individual does not have multicentric Castleman Disease (MCD) or KSHV-associated inflammatory cytokine syndrome (KICS);

OR

xxi. Individual has a diagnosis of Pleural Mesothelioma with Clinical Stage I that has epitheloid histology (NCCN 1); AND

A. Individual is using Opdivo in combination with Ipilimumab; **AND**
B. Opdivo is being used in any of the following settings:
   1. As induction systemic therapy (preferred) prior to surgical exploration; **OR**
   2. As initial treatment; **OR**
   3. Following surgical exploration (if induction systemic therapy not given)

AND

C. Individual has an ECOG performance status of 0-2; **AND**
D. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxii. Individual has a diagnosis of unresectable Malignant Pleural Mesothelioma or Peritoneal Mesotheliona and using as first line therapy (Label, NCCN 1 and NCCN 2A); AND

A. Individual is using in combination with ipilimumab (Yervoy); **AND**
B. Individual has a ECOG performance status of 0-2; **AND**
C. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**

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D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxiii. Individual has a diagnosis of resectable Peritoneal Mesothelioma and using as first line therapy (NCCN 2A); AND

A. Individual is using in combination with ipilimumab (Yervoy); **AND**
B. Individual has a ECOG performance status of 0-2; **AND**
C. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxiv. Individual has a diagnosis of Malignant Pleural or Peritoneal Mesothelioma (NCCN 2A); AND

A. Individual is using as a single agent, or in combination with ipilimumab (Yervoy) for subsequent therapy; **AND**
B. Individual has a ECOG performance status of 0-2; **AND**
C. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxv. Individual has a diagnosis of Melanoma (Cutaneous or Uveal) and the following criteria are met (Label, NCCN 1):

A. Individual has unresectable or metastatic melanoma (cutaneous or uveal);
AND
1. Individual is using as first line systemic therapy; **AND**
    a. Opdivo is using as a single agent, or in combination with ipilimumab;
OR
2. Individual is using as second-line or subsequent systemic therapy; **AND**
    a. Using in combination with ipilimumab for disease progression on single-agent anti-PD-1 therapy; **OR**
    b. Using as a single agent or in combination with ipilimumab if disease control occurred with prior anti-PD-1 immunotherapy as re-induction therapy;
AND
3. Current ECOG performance status of 0-2; **AND**

4. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

B. Individual has resected advanced melanoma (Cutaneous) (Label, NCCN 2A); **AND**
   1. Individual is using as a single agent for up to 12 months of adjuvant therapy; **AND**
   2. Individual has resected stage IIB, Stage IIC, IIIB, IIIC, or stage IV disease; **AND**
   3. Current ECOG performance status of 0-2; **AND**
   4. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
   5. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

C. Individual has resected metastatic melanoma (Cutaneous) (Label); **AND**
   1. Individual has metastatic melanoma and has undergone complete resection; **AND**
   2. Individual is using in combination with ipilimumab as adjuvant therapy;

OR

D. Individual has a diagnosis of Melanoma (Cutaneous) (Label, NCCN 1 and 2A); **AND**
   1. Individual is using Opdivo as initial or subsequent treatment prior to surgery (neoadjuvant)**; AND**
   2. Individual is receiving systemic therapy with Opdivo as a single agent;

OR

xxvi. Individual has a diagnosis of metastatic Melanoma with brain metastases and the following criteria are met (NCCN 2A):

A. Individual has a primary diagnosis of melanoma; **AND**
B. Using in one of the following way:
   1. Individual has asymptomatic brain metastases (Long 2017, 2018, Tawbi 2017); **OR**
   2. Individual has BRAF non-specific asymptomatic brain metastases;
C. Individual is using as monotherapy or in combination with ipilimumab; **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxvii. Individual has a diagnosis of Merkel Cell Carcinoma and the following criteria are met (Label, NCCN 2A):

A. Individual is using Opdivo prior to curative surgery (neoadjuvant) as a single agent**; OR**
B. Individual has presence of metastatic or recurrent locoregional MCC determined to be not amenable to definitive surgery or radiation therapy; **AND**
    1. Individual is using as a single agent (preferred) or in combination with ipilimumab;

AND

C. Current ECOG performance status of 0-2; **AND**
D. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxviii. Individual has a diagnosis of Non-Small Cell Lung Cancer (NSCLC) and the following criteria are met (Label, NCCN 2A):

OR

A. Individual has recurrent, advanced, or metastatic NSCLC and using as first-line therapy (Label, NCCN 1, 2A);
    AND
    1. Individual is using in combination with ipilimumab; **AND**
        a. Individual has PD-L1 expression positive (≥1%) tumor;

    OR

    2. Individual is using in combination with ipilimumab *and* 2 (two) cycles of platinum-doublet chemotherapy (i.e., platinum-based chemotherapy with pemetrexed, or carboplatin with paclitaxel); **AND**
    3. Individual does not have presence of actionable molecular markers*; **AND**
    4. Current ECOG performance status of 0-2; **AND**
    5. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
    6. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

B. Individual is using for continuation treatment of recurrent, advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) (NCCN 1, 2A); **AND**
    1. Individual is using in combination with ipilimumab (Yervoy); **AND**
    2. Individual achieved a response or has stable disease following first line therapy of nivolumab + ipilimumab +/- chemotherapy given; **AND**
    3. Individual does not have presence of actionable molecular markers*; **AND**
    4. Current ECOG performance status of 0-2; **AND**

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5. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

C. Individual has recurrent, advanced, or metastatic NSCLC and using as subsequent therapy ((i.e., after disease progression on prior treatment) (NCCN 2A); **AND**
   1. Individual is using Opdivo in any of the following ways:
      a. Single-agent pathway (mutation-negative disease)
         i. Opdivo is being used as a single agent; **AND**
         ii. Tumor does not have actionable molecular markers*;

      OR

      b. Mutation-specific combination pathway
         i. Individual is using Opdivo in combination with ipilimumab, with or without chemotherapy; **AND**
         ii. Tumor is EGFR S768I, L861Q, and/or G719X mutation positive; **AND**
         iii. Individual has received prior EGFR tyrosine kinase inhibitor therapy (e.g., afatinib, osimertinib, erlotinib, gefitinib, or dacomitinib);

   AND

   2. Individual has not experienced disease progression on prior treatment with a PD-1 or PD-L1 inhibitor; **AND**
   3. Current ECOG performance status of 0-2; **AND**
   4. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

D. Individual has resectable NSCLC and using as neoadjuvant therapy (Label, NCCN 1); **AND**

   1. Individual is using in combination with platinum-doublet chemotherapy (e.g. paclitaxel and carboplatin);

   AND

   2. Disease is considered resectable, defined as tumors ≥ 4 cm or node positive; **AND**
   3. Tumor has no known EGFR mutations or ALK rearrangements; **AND**
   4. One (1) of the following applies:
      a. Individual is continuing Opdivo as a single agent for adjuvant treatment after surgery; **OR**

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b. Individual has undergone surgical resection with positive margins (R1 or R2) and has completed adjuvant chemoradiation, and Opdivo is being used as single-agent systemic therapy following chemoradiation;

AND

5. Current ECOG performance status of 0-2; **AND**
6. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
7. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

* Actionable molecular markers may include EGFR exon 19 deletion or L858R mutation; ALK, ROS1, or RET gene fusions, which are associated with reduced benefit from PD-1/PD-L1 inhibitors.

OR

xxix. Individual has a diagnosis of metastatic NSCLC with brain metastases and the following criteria are met (NCCN 2A):

A. Individual has a primary diagnosis of non-small cell lung cancer; **AND**
B. Individual is using as single agent for brain metastases; **AND**
C. Individual has PD-L1 expression positive (≥ 1%) tumors; **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxx. Individual has a diagnosis of Small Cell Lung Cancer (NCCN 2A); AND

A. Individual is using nivolumab as a single agent; **AND**
B. Individual is receiving as subsequent systemic therapy for progression or relapse; **AND**
C. Individual has not previously been treated with an immune checkpoint inhibitor; **AND**
D. Individual has an ECOG performance status of 0–2; **AND**
E. Individual is not receiving systemic immunosuppressive therapy for an autoimmune disease or chronic condition;

OR

xxxi. Individual has a diagnosis of locoregional unresectable or metastatic Adrenocortical Carcinoma (NCCN 2A); AND

A. Individual is using nivolumab in combination with ipilimumab (Yervoy); **AND**
B. Individual is using as systemic therapy for unresectable or metastatic disease; **AND**
C. Current ECOG performance status is 0–2; **AND**

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D. Individual has not received prior treatment with another anti–PD-1 or anti–PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or a chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxxii. Individual has a diagnosis of Pediatric Primary Mediastinal Large B-Cell Lymphoma (NCCN 2A); **AND**

A. Individual has relapsed or refractory disease; **AND**
B. Nivolumab is being used in one (1) of the following ways:
    1. As a single agent or in combination with brentuximab vedotin; **OR**
    2. As consolidation or additional therapy in combination with brentuximab vedotin after partial response to therapy; **AND**
C. Individual has not received another anti–PD-1 or anti–PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring systemic immunosuppressant.

OR

xxxiii. Individual has a diagnosis of Rectal Adenocarcinoma (NCCN 2A); AND

A. Tumor exhibits one of the following biomarkers:
    1. Deficient mismatch repair (dMMR) or microsatellite instability–high (MSI-H); **OR**
    2. Polymerase epsilon/delta (POLE/POLD1) mutation with ultra-hypermutated phenotype (e.g., TMB >50 mut/Mb); **AND**
B. Individual is using nivolumab in any of the following settings:
    1. As a single agent or in combination with ipilimumab:
        a. As primary treatment for Metastatic disease (synchronous or metachronous); **OR**
        b. Recurrent disease (pelvic or anastomotic); **OR**
        c. As initial treatment for resectable metachronous metastases and no prior immunotherapy; **OR**
    2. In combination with ipilimumab (no monotherapy) for advanced or metastatic disease if checkpoint inhibitor monotherapy was previously received; **OR**
    3. As a single agent as neoadjuvant or definitive immunotherapy (preferred) for stage II–III disease, locally advanced tumors, or for locally unresectable or medically inoperable disease;

AND

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C. Individual has not received prior anti–PD-1 or anti–PD-L1 therapy (unless specified above); **AND**
D. ECOG performance status is 0–2; **AND**
E. Individual is not receiving systemic immunosuppressive therapy for autoimmune or chronic conditions.

OR

xxxiv. Individual has a diagnosis of Renal Cell Carcinoma (RCC) (Label, NCCN 2A); AND

A. Individual has stage IV or relapsed advanced or metastatic RCC; **AND**
   1. Individual is using as monotherapy; **AND**
   2. Histological confirmation of Clear Cell Component RCC; **AND**
   3. Individual is immune checkpoint inhibitor–naïve (i.e., has not previously received nivolumab, pembrolizumab, ipilimumab, atezolizumab, or other PD-1, PD-L1, or CTLA-4–targeting therapies); **OR**
   4. Current ECOG performance status of 0-2; **AND**
   5. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
   6. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

B. Individual has intermediate - or poor-risk, advanced RCC; **AND**
   1. Individual is using in combination with ipilimumab for four cycles followed by single agent Opdivo (nivolumab), as first-line therapy for previously untreated RCC; **OR**
   2. Individual is using in combination with ipilimumab for four cycles followed by single agent Opdivo (nivolumab), as subsequent therapy, if no checkpoint blockade (PD-1, PD-L1, or CTLA-4) antibody treatment has been previously administered (NCCN 2A); **AND**
   3. Histological confirmation of RCC with clear-cell component; **AND**
   4. Current ECOG performance status of 0-2; **AND**
   5. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
   6. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

C. Individual has relapsed, recurrent, or advanced RCC (Label, NCCN 1); **AND**
   1. Individual is using as first-line or subsequent therapy in combination with cabozantinib tablets; **AND**
   2. Current ECOG performance status of 0-2; **AND**

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3. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
4. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

D. Individual has relapse or metastatic non-clear cell RCC (nccRCC) (NCCN 2A); **AND**
   1. Individual is using as systemic therapy as a single agent or in combination with cabozantinib; **AND**
   2. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
   3. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxxv. Individual has a diagnosis of Small Bowel Adenocarcinoma (SBA) and meets the following criteria (NCCN 2A):

A. Individual has disease that is 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]; **AND**
B. One of the following clinical settings apply:
   1. Individual has advanced or metastatic disease and is using Opdivo (nivolumab) as a single agent or in combination with ipilimumab, for any line of therapy; **OR**
   2. Individual has locally unresectable or medically inoperable disease and is using Opdivo (nivolumab) as a single agent or in combination with ipilimumab as primary treatment; **OR**
   3. Individual has resectable disease and is using Opdivo (nivolumab) as a single agent or in combination with ipilimumab as neoadjuvant therapy;

AND

C. Current ECOG performance status of 0-2; **AND**
D. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **OR**
E. If the individual previously received immune checkpoint inhibitor monotherapy (e.g., PD-1 or PD-L1 agent) for advanced or metastatic disease, the combination of nivolumab with ipilimumab may be used as subsequent therapy; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxxvi. Individual has a diagnosis of Extranodal NK/T-cell lymphomas (NCCN 2A)

A. Individual has relapsed/refractory disease; **AND**

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B. Individual is using Opdivo as monotherapy following alternate combination chemotherapy not previously used (asparaginase-based regimen);
C. There is no clinical trial available; **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual has a current ECOG performance status of 0-2; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxxvii. Individual has a diagnosis of advanced, unresectable, progressive, or metastatic Soft Tissue Sarcoma and Aggressive Soft Tissue Neoplasms (NCCN 2A); AND

A. Individual is using Opdivo wither:
   1. as a single agent; **OR**
   2. In combination with ipilimumab;

AND

B. One of the following histologic or biomarker settings applies:
   1. Individual has one of the following sarcoma subtypes:
      a. Myxofibrosarcoma
      b. Undifferentiated pleomorphic sarcoma (UPS)
      c. Dedifferentiated liposarcoma
      d. Undifferentiated sarcoma
      e. Cutaneous angiosarcoma
      f. Pleomorphic rhabdomyosarcoma

   OR

   2. Individual has angiosarcoma and is receiving therapy in combination with ipilimumab;

   OR

   3. Tumor is tumor mutational burden-high (TMB-H) (≥10 mutations/megabase), as determined by an FDA-approved test, and:
      a. Disease has progressed following prior treatment, **AND**
      b. No satisfactory alternative treatment options are available;

   OR

   4. Individual has epithelioid hemangioendothelioma that is TMB-H (≥10 mut/Mb) and has progressed following prior therapy;

   OR

   5. Individual has borderline or malignant phyllodes tumor of the breast that is TMB-H (≥10 mut/Mb) and has progressed following prior therapy

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OR

C. Therapy is being used subsequent or palliative systemic treatment for advanced/metastatic disease with disseminated metastases, or as alternative systemic therapy for unresectable or progressive disease after prior therapy.;

AND

D. Has not received another anti-PD-1 or anti-PD-L1 agent; **AND**

E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxxviii. Individual has a diagnosis of Squamous Cell Carcinoma of the Head and Neck (SCCHN) (Label, NCCN 1 and 2A) and meet the following criteria:

A. One of the following settings apply:

1. Individual is using as a single therapy for recurrent, unresectable, or metastatic non-nasopharyngeal SCCHN with disease progression on or after platinum-containing chemotherapy; **OR**
2. Individual has non-nasopharyngeal SCCHN and is using nivolumab in combination with cetuximab as first-line or subsequent systemic therapy for:
    a. Metastatic disease at initial presentation; **OR**
    b. Unresectable disease after prior radiation (RT); **OR**
    c. Recurrent or persistent disease with distant metastases; **OR**
    d. Resectable locoregional recurrence or persistent disease without prior RT;

OR

3. Individual has nasopharyngeal SCCHN and is using nivolumab in combination with cisplatin and gemcitabine as first line or subsequent-line systemic therapy for unresectable or metastatic disease;

AND

B. Current ECOG performance status of 0-2; **AND**

C. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**

D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxxix. Individual has metastatic Anaplastic Thyroid carcinoma (NCCN 2A); AND

A. Individual is using as a single agent; **AND**

B. Current ECOG performance status of 0-2; **AND**

C. Has not received another anti-PD-1 or anti-PD-L1 agent; **AND**

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D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xl. Individual has Urothelial carcinoma (Label, NCCN 1, 2A); AND

A. Individual has locally advanced, recurrent, or metastatic disease; **AND**
   3. Individual is using as a single agent; **AND**
   4. Individual meets one of the following criteria:
      a. Confirmation of disease progression on or after platinum-containing or other chemotherapy; **OR**
      b. Confirmation of disease progression within 12 months of receiving neoadjuvant or adjuvant treatment with platinum-containing chemotherapy;

   OR
   5. Individual is using as single agent for adjuvant therapy; **AND**
   6. Individual is at high risk of recurrence after having radical resection; **AND**

B. Current ECOG performance status of 0-2; **AND**

C. Has not received another anti-PD-1 or anti-PD-L1 agent; **AND**

D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xli. Individual has Urothelial carcinoma (Label, NCCN 1, 2A); AND

A. Individual has unresectable, recurrent, or metastatic disease; **AND**

B. Individual is using in combination with cisplatin and gemcitabine; **AND**
   A. Individual is using as first-line systemic treatment followed by nivolumab as a single maintenance therapy; **OR**
   B. individual has recurrent or metastatic disease and is using nivolumab in combination with cisplatin and gemcitabine as second-line systemic therapy, in the setting where:
      a. Individual previously received immunotherapy and enfortumab vedotin-ejfv, but has not received prior chemotherapy; **OR**
      b. Individual previously received immunotherapy, but has not received prior chemotherapy or enfortumab vedotin-ejfv;

AND

C. Current ECOG performance status of 0-2; **AND**

D. Has not received another anti-PD-1 or anti-PD-L1 agent (unless specified in B.2); **AND**

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E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xlii. Individual has a diagnosis of primary urothelial carcinoma of the urethra (NCCN 1); AND

A. Individual has locally advanced urothelial carcinoma of the urethra with regional lymph node involvement (clinical stage T3-4, cN1-2 disease or cN1-2 palpable inguinal lymph nodes); **AND**
B. Individual is using nivolumab in combination with cisplatin and gemcitabine as first-line induction systemic therapy, followed by nivolumab monotherapy as maintenance therapy; **AND**
C. Current ECOG performance status is 0–2; **AND**
D. Individual has not received prior treatment with another anti–PD-1 or anti–PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring systemic immunosuppressant;

OR

xliii. Individual has a diagnosis of Urothelial carcinoma of the Prostate (NCCN 2A); AND

A. Individual is using as adjuvant therapy; **AND**
B. Individual is using for tumors with stromal invasion if platinum-based neoadjuvant chemotherapy not given and pT3, pT4a, pN+; **AND**
C. Individual is using as a single agent;

OR

xliv. Individual has a diagnosis of Central Nervous System Cancers- Pediatric Diffuse High-Grade Gliomas (NCCN 2A); AND

A. Individual is using as single agent for hypermutant tumor; **AND**
B. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xlv. Individual has a diagnosis of recurrent or metastatic Vaginal Cancer (NCCN 2A);

A. Individual is using a single agent; **AND**
C. Individual is using as second-line or subsequent therapy;

OR

B. Individual is using Opdivo in combination with ipilimumab;

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AND

C. Individual has PD-L1 expression positive (CPS ≥ 1%) tumor; **AND**
D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xlvi. Individual has a diagnosis of recurrent or metastatic Vulvar Cancer (NCCN 2A); AND

A. Individual is using as a single agent; **AND**
   1. Individual has HPV-related tumor;

OR

B. Individual is using Opdivo with ipilimumab;

AND

C. Individual is using as second-line or subsequent therapy; **AND**
D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant.

***Note:** Actionable molecular markers include EGFR, ALK, ROS1, BRAF, NTRK, MET, RET, and ERBB2 (HER2) mutations. The NCCN panel recommends testing prior to initiating therapy to help guide appropriate treatment. If there is insufficient tissue to allow testing for all of these markers, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes (NCCN 1, 2A).

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Nivolumab and hyaluronidase-nvhy (Opdivo Qvantig®)

Note: Nivolumab (Opdivo®) and nivolumab and hyaluronidase-nvhy (Opdivo Qvantig®) are not used interchangeably for each indication. Nivolumab and hyaluronidase-nvhy (Opdivo Qvantig®) is not approved for concurrent use with IV ipilimumab (Yervoy®).

NCCN guidelines states for nivolumab (Opdivo®) monotherapy, nivolumab and hyaluronidase-nvhy (Opdivo Qvantig®) subcutaneous injection may be substituted for IV nivolumab (Opdivo®). Nivolumab and hyaluronidase-nvhy (Opdivo Qvantig®) different dosing and administration instructions compared to IV nivolumab (Opdivo®).

i. Individual has a diagnosis of Ampullary Adenocarcinoma (NCCN 2A):**AND**
   - A. Using in one of the following ways:
     1. As first-line therapy for metastatic intestinal type disease; **OR**
     2. For disease progression; **AND**
   - B. Individual has deficient mismatch repair or microsatellite instability-high [dMMR or MSI-H] disease; **AND**
   - C. Individual is using as monotherapy; **AND**
   - D. Individual has an Eastern Cooperative Oncology Group (ECOG) performance status of 3; **AND**
   - E. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
   - F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

ii. Individual has a diagnosis of Appendiceal Adenocarcinoma, including: Appendiceal Adenocarcinoma, Goblet Cell Adenocarcinoma, or Undifferentiated Carcinoma (not otherwise specified) (NCCN 2A); **AND**
   - A. Individual is using therapy as a single agent; **AND**
   - B. Individual has ONE of the following biomarkers (NCCN 2A):
     1. Deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H); **OR**
     2. Polymerase epsilon/delta (POLE/POLD1) mutation with ultra-hypermutated phenotype (e.g., tumor mutational burden [TMB] >50 mutations/Mb);

   AND
   - C. Individual meets ONE of the following treatment settings (NCCN 2A):
     1. Neoadjuvant systemic therapy (NCCN 2A); **AND**

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a. Biopsy-proven recurrence of high-risk disease (with or without prior cytoreductive surgery); **OR**
b. Metastatic peritoneal-only disease (either as neoadjuvant therapy or after inadequate response to prior neoadjuvant therapy);

OR

2. Therapy for recurrent, progressive or metastatic disease

AND

D. Individual has not previously received treatment with a checkpoint inhibitor; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

ii. Individual has a diagnosis of Anal carcinoma (NCCN 2A); **AND**

A. Individual is using as second-line and subsequent therapy; **AND**
B. Individual is using in metastatic disease; **AND**
C. Individual is using as a single agent; **AND**
D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

iii. Individual is using for the treatment of Bone cancer, including osteosarcoma, Ewing Sarcoma, chondrosarcoma, and chordoma (NCCN 2A); **AND**

A. Individual is using as single agent or in combination with suntinib (NCCN 2A); **AND**
B. Individual has dedifferentiated chondrosarcoma;

AND

C. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

iv. Individual has a diagnosis of Cervical Cancer (NCCN 2A); **AND**

A. Individual is using as a single agent; **AND**
B. Individual is using for second-line or subsequent therapy; **AND**
C. Individual has CPS ≥ 1 for local/regional recurrence or stage IVB or recurrence with distant metastases; **AND**
D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**

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E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

v. Individual has a diagnosis of Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia (CLL/SLL) (NCCN 2A); **AND**

A. Individual is using as a single agent or in combination with ibrutinib; **AND**
B. Individual is using for histologic (Richter) transformation to diffuse large B-cell lymphoma; **AND**
C. Meets one of the following (per NCCN):
   1. Untreated CLL or clonally unrelated disease at initial diagnosis, and requested therapy is being used as additional therapy for partial response, refractory disease, or progression while on chemoimmunotherapy (CIT) regimens; **OR**
   2. Previously treated CLL with clonally related disease or clonal relation unknown, and requested therapy is being used as first-line treatment for Richter transformation; **OR**
   3. Previously treated CLL with clonally related disease or clonal relation unknown, and requested therapy is being used as:
      a. Continuation therapy for complete response until progression; **OR**
      b. Additional therapy (not previously used) for partial response, refractory disease, or progression while on treatment with CIT or non-CIT regimens;

AND

D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

vi. Individual has a diagnosis of Colorectal Cancer (Label, NCCN 2A); **AND**

A. Individual is using nivolumab as monotherapy; **AND**
B. Individual has one of the following biomarkers (NCCN 2A):
   1. Deficient mismatch repair (dMMR) or microsatellite instability-high (MSI-H); **OR**
   2. POLE/POLD1 mutation with ultra-hypermutated phenotype (e.g., TMB >50 mutations/Mb); **AND**
   3. Individual is using therapy in **one** of the following settings:
      a. Unresectable, metastatic, or recurrent disease (synchronous or metachronous); **OR**
      b. Neoadjuvant therapy for T4b tumors, bulky nodal disease, or resectable liver/lung metastases; **OR**

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c. Primary treatment of non-obstructing abdominal/peritoneal metastases, or following local therapy for obstruction; **OR**
d. Label-based use following progression on fluoropyrimidine, oxaliplatin, and irinotecan;

AND

4. Individual has not received anti–PD-1, anti–PD-L1, or anti–CTLA-4 therapy in the same clinical setting; **AND**
5. Individual is not receiving treatment for an autoimmune condition or chronic systemic immunosuppression.

OR

vii. Individual has a diagnosis of Esophageal and Esophagogastric Junction cancer (NCCN 1, 2A); **AND**

A. Individual is using for induction systemic therapy; **AND**
B. Individual is using to relieve dysphagia; **AND**
C. Individual is medically fit and planned for esophagectomy; **AND**
D. Meets one of the following:
   1. Individual has microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors (independent of PD-L1 status) (NCCN 2A); **OR**
   2. Tumor has expression of PD-L1 CPS ≥ 1 (NCCN 1);
E. Individual is using in combination with platinum-containing chemotherapy and capecitabine or fluorouracil (NCCN 1); **AND**
F. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
G. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

viii. Individual has a diagnosis of Gastric, Esophageal and Esophagogastric Junction Adenocarcinoma and has microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumor (NCCN, 2A); **AND**

A. Individual is using as a single agent for adenocarcinoma as postoperative management following completely resected disease in those who received preoperative therapy with nivolumab + ipilimumab; **AND**
B. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

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ix. Individual has a diagnosis of Gastric, Esophageal or Esophagogastric Junction (EGJ Cancer and is using nivolumab as palliative therapy (NCCN 1 and 2A)

A. Individual is not a surgical candidate OR has unresectable locally advanced, recurrent, or metastatic disease, including peritoneal-only metastatic disease and/or positive cytology when applicable; **AND**
B. Individual has Karnofsky performance score ≥60% OR ECOG performance score 0-2; **AND**
C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant; **AND**
D. Individual meets **ONE** of the regimen-specific criteria below:
    1. Adenocarcinoma (HER2 negative) of the gastric, esophageal, or EGJ region – Used as preferred first line therapy with oxaliplatin + 5FU/capecitabine:
        a. Individual has HER2 negative disease; **AND**
        b. Individual has PD-L1 CPS ≥1 (NCCN 1 if CPS ≥5); **AND**
        c. Individual is using nivolumab in combination with
            i. oxaliplatin + fluorouracil
            ii. oxaliplatin + capecitabina; **AND**
        d. Individual has no prior checkpoint inhibitor therapy OR no tumor progression while on therapy with a checkpoint inhibitor

    OR

    2. Esophageal squamous cell carcinoma (ESCC) – Preferred first line therapy in combination with fluorouracil/capecitabine and cisplatin/oxaliplatin (Label, NCCN 2A):
        a. Individual has esophageal squamous cell carcinoma (ESCC); **AND**
        b. Individual has PD-L1 CPS ≥1; **AND**
        c. Individual is using novolumab in combination with fluorouracil or capecitabine AND cisplatin or oxaliplatin; **AND**
        d. Individual has no prior checkpoint inhibitor therapy OR no tumor progression while on therapy with a checkpoint inhibitor

    OR

    3. Esophageal squamous cell carcinoma (ESCC) – Preferred second line therapy (Label, NCCN1)
        a. Individual has esophageal squamous cell carcinoma (ESCC); **AND**
        b. Individual is using nivolumab single therapy as preferred second-line or subsequent therapy; **AND**

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c. Individual has no prior checkpoint inhibitor therapy OR no tumor progression while on therapy with a checkpoint inhibitor.

OR

4. Esophageal, Gastric, or EGJ adenocarcinoma or esophageal squamous cell carcinoma– microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors - preferred first line (PD-L1 independent) (NCCN 2A):
   a. Individual has a diagnosis of adenocarcinoma or ESCC of the gastric, esophageal, or EGJ region; **AND**
   b. Individual has microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors; **AND**
   c. Individual is using novolumab as preferred first-line therapy in combination with oxaliplatin + fluorouracil/capecitabine; **OR**
   d. Individual is using novlumab as a single therapy after completing nivolumab with ipilimumab palliative treatment**; AND**
   e. Individual has no prior checkpoint inhibitor therapy OR no tumor progression while on therapy with a checkpoint inhibitor.

OR

x. Individual has a diagnosis of completely resected Esophageal or Esophagogastric Junction Cancer (Label, NCCN 1); **AND**
   A. Individual is using as single agent for residual pathologic disease; **AND**
   B. Individual has received neoadjuvant chemoradiotherapy (CRT); **AND**
   C. Individual has a current ECOG performance status of 0-2; **AND**
   D. Individual has not received treatment with another anti-PD-1, anti-PD-L1 agent, or other checkpoint inhibitor;
   AND
   E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xi. Individual has a diagnosis of Gastric Cancer (adenocarcinoma) (NCCN 1, 2A)

   A. Individual is using nivolumab as primary treatment (preferred) In combination with oxaliplatin and fluorouracil or capecitabine; **AND**
      a. Individual meets one of the following biomarker criteria:
         i. HER2 negative disease AND PD-L1 CPS ≥ 1 (NCCN 1 if PD-L1 CPS ≥ 5);
         OR

ii. microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumor (independent of PD-L1 Status);

AND

B. Individual is medically fit for surgery; **AND**
C. Individual has surgically unresectable locoregional disease; **AND**
D. Individual has a current ECOG performance status of 0–2; **AND**
E. Individual has not received treatment with another anti-PD-1, anti-PD-L1 agent, or other checkpoint inhibitor; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant.

OR

xii. Individual has a diagnosis of multi-agent chemotherapy-resistant gestational trophoblastic neoplasia; **AND**

A. Individual has Individual has recurrent or progressive intermediate or high-risk disease; **AND**
B. Individual is using as single-agent therapy; **AND**
C. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xiii. Individual has a diagnosis of advanced Hepatocellular Carcinoma and the following criteria are met (Label, NCCN 2A):

A. Individual is using nivolumab as a single agent as subsequent-line systemic therapy after progression on or after prior systemic therapy; **AND**
B. Individual has not previously been treated with ipilimumab; **AND**
C. Individual has not been previously treated with anti-CTLA4-based combinations (CTLA-4 examples include ipilimumab, tramelimumab); **AND**
D. Individual has a current ECOG performance status of 0-2; **AND**
E. Individual has not received treatment with another anti-PD-1 or anti-PD-1 agent; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xiv. Individual has a diagnosis of Endometrial Carcinoma (NCCN 2A); **AND**

A. Histology is one of the following:
   1. Endometrioid adenocarcinoma; **OR**
   2. Serous carcinoma; **OR**

3. Clear cell carcinoma; **OR**
4. Carcinosarcoma; **OR**
5. Undifferentiated or dedifferentiated carcinoma;

AND

B. Tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); **AND**

C. Individual is using as a single agent for recurrent or metastatic disease as second-line or subsequent therapy; **AND**

D. Individual has not received another anti–PD-1 or anti–PD-L1 agent; AND E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring systemic immunosuppressant

OR

xv. Individual has a diagnosis of relapsed/refractory advanced classic Kaposi Sarcoma and the following criteria are met (NCCN 2A):

A. Individual is using as a single agent subsequent systemic therapy; **AND**

B. Individual does not have multicentric Castleman Disease (MCD) or KSHV-associated inflammatory cytokine syndrome (KICS);

OR

xvi. Individual has a diagnosis of Pleural or Peritoneal Mesothelioma (NCCN 2A); **AND**

A. Individual is using as a single agent for subsequent therapy; **AND**
B. Individual has a ECOG performance status of 0-2; **AND**
C. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

xvii. Individual has a diagnosis of Melanoma (Cutaneous or Uveal) and the following criteria are met (Label, NCCN 1):

A. Individual has unresectable or metastatic melanoma (cutaneous or uveal); **AND**
1. Individual is using as first line systemic therapy; **AND**
a. Opdivo is using as a single agent,;

OR

2. Individual is using as second-line or subsequent systemic therapy; **AND**
a. Using as a single agent if disease control occurred with prior anti-PD-1 immunotherapy as re-induction therapy;

AND

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3. Current ECOG performance status of 0-2; **AND**
4. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

B. Individual has resected advanced melanoma (Cutaneous) (Label, NCCN 2A); **AND**
   1. Individual is using as a single agent for up to 12 months of adjuvant therapy; **AND**
   2. Individual has resected stage IIB, Stage IIC, IIIB, IIIC, or stage IV disease; **AND**
   3. Current ECOG performance status of 0-2; **AND**
   4. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
   5. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

C. Individual has a diagnosis of Melanoma (Cutaneous) (Label, NCCN 1 and 2A); **AND**
   1. Individual is using Opdivo as initial or subsequent treatment prior to surgery (neoadjuvant)**; AND**
   2. Individual is receiving systemic therapy with Opdivo as a single agent;

OR

xviii. Individual has a diagnosis of metastatic Melanoma with brain metastases and the following criteria are met (NCCN 2A):

F. Individual has a primary diagnosis of melanoma; **AND**

G. Using in one of the following way:

D. Individual has asymptomatic brain metastases (Long 2017, 2018, Tawbi 2017); **OR**

E. Individual has BRAF non-specific asymptomatic brain metastases;

H. Individual is using as monotherapy ; **AND**

I. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**

J. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xix. Individual has a diagnosis of Merkel Cell Carcinoma and the following criteria are met (Label, NCCN 2A):

A. Individual is using as a single agent; **AND**

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B. Individual has presence of metastatic or recurrent locoregional MCC determined to be not amenable to definitive surgery or radiation therapy; **OR**
C. Individual is using prior to curative surgery (neoadjuvant); **AND**
D. Current ECOG performance status of 0-2; **AND**
E. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant; **OR**

OR

xx. Individual has recurrent, advanced, or metastatic NSCLC and using as subsequent therapy ((i.e., after disease progression on prior treatment) (NCCN 2A); **AND**
A. Opdivo is being used as a single agent; AND
B. Tumor does not have actionable molecular markers*; AND
C. Individual has not experienced disease progression on prior treatment with a PD-1 or PD-L1 inhibitor; AND
D. Current ECOG performance status of 0-2; AND
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

xxi. Individual has resectable NSCLC and using as neoadjuvant therapy (Label, NCCN 1); **AND**
A. Individual is using in combination with platinum-doublet chemotherapy (e.g. paclitaxel and carboplatin); **AND**
B. Disease is considered resectable, defined as tumors ≥ 4 cm or node positive; **AND**
C. Tumor has no known EGFR mutations or ALK rearrangements; **AND**
D. One (1) of the following applies:
1. Individual is continuing Opdivo as a single agent for adjuvant treatment after surgery; **OR**
2. Individual has undergone surgical resection with positive margins (R1 or R2) and has completed adjuvant chemoradiation, and Opdivo is being used as single-agent systemic therapy following chemoradiation;

AND
G. Current ECOG performance status of 0-2; **AND**
H. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**

I. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxii. Individual has a diagnosis of metastatic NSCLC with brain metastases, and the following criteria are met (NCCN 2A):

A. Individual has a primary diagnosis of non-small cell lung cancer; **AND**
B. Individual is using as single agent for brain metastases; **AND**
C. Individual has PD-L1 expression positive (≥ 1%) tumors; **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxiii. Individual has a diagnosis of Small Cell Lung Cancer (NCCN 2A); AND

A. Individual is using nivolumab as a single agent; **AND**
B. Individual is receiving as subsequent systemic therapy for progression or relapse; **AND**
C. Individual has not previously been treated with an immune checkpoint inhibitor; **AND**
D. Individual has an ECOG performance status of 0–2; **AND**
E. Individual is not receiving systemic immunosuppressive therapy for an autoimmune disease or chronic condition;

OR

xxiv. Individual has a diagnosis of Rectal Adenocarcinoma (NCCN 2A); AND

A. Tumor exhibits one of the following biomarkers:
   1. Deficient mismatch repair (dMMR) or microsatellite instability–high (MSI-H); **OR**
   2. Polymerase epsilon/delta (POLE/POLD1) mutation with ultra-hypermutated phenotype (e.g., TMB >50 mut/Mb); **AND**
B. Individual is using nivolumab as a single agent in any of the following settings:
   1. As primary treatment for Metastatic disease (synchronous or metachronous); **OR**
   2. Recurrent disease (pelvic or anastomotic); **OR**
   3. As initial treatment for resectable metachronous metastases and no prior immunotherapy; **OR**
   4. As neoadjuvant or definitive immunotherapy (preferred) for stage II–III disease, locally advanced tumors, or for locally unresectable or medically inoperable disease;

AND

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C. Individual has not received prior anti–PD-1 or anti–PD-L1 therapy;**AND**
D. ECOG performance status is 0–2; **AND**
E. Individual is not receiving systemic immunosuppressive therapy for autoimmune or chronic conditions.

OR

xxv. Individual has stage IV or relapsed advanced or metastatic RCC; AND
A. Individual is using as monotherapy; **AND**
B. Histological confirmation of Clear Cell Component RCC; **AND**
C. Individual is immune checkpoint inhibitor–naïve (i.e., has not previously received nivolumab, pembrolizumab, ipilimumab, atezolizumab, or other PD-1, PD-L1, or CTLA-4–targeting therapies); **OR**
D. Current ECOG performance status of 0-2; **AND**
E. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxvi. Individual has intermediate - or poor-risk, advanced RCC; AND
A. Individual is using subcutaneous Opdivo (nivolumab QVANTIG) as monotherapy only (i.e., not in combination with ipilimumab); **AND**
B. Individual is continuing treatment after completion of four (4) cycles of nivolumab in combination with ipilimumab (i.e., transitioning to monotherapy phase); **AND**
C. Current ECOG performance status of 0–2; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring systemic immunosuppressive treatment.

OR

xxvii. Individual has relapsed, recurrent, or advanced RCC (Label, NCCN 1); **AND**

A. Individual is using as first-line or subsequent therapy in combination with cabozantinib tablets; **AND**
B. Current ECOG performance status of 0-2; **AND**
C. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant.

OR

xxviii. Individual has relapse or metastatic non-clear cell RCC (nccRCC) (NCCN 2A); **AND**
A. Individual is using as systemic therapy as a single agent or in combination with cabozantinib; **AND**

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B. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxix. Individual has a diagnosis of Small Bowel Adenocarcinoma (SBA) and meets the following criteria (NCCN 2A):

A. Individual has disease that is 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]; **AND**
B. Individual is using Opdivo as a single agent; **AND**
C. One of the following clinical settings apply:
    1. Individual has advanced or metastatic disease and is using Opdivo (nivolumab) as a single agent, for any line of therapy; **OR**
    2. Individual has locally unresectable or medically inoperable disease and is using Opdivo (nivolumab) as as primary treatment; **OR**
    3. Individual has resectable disease and is using Opdivo (nivolumab) as neoadjuvant therapy;

AND

D. Current ECOG performance status of 0-2; **AND**
E. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxx. Individual has a diagnosis of Squamous Cell Carcinoma of the Head and Neck (SCCHN) (Label, NCCN 1 and 2A) and meet the following criteria:

A. One of the following settings apply:
    1. Individual is using as a single therapy for recurrent, unresectable, or metastatic non-nasopharyngeal SCCHN with disease progression on or after platinum-containing chemotherapy; **OR**
    2. Individual has non-nasopharyngeal SCCHN and is using nivolumab in combination with cetuximab as first-line or subsequent systemic therapy for:
        a. Metastatic disease at initial presentation; **OR**

b. Unresectable disease after prior radiation (RT); **OR**
c. Recurrent or persistent disease with distant metastases; **OR**
d. Resectable locoregional recurrence or persistent disease without prior RT;

OR

3. Individual has nasopharyngeal SCCHN and is using nivolumab in combination with cisplatin and gemcitabine as first line or subsequent-line systemic therapy for unresectable or metastatic disease;

AND

B. Current ECOG performance status of 0-2; **AND**
C. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxxi. Individual has metastatic Anaplastic Thyroid carcinoma (NCCN 2A); **AND**

A. Individual is using as a single agent; **AND**
B. Current ECOG performance status of 0-2; **AND**
C. Has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxxii. Individual has Urothelial carcinoma (Label, NCCN 1, 2A); **AND**

A. Individual has locally advanced, recurrent, or metastatic disease; **AND**
1. Individual is using as a single agent; **AND**
2. Individual meets one of the following criteria:
a. Confirmation of disease progression on or after platinum-containing or other chemotherapy; **OR**
b. Confirmation of disease progression within 12 months of receiving neoadjuvant or adjuvant treatment with platinum-containing chemotherapy;

OR

3. Individual is using as single agent for adjuvant therapy; **AND**
4. Individual is at high risk of recurrence after having radical resection; **AND**

B. Current ECOG performance status of 0-2; **AND**
C. Has not received another anti-PD-1 or anti-PD-L1 agent; **AND**

D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxxiii. Individual has Urothelial carcinoma (Label, NCCN 1, 2A); **AND**

A. Individual has unresectable, recurrent, or metastatic disease; **AND**

B. Individual is using in combination with cisplatin and gemcitabine; **AND**

1. Individual is using as first-line systemic treatment followed by nivolumab as a single maintenance therapy; **OR**
2. individual has recurrent or metastatic disease and is using nivolumab in combination with cisplatin and gemcitabine as second-line systemic therapy, in the setting where:
   a. Individual previously received immunotherapy and enfortumab vedotin-ejfv, but has not received prior chemotherapy; **OR**
   b. Individual previously received immunotherapy, but has not received prior chemotherapy or enfortumab vedotin-ejfv;

AND

C. Current ECOG performance status of 0-2; **AND**

D. Has not received another anti-PD-1 or anti-PD-L1 agent (unless specified in B.2); **AND**

E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxxiv. Individual has a diagnosis of primary urothelial carcinoma of the urethra (NCCN 1); **AND**

A. Individual has locally advanced urothelial carcinoma of the urethra with regional lymph node involvement (clinical stage T3-4, cN1-2 disease or cN1-2 palpable inguinal lymph nodes); **AND**

B. Individual is using nivolumab in combination with cisplatin and gemcitabine as first-line induction systemic therapy, followed by nivolumab monotherapy as maintenance therapy; **AND**

C. Current ECOG performance status is 0–2; **AND**

D. Individual has not received prior treatment with another anti–PD-1 or anti–PD-L1 agent; **AND**

E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring systemic immunosuppressant;

OR

xxxv. Individual has a diagnosis of Urothelial carcinoma of the Prostate (NCCN 2A); **AND**

A. Individual is using as adjuvant therapy; **AND**
B. Individual is using for tumors with stromal invasion if platinum-based neoadjuvant chemotherapy not given and pT3, pT4a, pN+; **AND**
C. Individual is using as a single agent;

OR

xxxvi. Individual has a diagnosis of recurrent or metastatic Vaginal Cancer (NCCN 2A);
A. Individual is using a single agent; **AND**
B. Individual is using as second-line or subsequent therapy; **AND**
C. Individual has PD-L1 expression positive (CPS ≥ 1%) tumor; **AND**
D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xxxvii. Individual has a diagnosis of recurrent or metastatic Vulvar Cancer (NCCN 2A); **AND**
A. Individual is using as a single agent; **AND**
B. Individual is using as second-line or subsequent therapy; **AND**
C. Individual has HPV-related tumor; **AND**
D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant.

***Note:** Actionable molecular markers include EGFR, ALK, ROS1, BRAF, NTRK, MET, RET, and ERBB2 (HER2) mutations. The NCCN panel recommends testing prior to initiating therapy to help guide appropriate treatment. If there is insufficient tissue to allow testing for all of these markers, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes (NCCN 1, 2A).

B. Criteria For Continuation of Therapy

i. MMM considers continuation of nivolumab (Opdivo®) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of unacceptable toxicity or disease progression while on the current regimen, and the recommended duration of therapy has not been exceeded. The following information should be submitted for reauthorization:

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F. A current oncology note documenting the patient's response to treatment showing no progression of disease.
G. Current imaging studies and other objective measures, as appropriate, showing no progression of disease when compared with previous results (every six months).

ii. Total duration of therapy (please refer to the most updated prescribing information for treatment duration)
H. Adjuvant treatment as monotherapy: Up to 12 months
I. In combination with other drugs
1. Melanoma:
a. Neoadjuvant: Up to 3 cycles
b. Unresectable and metastatic: After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity.
2. NSCLC:
a. Neoadjuvant and adjuvant: Neoadjuvant treatment in combination with chemotherapy for up to 4 cycles or until disease progression or unacceptable toxicity, followed by adjuvant treatment with OPDIVO as a single agent after surgery for up to 13 cycles (approximately 1 year) or until disease recurrence or unacceptable toxicity.
b. Metastatic or recurrent: In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression
3. Malignant pleural mesothelioma: In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.
4. Advanced Renal Carcinoma: After completing 4 doses of combination therapy with ipilimumab, administer as single agent until disease progression or unacceptable toxicity
5. Unresectable or metastatic urothelial carcinoma: After completing up to 6 cycles of combination therapy, administer as single agent until disease progression, unacceptable toxicity, or up to 2 years from first dose
6. Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer, Hepatocelular Carcinoma: In combination with ipilimumab for a maximum of 4 doses; then up to 2 years as monotherapy.
7. Esophageal squamous cell carcinoma in combination with ipilimumab or chemotherapy for up to 24 months.

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8. Gastric cancer, esophagogastric junction cancer, and esophageal adenocarcinoma in combination with chemotherapy for up to 24 months.

C. Authorization Duration

ii. Initial Approval Duration: Up to 6 months
iii. Reauthorization Approval Duration: Up to 6 months

D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

Opdivo (nivolumab) may not be approved when the above criteria (Section A: Criteria for Initial Approval) are not met and for all other indications.

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Limits or Restrictions

A. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Use	Recommended Regimen		Treatment Duration
	Nivolumab (Opdivo®)	**Nivolumab and hyaluronidase-nvhy (Opdivo Qvantig®)**	
Unresectable or metastatic melanoma	Adult and pediatric patients weighing 40 kg or greater: 240 mg every 2 weeks or 480 mg every 4 weeks. Pediatric patients weighing less than 40 kg: 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks Adult and pediatric patients weighing 40 kg or greater: 1 mg/kg followed by ipilimumab 3 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks. Pediatric patients weighing less than 40 kg: 1 mg/kg followed by ipilimumab 3 mg/kg on the same day every 3 weeks for 4 doses, then 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks.	600 mg nivolumab and 10,000 units hyaluronidase* every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase* every 4 weeks.	As a single agent: Until disease progression or unacceptable toxicity When administered with ipilimumab: Administer with ipilimumab for 4 doses, then continue Opdivo until disease progression or unacceptable
Adjuvant treatment of melanoma	Adult and pediatric patients weighing 40 kg or greater: 240 mg every 2 weeks or 480 mg every 4 weeks. Pediatric patients weighing less than 40 kg: 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks	600 mg nivolumab and 10,000 units hyaluronidase* every 2 weeks or 1,200 mg nivolumab and 20,000 units	Until disease recurrence or unacceptable toxicity for up to 1 year

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		hyaluronidase* every 4 weeks	
Neoadjuvant treatment of resectable (tumors ≥4 cm or node positive) non- small cell lung cancer	360 mg with platinum-doublet chemotherapy on the same day every 3 weeks for 3 cycles	900 mg nivolumab and 15,000 units hyaluronidase* with platinum-doublet chemotherapy on the same day every 3 weeks	In combination with platinum-doublet chemotherapy for 3 cycles
Neoadjuvant and adjuvant treatment of resectable non-small cell lung cancer	Neoadjuvant: 360 mg every 3 weeks* with platinum-doublet chemotherapy on the same day every 3 weeks Adjuvant: 480 mg every 4 weeks*	Neoadjuvant: 900 mg nivolumab and 15,000 units hyaluronidase* with platinum-doublet chemotherapy on the same day every 3 weeks. Adjuvant: 1,200 mg nivolumab and 20,000 units hyaluronidase* every 4 weeks.	Neoadjuvant treatment in combination with chemotherapy for up to 4 cycles or until disease progression or unacceptable toxicity, followed by adjuvant treatment with OPDIVO as a single agent after surgery for up to 13 cycles (approximately 1 year) or until disease recurrence or unacceptable toxicity
Metastatic non-small cell lung cancer	240 mg every 2 weeks or 480 mg every 4 weeks.	600 mg nivolumab and 10,000 units hyaluronidase* every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase* every 4 weeks.	Until disease progression or unacceptable toxicity
	360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks.		Until disease progression, unacceptable toxicity, or up to 2 years.

	360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks and 2 cycles of platinum-doublet chemotherapy.		In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years. 2 cycles of histology- based platinum-doublet chemotherapy
Malignant pleural mesothelioma	360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks.	Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab	Until disease progression, unacceptable toxicity, or up to 2 years.
Advanced renal cell carcinoma	3 mg/kg followed by ipilimumab 1 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks.	600 mg nivolumab and 10,000 units hyaluronidase* every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase* every 4 weeks	Opdivo: The 3 mg/kg dose should be administered with ipilimumab every 3 weeks for 4 doses. Then, administer Opdivo 240 mg every 2 weeks or 480 mg every 4 weeks until disease progression or unacceptable toxicity. Ipilimumab: 4 doses

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	240 mg every 2 weeks or 480 mg every 4 weeks administered in combination with cabozantinib 40 mg once daily without food.		Opdivo: Until disease progression, unacceptable toxicity, or up to 2 years Cabozantinib: Until disease progression or unacceptable toxicity.
	240 mg every 2 weeks or 480 mg every 4 weeks as a single agent		Until disease progression or unacceptable toxicity
Classical Hodgkin lymphoma	240 mg every 2 weeks or 480 mg every 4 weeks	Not used	Until disease progression or unacceptable toxicity
Recurrent or metastatic squamous cell carcinoma of the head and neck	240 mg every 2 weeks or 480 mg every 4 weeks	600 mg nivolumab and 10,000 units hyaluronidase* every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase* every 4 weeks	Until disease progression or unacceptable toxicity
Adjuvant treatment of urothelial carcinoma	240 mg every 2 weeks or 480 mg every 4 weeks	600 mg nivolumab and 10,000 units hyaluronidase* every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase* every 4 weeks	Until disease recurrence or unacceptable toxicity for up to 1 year
Locally advanced or metastatic urothelial carcinoma	240 mg every 2 weeks or 480 mg every 4 weeks	600 mg nivolumab and 10,000 units hyaluronidase* every 2 weeks	Until disease progression or unacceptable toxicity

		or 1,200 mg nivolumab and 20,000 units hyaluronidase* every 4 weeks	
First-line unresectable or metastatic urothelial carcinoma	360 mg every 3 weeks administer in combination with cisplatin and gemcitabine on the same day every 3 weeks	900 mg nivolumab and 15,000 units hyaluronidase* every 3 weeks Administer OPDIVO QVANTIG in combination with cisplatin and gemcitabine on the same day every 3 weeks.	Opdivo: In combination with cisplatin and gemcitabine for up to 6 cycles
First-line unresectable or metastatic urothelial carcinoma	240 mg every 2 weeks or 480 mg every 4 weeks	600 mg nivolumab and 10,000 units hyaluronidase* every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase* every 4 weeks	After completing up to 6 cycles of combination therapy, administer as single agent until disease progression, unacceptable toxicity, or up to 2 years from first dose
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer	Adult and pediatric patients weighing 40 kg or greater: 240 mg every 2 weeks or 480 mg every 4 weeks. Pediatric patients weighing less than 40 kg: 3 mg/kg every 2 weeks. Adult and pediatric patients weighing 40 kg or greater: 3 mg/kg followed by ipilimumab 1 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks.	600 mg nivolumab and 10,000 units hyaluronidase* every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase* every 4 weeks	Until disease progression or unacceptable toxicity
Hepatocellular carcinoma	1 mg/kg followed by ipilimumab 3 mg/kg on the same day every 3	600 mg nivolumab and 10,000 units	Opdivo: The 1 mg/kg dose should be administered

	weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks.	hyaluronidase* every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase* every 4 weeks.	with ipilimumab every 3 weeks for 4 doses. Then, administer Opdivo 240 mg every 2 weeks or 480 mg every 4 weeks until disease progression or unacceptable toxicity. Ipilimumab: 4 doses
Adjuvant treatment of resected esophageal or gastroesophageal cancer	240 mg every 2 weeks or 480 mg every 4 weeks.	600 mg nivolumab and 10,000 units hyaluronidase* every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase* every 4 weeks	Until disease progression or unacceptable toxicity for a total treatment duration of 1 year
Esophageal squamous cell carcinoma	240 mg every 2 weeks or 480 mg every 4 weeks in combination with chemotherapy regimen of fluoropyrimidine- and platinum-containing chemotherapy. 3mg/kg every 2 weeks or 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks.	600 mg nivolumab and 10,000 units hyaluronidase* every 2 weeks or 1,200 mg nivolumab and 20,000 units hyaluronidase* every 4 weeks Administer OPDIVO QVANTIG in combination with fluoropyrimidine- and platinum-containing chemotherapy.	Opdivo should be administered until disease progression, unacceptable toxicity, or up to 2 years.
	240 mg every 2 weeks or 480 mg every 4 weeks.		Until disease progression or unacceptable toxicity.
Gastric cancer, Gastroesophageal junction cancer, and Esophageal adenocarcinoma	360 mg every 3 weeks with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks. 240 mg every 2 weeks with fluoropyrimidine- and platinum-containing chemotherapy every 2 weeks.	600 mg nivolumab and 10,000 units hyaluronidase* with fluoropyrimidine- and platinum-containing chemotherapy every 2 weeks or	Until disease progression, unacceptable toxicity, or up to 2 years

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		900 mg nivolumab and 15,000 units hyaluronidase* with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks	

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r. Hodgkin Lymphoma V1.2026. Revised January 27, 2026.
s. Sarcoma. V2.2026. Revised January 30, 2026.
t. Kidney Cancer. V1.2026. Revised January 30, 2026.
u. Merkel Cell Carcinoma. V2.2026. Revised January 23, 2026.
v. Pleural Mesothelioma V2.2026. Revised January 30, 2026.
w. Peritoneal Mesothelioma. V2.2026. Revised January 30, 2026.
x. Cutaneous Melanoma V2.2025. Revised January 30, 2026..
y. Neuroendocrine and Adrenal Tumors. V3.2026. Revised February 5,2026.
z. Non-Small Cell Lung Cancer. V3.2026. Revised January 30, 2026.
aa. Pediatric Aggressive Mature B-Cell Lymphomas. V2.2025. Revised February 4, 2026.
bb. Pediatric Central Nervous System Cancers. V1.2026. Revised February 4, 2026.
cc. Pediatric Hodgkin Lymphoma. V2.2025. Revised January 27, 2026.
dd. Rectal Cancer V5.2025. Revised February 4, 2026.
ee. Small Bowel Adenocarcinoma V1.2026. Revised February 3, 2026.
ff. Small Cell Lung Cancer. V2.2026. Revised February 3, 2026.
gg. T-Cell Lymphomas. V1.2023. Revised February 4, 2026.
hh. Thyroid Carcinoma. V1 2025. Revised February 3, 2026.
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jj. Uveal Melanoma V2.2025. Revised January 30, 2026.
kk. Vaginal Cancer V2.2026. Revised February 4, 2026.
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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

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Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Annual Review	Adrenal Gland Tumors (Adrenocortical Carcinoma): New criteria added for Adrenocortical Carcinoma in alignment with NCCN Category 2A recommendation to allow use of nivolumab in combination with ipilimumab for treatment of locoregional unresectable or metastatic disease; Non-Small Cell Lung Cancer (NSCLC): Updated criteria to align with current NCCN 1 and 2A recommendations, including preferred first-line systemic therapies and expanded subsequent-line uses, and clarified biomarker-based stratification and combination uses with ipilimumab. updated Opdivo Qvantig criteria. Small Cell Lung Cancer (SCLC): Added new criteria for subsequent systemic therapy based on NCCN Category 2A recommendations. updated Opdivo Qvantig criteria. Squamous Cell Carcinoma of the Head and Neck (SCCHN): Updated criteria to align with NCCN Category 1 and 2A recommendations; added multiple combination regimens including cetuximab combos and cisplatin/gemcitabine; clarified performance status and immunotherapy history requirements; updated Opdivo Qvantig criteria. Anaplastic Thyroid	3/17/2026	03/24/2026

	Carcinoma: New criteria added for metastatic disease per NCCN guidance; updated Qvantig criteria. Urothelial Carcinoma: Updated criteria to include both bladder cancer and primary urethral carcinoma; incorporated Category 1 first-line use with cisplatin + gemcitabine followed by maintenance nivolumab; Category 2A second-line use after prior immunotherapy; excluded 2B uses; updated Qvantig criteria. Central Nervous System Cancers – Pediatric Diffuse High-Grade Gliomas: Added policy statement excluding Qvantig; updated wording and Qvantig criteria. Vaginal and Vulvar Cancer: Added NCCN 2A criteria for vaginal cancer; updated vulvar cancer criteria to broaden monotherapy and combination uses; updated Qvantig criteria. Ampullary Adenocarcinoma: New NCCN 2A criteria for metastatic intestinal-type disease and progression settings, including combination and monotherapy; updated Qvantig criteria. Hepatocellular Carcinoma (HCC): Replaced liver function–based criteria with treatment-setting–based guidance for first-line and subsequent therapy, clarified use with/without ipilimumab, removed outdated subclassifications, and updated Qvantig criteria. Appendiceal Adenocarcinoma: New NCCN 2A criteria; included dMMR/MSI-H and POLE/POLD1 mutation status, neoadjuvant and		

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	recurrent/metastatic settings, and allowance for subsequent ipilimumab combinations; updated Qvantig criteria. Biliary Tract Cancers: Expanded NCCN 2A use of nivolumab + ipilimumab for TMB-H tumors; added neoadjuvant locoregionally advanced criteria; clarified progression settings; removed prior Qvantig monotherapy due to 2B status. Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): New NCCN 2A criteria for use in Richter transformation to DLBCL; added monotherapy and combination with ibrutinib across multiple scenarios; updated Qvantig interchangeability. Esophageal, Gastroesophageal Junction (EGJ), and Gastric Cancers: Expanded scope to include adenocarcinoma and squamous histologies, organized clinical scenarios (neoadjuvant, adjuvant, first-line, subsequent), refined biomarker stratification (PD-L1, HER2, MSI-H/dMMR), incorporated Category 1 and 2A uses including monotherapy and combination strategies, specified surgical candidacy and performance status, and updated Qvantig criteria. Colorectal Cancer: Reorganized and expanded criteria consistent with NCCN 2A and label indications, added POLE/POLD1 ultra-hypermutated phenotype, broadened clinical settings (unresectable/metastatic, neoadjuvant,		

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	primary peritoneal, subsequent post-IO monotherapy, post-chemotherapy), removed outdated adjuvant timing limitations, clarified exclusions, and updated Qvantig criteria. Classical Hodgkin Lymphoma (cHL): Expanded criteria to include first-line and subsequent therapy per NCCN Category 1 and 2A, added age/fitness stratification for frontline regimens, widened second-line pathways distinguishing transplant eligibility and prior checkpoint exposure, included radiation-integrated salvage and single-agent palliative uses, added post-allo transplant use, removed relapsed/refractory-only restrictions, and clarified exclusions. Pediatric Classic Hodgkin Lymphoma (CHL): New criteria added per NCCN Category 1 and 2A, including preferred use of nivolumab + AVD for Stage III–IV in patients ≥12 years, combination with brentuximab vedotin (± bendamustine/ISRT) for relapsed/refractory disease, single-agent or ICE combinations where appropriate, with pediatric evidence considerations. Pediatric Primary Mediastinal Large B-Cell Lymphoma: New criteria added for Pediatric Primary Mediastinal Large B-Cell Lymphoma in alignment with NCCN Category 2A recommendations to allow for use of nivolumab as a single agent or in combination with brentuximab vedotin for		

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	relapsed/refractory disease, including as consolidation/additional therapy after partial response. Endometrial Carcinoma and Uterine Sarcoma: New NCCN 2A criteria added; endometrial criteria include specific histologies with MSI-H/dMMR status for single-agent second-line/subsequent use; uterine sarcoma criteria include specific histologies with TMB-H status for nivolumab + ipilimumab use, with updated Qvantig criteria. Kaposi Sarcoma: Expanded criteria to allow nivolumab monotherapy as an alternative to combination with ipilimumab; updated Qvantig criteria. Pleural and Peritoneal Mesothelioma: Expanded criteria to include resectable pleural mesothelioma (epithelioid Stage I) for neoadjuvant/initial/post-surgical nivolumab + ipilimumab per Category 1, added resectable peritoneal mesothelioma first-line use, preserved unresectable/subsequent uses, and updated Qvantig criteria. Melanoma: Reorganized to distinguish cutaneous and uveal melanoma in unresectable/metastatic and adjuvant settings; added criteria for resected metastatic melanoma with nivolumab + ipilimumab adjuvant therapy, neoadjuvant nivolumab monotherapy, and brain metastases; updated Qvantig criteria. Merkel Cell Carcinoma: Added		

	neoadjuvant nivolumab use, allowed ipilimumab combinations as an alternative to monotherapy in unresectable/metastatic disease, consolidated duplicative language, and updated Qvantig criteria. Rectal Cancer: New criteria added for Rectal Adenocarcinoma based on NCCN Category 2A recommendations. Modified Opdivo Qvantig criteria to reflect approved uses by indication and NCCN criteria in settings where ipilimumab combination is not required. Coding Reviewed: The following ICD-10 diagnostic codes were added: C17.0–C17.9, C18.0–C18.9, C19, C20, C21.0–C21.8, C22.0, C22.1, C22.8, C22.9, C23.0, C24.0–C24.9, C30.0, C31.0–C31.1, C32.0–C32.9, C33, C34.00–C34.92, C40.92, C44.02, C44.320, C45.1–C45.9, C48.0–C48.8, C49.0–C49.9, C51.0–C51.9, C52, C53.0–C53.9, C54.0–C54.9, C58, C71.0–C71.9, C72.0, C72.1, C72.9, C73, C77.0, C83.00–C83.09, C83.38, C83.398, C84.90–C84.99, C84.Z0–C84.Z9, C85.20–C85.29, C86.00, C91.10–C91.12, D37.3, and Z85.09; no ICD-10 codes were deleted. Additionally, HCPCS code J9999 was deleted and J9289 was added (effective 7/1/2025). Updated duration of treatment to align with the most recent prescribing information. Revisions were made throughout the background section to reflect updated NCCN		

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	recommendations and new clinical data. "Other Uses" were removed, with a reference added directing readers to the background section. Additional wording and formatting changes were made for clarity and consistency.		
Annual Review	Addition of Opdivo Qvantig indications and approved uses. Disclaimer Opdivo Qvantig is not approved for concurrent use with IV Yervoy. NCCN guidelines have included this new dosage form. Guidelines where Opdvio Qvantig is not mentioned: Bone Cancer, Soft Tissue Sarcoma, T-Cell Lymphoma and Hodgkin Lymphomas. Opdivo Qvantig doses where added, not all doses where available for every use.	3/17/2025	4/2/2025
Annual Review	ADD NCCN category 2A recommendation for Anal Carcinoma in second-line and subsequent therapy as a single agent for metastatic disease if no prior immunotherapy received. Modify Bone cancer, including osteosarcoma, Ewing Sarcoma, chondrosarcoma, and chordoma to add evaluation to previous use of PD-L1 and use of systemic immunosuppressant. Add NCCN category 2A recommendation for Biliary Tract Cancers in combination with ipilimumab. Update existing NCCN criteria for use in ESCC for second-line/subsequent therapy with combination use of Yervoy and removing criteria language restricting use of prior PD-1, PD-L1 agents or checkpoint inhibitors. Add NCCN category 2A recommendation for Cervical cancer in second-line or subsequent therapy as a single agent if CPS ≥ 1 for local/regional recurrence	2/24/2025	3/6/2025

	or stage IVB or recurrence with distant metastases. Update existing NCCN 2A criteria in Gastric or Esophageal and Esophagogastric Junction Cancers by adding criteria for disease states and use in MSI-H/dMMR tumor as a single agent or in combination with ipilimumab. Add NCCN 2A recommendation for use in Gestational Trophoblastic Neoplasia in multiagent chemotherapy-resistant Gestational Trophoblastic Neoplasia that is high or intermediate risk. Update existing NCCN 2A criteria in Hepatocellular carcinoma for use as a single agent vs. in combination with ipilimumab. Update existing NCCN 2A criteria for use in Hodgkin Lymphoma as a single agent or in combination with brentuximab vedotin or ICE. Update existing NCCN 2A criteria for use in classic Kaposi sarcoma for appropriate population usage. Update existing NCCN 2A criteria to include use as a single agent or combination use with ipilimumab for use in BRAF-non-specific asymptomatic brain metastases from melanoma. Add NCCN 2A recommendation for use in metastatic or unresectable melanoma in combination with ipilimumab if disease progression occurred on prior single-agent anti-PD-1 therapy. Also continue as a single agent or in combination with ipilimumab if disease control occurred with prior anti-PD-1 therapy as re-induction therapy. Add NCCN 2A recommendation for use in Merkel Cell Carcinoma as a single agent or in combination with ipilimumab in M1 disseminated disease if progression on anti-PD-1 or anti PD-L1 monotherapy or anti-PD-1 or anti-PD-L1 is contraindicated. Add NCCN 2A		

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	recommendation for use in relapse, recurrent, or advanced RCC when used as subsequent therapy in combination with cabozantinib and individual had prior immune-oncology therapy (e.g. pembrolizumab). Add NCCN 2A recommendation for use in non-clear cell RCC as a single agent or in combination with cabozantinib. Clarify existing Small Bowel Adenocarcinoma criteria and Ampullary Adenocarcinoma criteria from NCCN guidelines. Add NCCN 2A recommendation for use in relapsed/refractory extranodal NK-T cell lymphoma. Add NCCN 2A recommendation for use in metastatic soft tissue sarcoma as a single agent or in combination with ipilimumab. Add NCCN 2A recommendation for use in nasopharyngeal and non-nasopharyngeal cancers. Add NCCN 2A recommendation for use in Pediatric Diffuse High-Grade gliomas as a single agent for use in hypermutant tumors. Add NCCN 2A recommendation for use in recurrent or metastatic vulvar cancer as a single agent in HPV-related tumor. Wording and formatting updates. Add new FDA approval for use in first-line treatment in unresectable or metastatic urothelial carcinoma in combination with cisplatin and gemcitabine. Remove NCCN use in Primary mediastinal B-cell lymphoma as recommendation changed from 2A to 2B when used in combination with brentuximab vedotin. Coding Reviewed: No changes.		
Select Review	Update statement for criteria for initial approval: Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information]	3/25/2024	5/9/2024

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	supporting the patient's diagnosis for the drug and confirming that the patient has met all approval criteria.		
Policy Inception	Elevance Health's Medical Policy adoption.	N/A	11/30/2023