



Medical Policy Manual **Approved Revision: Do Not Implement until 6/2/21**

Nivolumab (Opdivo®) (Intravenous)

NDC CODE(S) 00003-3772-XX OPDIVO 10MG/ML Solution (B-M SQUIBB U.S. (PRIMARY CARE)
00003-3774-XX OPDIVO 100MG/10ML Solution (B-M SQUIBB U.S. (PRIMARY CARE)
00003-3734-XX OPDIVO 240MG/24ML Solution (B-M SQUIBB U.S. (PRIMARY CARE)

DESCRIPTION

Nivolumab is a human monoclonal antibody classified as an IgG4 kappa immunoglobulin. It blocks the interaction with PD-1, programmed death receptor-1, and its ligands PD-L1 and PD-L2. When the PD-1 receptor found on T-cells binds with its ligands, T-cell proliferation and cytokine production is inhibited. Some tumors cause increased production of PD-1 ligands and can contribute to the inhibition of active T-cell immune surveillance of tumors. Nivolumab releases pathway-mediated inhibition of the immune response, including the anti-tumor immune response, which results in decreased tumor growth

POLICY

- Nivolumab for the treatment of the following is considered **medically necessary** if the medical appropriateness criteria are met: **(See Medical Appropriateness below.)**
 - Anal Carcinoma
 - Central Nervous System Cancer
 - Colorectal Cancer (CRC)
 - Endometrial Carcinoma (Uterine Neoplasms)
 - Esophageal **and Esophagogastric Junction Cancers**
 - Extranodal NK/ T-Cell Lymphoma
 - **Gastric Cancer**
 - Gestational Trophoblastic Neoplasia
 - Hepatocellular Carcinoma (HCC)
 - **Adult Classical Hodgkin lymphoma (cHL)**
 - **Pediatric Classical Hodgkin Lymphoma (cHL)**
 - Malignant Pleural Mesothelioma
 - Melanoma, Cutaneous
 - Melanoma, Uveal
 - Merkel Cell Carcinoma
 - Non-small cell lung cancer (NSCLC)
 - Renal cell carcinoma
 - Small bowel adenocarcinoma (SBA)
 - Squamous cell carcinoma of the head and neck **(SCCHN)**
 - Urothelial carcinoma (Bladder Cancer)
 - Vulvar Cancer (Squamous Cell Carcinoma)
- Nivolumab for the treatment of other conditions/diseases is considered **investigational**.

MEDICAL APPROPRIATENESS

INITIAL APPROVAL CRITERIA



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- Patient is at least 18 years of age (unless otherwise specified); **AND**

Universal Criteria

- Patient has not received previous therapy with a programmed death (PD-1/PD-L1)-directed therapy (e.g., cemiplimab, avelumab, pembrolizumab, atezolizumab, durvalumab, etc.) prior to initiation of therapy, unless otherwise specified; **AND**

Cutaneous Melanoma

- Used as first-line therapy for unresectable or metastatic disease; **AND**
 - Used as a single agent or in combination with ipilimumab; **OR**
- Used as subsequent therapy for unresectable or metastatic* disease; **AND**
 - Used for retreatment of disease as re-induction as a single agent or in combination with ipilimumab in patients who experienced disease control (i.e., complete or partial response or stable disease) from prior checkpoint inhibitor therapy, but subsequently have disease progression/relapse > 3 months after treatment discontinuation; **OR**
 - Used after disease progression on first-line therapy or maximum clinical benefit from BRAF-targeted therapy (e.g., dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib, etc.); **AND**
 - Used as a single agent or in combination with ipilimumab if checkpoint inhibitor immunotherapy was not previously used; **OR**
 - Used in combination with ipilimumab for patients who progressed on single agent checkpoint inhibitor immunotherapy; **OR**
- Used as adjuvant treatment as a single agent; **AND**
 - Patient has lymph node involvement and has undergone complete resection, complete lymph node dissection (CLND), therapeutic lymph node dissection (TLND), or nodal basin ultrasound surveillance; **OR**
 - Patient has satellite/in-transit metastases or recurrence and has no evidence of disease after complete excision; **OR**
 - Patient has undergone TLND and/or complete resection of nodal recurrence; **OR**
 - Patient has undergone complete resection of distant metastatic disease

**Metastatic disease includes stage III clinical satellite/in transit metastases or local satellite/in-transit recurrence in patients with limited resectable and unresectable disease, unresectable nodal recurrence, and disseminated (unresectable) distant metastatic disease*

Uveal Melanoma

- Patient has distant metastatic disease; **AND**
- Used as a single agent or in combination with ipilimumab

Hepatocellular Carcinoma (HCC)

- Patient has locally advanced, unresectable, inoperable, or metastatic disease; **AND**
- Used as subsequent therapy; **AND**
 - Patient has Child-Pugh Class A or B disease; **AND**
 - Used as a single agent; **OR**
 - Patient has Child-Pugh Class A disease; **AND**
 - Used in combination with ipilimumab

Non-Small Cell Lung Cancer (NSCLC)

- Used for recurrent, advanced, or metastatic disease (excluding locoregional recurrence or symptomatic local disease without evidence of disseminated disease) or mediastinal lymph node recurrence with prior radiation therapy; **AND**
 - Used as first-line therapy; **AND**



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- Used for one of the following:
 - Used in patients with PS 0-1 who have EGFR, ALK, ROS1, BRAF, **NTRK1/2/3 gene fusion**, MET exon skipping mutation, and RET rearrangement negative** tumors and PD-L1 expression <1%
 - Used in patients with PS 0-1 who are positive for one of the following molecular biomarkers: BRAF V600E mutations, NTRK **1/2/3** gene fusions, MET exon 14 skipping mutations, or RET rearrangements
 - Used in patients with PS 0-2 for PD-L1 expression-positive (PD-L1 ≥1%) tumors, as detected by an FDA or CLIA compliant test❖, that are EGFR, ALK, ROS1, BRAF, **NTRK1/2/3 gene fusion**, MET exon skipping mutation, and RET rearrangement negative**; **AND**
 - Used in combination with ipilimumab; **OR**
 - Used in combination with ipilimumab and platinum-doublet chemotherapy (e.g., pemetrexed and either carboplatin or cisplatin for non-squamous cell histology, paclitaxel and carboplatin for squamous cell histology, etc.); **OR**
- Used as subsequent therapy; **AND**
 - Used as a single agent; **OR**
 - Used for one of the following:
 - Used in patients with PS 0-1 who have EGFR, ALK, or ROS1 positive tumors and have received prior targeted therapy§
 - Used in patients with PS 0-1 who are positive for one of the following molecular biomarkers: BRAF V600E mutations, NTRK **1/2/3** gene fusions, MET exon 14 skipping mutations, or RET rearrangements; **AND**
 - Used in combination with ipilimumab; **OR**
 - Used in combination with ipilimumab, pemetrexed, and either carboplatin or cisplatin for non-squamous cell histology; **OR**
 - Used in combination with ipilimumab, paclitaxel, and carboplatin for squamous cell histology; **OR**
- **Used as continuation maintenance therapy in combination with ipilimumab; AND**
 - **Patient has achieved a response or stable disease following first-line therapy with nivolumab and ipilimumab with or without chemotherapy**

**** Note: If there is insufficient tissue to allow testing for all of the EGFR, ALK, ROS1, BRAF, NTRK1/2/3, MET, and RET, 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.**

Renal Cell Carcinoma (RCC)

- Used in combination with ipilimumab for clear cell histology; **AND**
 - Used as first-line therapy in patients with advanced, relapsed, or stage IV disease with intermediate or poor risk; **OR**
 - Used as first-line therapy in patients with relapsed or stage IV disease with favorable risk; **OR**
 - Used as subsequent therapy in patients with relapsed or stage IV disease; **OR**
- Used as a single agent; **AND**
 - Used as subsequent therapy in patients with advanced, relapsed, or stage IV disease for **and** clear cell histology; **OR**
 - Patient has relapsed or stage IV disease and non-clear cell histology; **OR**
- **Used in combination with cabozantinib (Cabometyx only); AND**
 - **Used as first-line therapy for advanced disease**

Adult Classical Hodgkin Lymphoma (cHL)

- Used as a single agent; **AND**



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- Patient has relapsed or progressive disease after autologous hematopoietic stem cell transplantation (HSCT) **and brentuximab vedotin; OR**
- **Used as third-line or subsequent therapy; AND**
 - Patient has relapsed or progressive disease after autologous HSCT; **OR**
 - Patient has relapsed or refractory disease and is either transplant-ineligible based on comorbidities or has failure of second-line chemotherapy; **OR**
 - Patient is post-allogeneic stem-cell transplant; **OR**
- Used as palliative therapy in patients more than 60 years old; **AND**
 - Patient has relapsed or progressive disease after autologous HSCT; **OR**
 - Patient has relapsed or refractory disease and is either transplant-ineligible based on comorbidities or has failure of second-line chemotherapy; **OR**
 - Patient is post-allogeneic stem-cell transplant; **OR**
- Used in combination with brentuximab vedotin; **AND**
 - Used as subsequent therapy (if not previously used) **for relapsed or refractory disease**

Pediatric Classical Hodgkin Lymphoma (cHL)

- Patient age is 18 years and under*; **AND**
- Used as a single agent; **AND**
 - Used as subsequent therapy (**if not previously used**) for relapsed or refractory disease; **AND**
 - Used in patients heavily pretreated (with platinum or anthracycline-based chemotherapy) or if a decrease in cardiac function observed; **OR**
- Used in combination with brentuximab vedotin; **AND**
 - Used as subsequent therapy (**if not previously used**) for relapsed or refractory disease; **AND**
 - Used in patients heavily pretreated (with platinum or anthracycline-based chemotherapy) or if a decrease in cardiac function observed; **OR**
 - Used as re-induction therapy; **AND**
 - Used in patients heavily pretreated (with platinum or anthracycline-based chemotherapy) or if a decrease in cardiac function observed; **OR**
 - Used with radiation therapy (ISRT) **for relapsed or refractory disease** in highly favorable patients who may avoid autologous stem cell rescue (ASCR) (i.e., initial stage other than IIIB or IVB, no prior exposure to RT, duration of CR1 >1 year, absence of extranodal disease or B symptoms at relapse)

** Pediatric Hodgkin Lymphoma may be applicable to adolescent and young adult (AYA) patients up to the age of 39 years.*

Squamous Cell Carcinoma of the Head and Neck (SCCHN)

- Used as single-agent therapy; **AND**
- Patient has unresectable, recurrent, persistent, or metastatic disease; **AND**
- Disease has progressed on or after platinum-based therapy; **AND**
- Patient does not have nasopharyngeal disease

Urothelial Carcinoma (Bladder Cancer)

- Used as a single agent; **AND**
- Used as subsequent systemic therapy after previous platinum treatment*; **AND**
- Patient has one of the following diagnoses:
 - Locally advanced or metastatic urothelial carcinoma; **OR**
 - **Muscle invasive bladder cancer with** local recurrence or persistent disease in a preserved bladder; **OR**
 - Metastatic **or local** bladder cancer recurrence post-cystectomy; **OR**
 - Recurrent or metastatic primary carcinoma of the urethra; **AND**
 - Patient does not have recurrence of stage T3-4 disease or palpable inguinal lymph nodes; **OR**



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- Metastatic upper genitourinary (GU) tract tumors; **OR**
- Metastatic urothelial carcinoma of the prostate

***Note:**

– If platinum treatment occurred greater than 12 months ago, the patient should be re-treated with platinum-based therapy if the patient is still platinum eligible (see below for cisplatin- or carboplatin-ineligible comorbidities).

- Cisplatin-ineligible comorbidities may include the following: GFR < 60 mL/min, PS ≥ 2, hearing loss of ≥ 25 decibels (dB) at two contiguous frequencies, or grades ≥ 2 peripheral neuropathy. Carboplatin may be substituted for cisplatin particularly in those patients with a GFR < 60 mL/min or a PS of 2.
- Carboplatin-ineligible comorbidities may include the following: GFR < 30 mL/min, PS ≥ 3, grade ≥ 3 peripheral neuropathy, or NYHA class ≥ 3, etc.

Colorectal Cancer (CRC)

- Patient is at least 12 years of age; **AND**
- Patient's disease must be microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); **AND**
 - Used as a single agent or in combination with ipilimumab as subsequent therapy for advanced or metastatic disease that progressed following treatment with a fluoropyrimidine-, oxaliplatin-, and/or irinotecan-based chemotherapy; **OR**
 - Used as a single agent or in combination with ipilimumab; **AND**
 - **Used as primary treatment for unresectable or medically inoperable, advanced, or metastatic disease *; OR**
 - **Used as primary treatment for unresectable liver and/or lung metastases; OR**
 - **Used as primary treatment for resectable liver and/or lung metastases (Rectal cancer only); OR**
 - **Used as neoadjuvant therapy for resectable liver and/or lung metastases (Colon cancer only); OR**
 - **Used for unresectable metastases that remains unresectable after primary systemic therapy*; OR**
 - **Used for disease progression on non-intensive therapy with improvement in functional status (excluding patients previously treated with fluoropyrimidine) *; OR**
 - **Used as primary treatment for unresectable metastases after previous adjuvant FOLFOX (fluorouracil, leucovorin and oxaliplatin) or CapeOX (capecitabine-oxaliplatin) within the past 12 months**

** Single agent nivolumab should be used in patients who are not candidates for intensive therapy*

Merkel Cell Carcinoma

- Used as a single agent; **AND**
- Patient has disseminated metastatic disease

Central Nervous System (CNS) Cancer

- Used in one of the following treatment settings:
 - Used as initial treatment in patients with small asymptomatic brain metastases; **OR**
 - Used for relapsed disease in patients with limited brain metastases and stable systemic disease or reasonable treatment options; **OR**
 - Patient has recurrent limited brain metastases; **OR**
 - Used for recurrent disease in patients with extensive brain metastases and stable systemic disease or reasonable systemic treatment options; **AND**
- Used as a single-agent or in combination with ipilimumab for the treatment of brain metastases in patients with melanoma; **OR**
- Used as a single-agent for the treatment of brain metastases in patients with PD-L1 positive non-small cell lung cancer (NSCLC)

Anal Carcinoma



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- Patient has metastatic squamous cell disease; **AND**
- Used as a single agent for subsequent therapy

Gestational Trophoblastic Neoplasia

- Used as single-agent therapy for multiagent chemotherapy resistant disease; **AND**
 - Patient has intermediate placental site trophoblastic tumor (PSTT) or epithelioid trophoblastic tumor (ETT); **AND**
 - Patient has recurrent or progressive disease; **AND**
 - Patient was previously treated with a platinum/etoposide containing regimen; **OR**
 - Patient has methotrexate-resistant high risk disease (i.e., FIGO stages II-III and ≥ 7 Prognostic score OR FIGO stage IV disease)

Malignant Pleural Mesothelioma

- Used as a single agent or in combination with ipilimumab as subsequent therapy; **OR**
- Used in combination with ipilimumab as first-line therapy in patients with unresectable disease

Small Bowel Adenocarcinoma

- Patient has advanced or metastatic disease that is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); **AND**
- Used as a single agent or in combination with ipilimumab in one of the following settings:
 - As subsequent therapy; **OR**
 - As initial therapy in patients with prior oxaliplatin exposure in the adjuvant setting or contraindication

Extranodal NK/ T-Cell Lymphoma

- Used as a single agent for relapsed or refractory nasal type disease; **AND**
- Disease progressed following additional treatment with an alternative asparaginase-based chemotherapy regimen not previously used; **AND**
- Participation in a clinical trial is unavailable

Esophageal and Esophagogastric Junction Cancers

- **Used for unresectable (or is not a surgical candidate), advanced, recurrent, or metastatic disease; AND**
 - **Patient has esophageal squamous cell carcinoma (SCC); AND**
 - **Used as a single agent for subsequent therapy; OR**
 - **Patient has adenocarcinoma histology; AND**
 - **Used in combination with oxaliplatin and either fluorouracil or capecitabine as first-line palliative therapy for HER2 negative disease; AND**
 - **Tumor expresses PD-L1 (CPS ≥ 5); OR**
- **Used as postoperative therapy in patients with an R0 resection and residual disease (i.e., yp T positive and/or N positive); AND**
 - **Used as a single agent in patients who have received preoperative chemoradiation**

Gastric Cancer

- **Patient has adenocarcinoma histology; AND**
- **Used in combination with oxaliplatin and either fluorouracil or capecitabine; AND**
- **Used as first-line palliative therapy for patients who are not surgical candidates or have unresectable, locally advanced, recurrent, or metastatic HER2 negative disease; AND**
- **Tumor expresses PD-L1 (CPS ≥ 5)**

Endometrial Carcinoma (Uterine Neoplasms)

- Used as a single agent; **AND**



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- Used as second-line therapy for mismatch repair deficient (dMMR) recurrent, metastatic, or high-risk disease

Vulvar Cancer (Squamous Cell Carcinoma)

- Used as a single agent; **AND**
- Used as second-line therapy for HPV-related advanced, recurrent, or metastatic disease

❖ *If confirmed using an immunotherapy assay-<http://www.fda.gov/CompanionDiagnostics>*

****Genomic Aberration/Mutational Driver Targeted Therapies (NOTE: not all inclusive, refer to guidelines for appropriate use)
<u>Sensitizing EGFR mutation-positive tumors</u> <ul style="list-style-type: none"> • Afatinib • Dacomitinib • Erlotinib • Gefitinib • Osimertinib
<u>ALK rearrangement-positive tumors</u> <ul style="list-style-type: none"> • Alectinib • Brigatinib • Ceritinib • Crizotinib • Lorlatinib
<u>ROS1 rearrangement-positive tumors</u> <ul style="list-style-type: none"> • Ceritinib • Crizotinib • Entrectinib
<u>BRAF V600E-mutation positive tumors</u> <ul style="list-style-type: none"> • Dabrafenib ± Trametinib • Vemurafenib
<u>NTRK Gene Fusion positive tumors</u> <ul style="list-style-type: none"> • Larotrectinib • Entrectinib
<u>PD-1/PD-L1 expression-positive tumors (≥1%)</u> <ul style="list-style-type: none"> • Pembrolizumab • Atezolizumab • Nivolumab ± ipilimumab
<u>MET Exon-14 skipping mutations</u> <ul style="list-style-type: none"> • Capmatinib • Crizotinib
<u>RET rearrangement-positive tumors</u> <ul style="list-style-type: none"> • Cabozantinib • Selpercatinib • Vandetanib

RENEWAL CRITERIA



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- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in initial approval criteria; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: severe infusion reactions, complications of allogeneic hematopoietic stem cell transplantation (HSCT), severe immune-mediated adverse reactions (i.e. pneumonitis, colitis, hepatitis, **hepatotoxicity**, endocrinopathies, nephritis/renal dysfunction, adverse skin reactions/rash, encephalitis), etc.; **AND**
- Disease response with treatment **as defined by** stabilization of disease or decrease in size of tumor or tumor spread; **AND**

Cutaneous Melanoma (adjuvant therapy)

- Patient has not exceeded a maximum of twelve (12) months of therapy

NSCLC (in combination with ipilimumab or in combination with ipilimumab and two (2) cycles of platinum-doublet chemotherapy)

- Patient has not exceeded a maximum of two (2) years of therapy

MPM (combination with ipilimumab)

- Patient has not exceeded a maximum of two (2) years of therapy

Vulvar Cancer

- Patient has not exceeded a maximum of two (2) years of therapy

Renal Cell Carcinoma (in combination with cabozantinib)

- Patient has not exceeded a maximum of two (2) years of therapy

Esophageal and Esophagogastric Junction Adenocarcinoma and Squamous Cell Carcinoma (single agent postoperative therapy)

- Patient has not exceeded a maximum of twelve (12) months of therapy

cHL (in combination with brentuximab vedotin)

- Coverage may not be renewed

Cutaneous Melanoma Re-induction

- Refer to initial approval for criteria (see Melanoma – Used for retreatment of disease as re-induction)

DOSAGE/ADMINISTRATION

INDICATION	DOSE
Merkel Cell	Administer 240 mg intravenously every 2 weeks or 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity
Anal Cancer	Administer 240 mg intravenously every 2 weeks, 480 mg intravenously every 4 weeks, or 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity
Cutaneous Melanoma	<u>Single agent (excluding adjuvant therapy):</u> <ul style="list-style-type: none"> • Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity <u>In combination with ipilimumab (excluding adjuvant therapy):</u>



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	<ul style="list-style-type: none"> Administer 1 mg/kg intravenously, with ipilimumab on the same day, every 3 weeks for 4 doses, then follow with single agent regimen <p><u>Adjuvant treatment:</u></p> <ul style="list-style-type: none"> Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease recurrence or unacceptable toxicity for up to 1 year
Uveal Melanoma	<p><u>Single agent:</u></p> <ul style="list-style-type: none"> Administer up to 10 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity <p><u>In combination with ipilimumab:</u></p> <ul style="list-style-type: none"> Administer 1 mg/kg intravenously, with ipilimumab on the same day, every 3 weeks for 4 doses, then 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity
NSCLC	<p><u>Single agent:</u></p> <ul style="list-style-type: none"> Administer 240 mg intravenously every 2 weeks OR 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity <p><u>In combination with ipilimumab:</u></p> <ul style="list-style-type: none"> Administer 3 mg/kg intravenously every 2 weeks, with ipilimumab 1 mg/kg every 6 weeks, until disease progression or unacceptable toxicity for up to 2 years <p><u>In combination with ipilimumab and platinum-doublet chemotherapy for metastatic or recurrent disease:</u></p> <ul style="list-style-type: none"> Administer 360 mg intravenously every 3 weeks, with ipilimumab 1 mg/kg every 6 weeks and histology-based platinum-doublet chemotherapy every 3 weeks for 2 cycles, then continue 360 mg every 3 weeks until disease progression or unacceptable toxicity for up to 2 years
SCCHN, Urothelial Carcinoma, & Gestational Trophoblastic Neoplasia (GTN)	Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity
cHL	<p><u>Single-agent:</u></p> <ul style="list-style-type: none"> Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity <p><u>In combination with brentuximab vedotin</u></p> <ul style="list-style-type: none"> Administer 3 mg/kg intravenously every 3 weeks for up to 12 weeks (4 cycles) (NOTE: brentuximab vedotin is given on day 1 and nivolumab is given on day 8 of cycle 1 and both are given on day 1 of all subsequent cycles)
MSI-H/dMMR CRC	<p>Adult patients and for pediatric patients ≥ 12 years and ≥ 40 kg</p> <ul style="list-style-type: none"> As a single agent: Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity In combination with ipilimumab: Administer 3 mg/kg intravenously, with ipilimumab 1 mg/kg on the same day, every 3 weeks for 4 doses, then follow with the single agent regimen <p><u>Pediatric patients ≥ 12 years and < 40 kg</u></p> <ul style="list-style-type: none"> As a single agent: Administer 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity In combination with ipilimumab: Administer 3 mg/kg intravenously, with ipilimumab 1 mg/kg on the same day, every 3 weeks for 4 doses, then follow with the single agent regimen
Renal Cell Carcinoma (RCC)	<u>Single-agent:</u>



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	<ul style="list-style-type: none"> • Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity <p><u>In combination with ipilimumab:</u></p> <ul style="list-style-type: none"> • Administer 3 mg/kg intravenously, with ipilimumab on the same day, every 3 weeks for 4 doses, then follow with single-agent regimen <p><u>In combination with cabozantinib (Cabometyx):</u></p> <ul style="list-style-type: none"> • Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity for up to 2 years
Hepatocellular Carcinoma (HCC)	<p><u>Single-agent:</u></p> <ul style="list-style-type: none"> • Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity <p><u>In combination with ipilimumab:</u></p> <ul style="list-style-type: none"> • Administer 1 mg/kg intravenously, with ipilimumab on the same day, every 3 weeks for 4 doses, then follow with single-agent regimen
Malignant Pleural Mesothelioma (MPM)	<p><u>Single agent:</u></p> <ul style="list-style-type: none"> • Administer 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity <p><u>In combination with ipilimumab:</u></p> <ul style="list-style-type: none"> • Subsequent Therapy <ul style="list-style-type: none"> – Administer 3 mg/kg intravenously every 2 weeks, with ipilimumab 1 mg/kg every 6 weeks, until disease progression or unacceptable toxicity for up to 2 years OR – Administer 240 mg intravenously every 2 weeks, with ipilimumab 1 mg/kg every 6 weeks (for a total of 4 ipilimumab doses); treatment with nivolumab is continued for up to 2 years or until disease progression or unacceptable toxicity • Initial Therapy <ul style="list-style-type: none"> – Administer 360 mg intravenously every 3 weeks, with ipilimumab 1 mg/kg every 6 weeks; until disease progression or unacceptable toxicity for up to 2 years
CNS Metastases from Melanoma	<p><u>Single agent:</u></p> <ul style="list-style-type: none"> • Administer 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity <p><u>In combination with ipilimumab:</u></p> <ul style="list-style-type: none"> • Administer 1 mg/kg intravenously, with ipilimumab on the same day, every 3 weeks for 4 doses, then 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity
CNS Metastases from NSCLC	Administer 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity
Small Bowel Adenocarcinoma	<p><u>Single agent:</u></p> <ul style="list-style-type: none"> • Administer 3 mg/kg intravenously every 2 weeks, or 240 mg intravenously every 2 weeks, or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity <p><u>In combination with ipilimumab:</u></p> <ul style="list-style-type: none"> • Administer 3 mg/kg intravenously, with ipilimumab on the same day, every 3 weeks for 4 doses, then 3 mg/kg or 240 mg intravenously every 2 weeks until disease progression or unacceptable toxicity
Esophageal and Esophagogastric Junction Cancer	<p><u>Esophageal Squamous Cell Carcinoma:</u></p> <ul style="list-style-type: none"> • Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity <p><u>Single agent for postoperative therapy:</u></p> <ul style="list-style-type: none"> • Administer 240 mg intravenously every 2 weeks for 16 weeks followed by 480 mg intravenously every 4 weeks for up to 1 year



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	<u>In combination with oxaliplatin and either fluorouracil or capecitabine:</u> • Administer 360 mg intravenously every 3 weeks or 240 mg intravenously every 2 weeks until disease progression or unacceptable toxicity
Gastric Cancer	<u>In combination with oxaliplatin and either fluorouracil or capecitabine:</u> Administer 360 mg intravenously every 3 weeks or 240 mg intravenously every 2 weeks until disease progression or unacceptable toxicity
Extranodal NK/ T-Cell Lymphoma	Administer 40 mg intravenously every 2 weeks until disease progression or unacceptable toxicity
Endometrial Carcinoma	Administer 3 mg/kg intravenously every 2 weeks for 8 doses and then 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity
Vulvar Cancer	Administer 240 mg intravenously every 2 weeks until disease progression or unacceptable toxicity for up to 2 years
<p><u>Dosing should be calculated using actual body weight and not flat dosing (as applicable) based on the following:</u></p> <p><u>Weight > 74 kg:</u></p> <ul style="list-style-type: none"> Standard dose 480 mg IV every 4 weeks <p><u>Weight is 67 kg to 73 kg:</u></p> <ul style="list-style-type: none"> Use 440 mg IV every 4 weeks <p><u>Weight is ≤ 66kg:</u></p> <ul style="list-style-type: none"> Use 400 mg IV every 4 weeks <p>-OR-</p> <p><u>Weight > 67 kg:</u></p> <ul style="list-style-type: none"> Standard dose 240 mg IV every 2 weeks <p><u>Weight is 53 kg to 67 kg:</u></p> <ul style="list-style-type: none"> Use 200 mg IV every 2 weeks <p><u>Weight is < 53kg:</u></p> <ul style="list-style-type: none"> Use 160 mg IV every 2 weeks <p><i>Note: This information is not meant to replace clinical decision making when initiating or modifying medication therapy and should only be used as a guide. Patient-specific variables should be taken into account.</i></p>	

LENGTH OF AUTHORIZATION

Coverage will be provided for six months and may be renewed (unless otherwise specified).

- Adjuvant use in the treatment of melanoma can be authorized up to a maximum of 12 months of therapy.
- Use in the treatment of NSCLC in combination with ipilimumab can be authorized up to a maximum of 2 years of therapy.
- Use in the treatment of NSCLC in combination with ipilimumab and two (2) cycles of platinum-doublet chemotherapy can be authorized up to a maximum of 2 years of therapy.



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- Use in the treatment of MPM in combination with ipilimumab can be authorized up to a maximum of 2 years of therapy.
- Use in the treatment of Vulvar Cancer can be authorized for up to a maximum of 2 years of therapy.
- Use in the treatment of renal cell carcinoma in combination with cabozantinib (Cabometyx) can be authorized for up to a maximum of 2 years of therapy.
- Postoperative treatment of esophageal and esophagogastric junction adenocarcinoma and squamous cell carcinoma can be authorized for up to a maximum of 12 months of therapy.
- Use in the treatment of classical Hodgkin Lymphoma in combination with brentuximab vedotin can be authorized for up to a maximum of 12 weeks of therapy and may not be renewed.

DOSAGE LIMITS

Max Units (per dose and over time) [HCPCS Unit]:

DIAGNOSIS	BILLABLE UNITS	PER UNIT TIME (days)
Merkel Cell & Anal Carcinoma	340 BU	14 days
Melanoma & HCC (both in combination with ipilimumab)	Initial: 140 BU	21 days x 4 doses
	Followed by: 480 BU	28 days
Esophageal and Esophagogastric Junction Cancer (single agent postoperative therapy)	Initial: 240 BU	14 days x 8 doses
	Followed by: 480 BU	28 days
Melanoma/HCC/NSCLC/cHL (as a single agent) RCC (as a single agent & in combination with cabozantinib), SCCHN, MSI-H/dMMR CRC (as a single agent), Gestational Trophoblastic Tumor, Esophageal Squamous Cell Carcinoma & Urothelial Carcinoma	480 BU	28 days
Metastatic NSCLC with PD-L1 expressing tumors (in combination with ipilimumab)	340 BU	14 days
Metastatic or recurrent NSCLC (in combination with ipilimumab and platinum-doublet chemotherapy), Esophageal and Esophagogastric Junction Cancer (in combination with oxaliplatin and either fluorouracil or capecitabine), Gastric Cancer	380 BU	21 days
Vulvar Cancer	240 BU	14 days
cHL (in combination with brentuximab vedotin)	340 BU	21 days x 4 doses
MSI-H/dMMR CRC (in combination with ipilimumab)	Initial: 340 BU	21 days x 4 doses
	Followed by: 480 BU	28 days



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Small Bowel Adenocarcinoma & CNS Metastases from NSCLC (both as single agents)	340 BU	14 days
Small Bowel Adenocarcinoma (in combination with ipilimumab)	Initial: 340 BU	21 days x 4 doses
	Followed by: 340 BU	14 days
RCC (in combination with ipilimumab)	Initial: 340 BU	21 days x 4 doses
	Followed by: 480 BU	28 days
MPM (as a single agent or in combination with ipilimumab)	340 BU	14 days
CNS Metastases from Melanoma & Uveal Melanoma (both in combination with ipilimumab)	Initial: 140 BU	21 days x 4 doses
	Followed by: 340 BU	14 days
CNS Metastases from Melanoma (as a single agent)	340BU	14 days
Uveal Melanoma (As a single agent)	1140 BU	14 days
Extranodal NK/T-cell Lymphoma	40 BU	14 days
Endometrial Carcinoma	Initial: 340 BU	14 days x 8 doses
	Followed by: 480 BU	28 days

APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

BlueCross BlueShield of Tennessee’s Medical Policy complies with Tennessee Code Annotated Section 56-7-2352 regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

IMPORTANT REMINDER

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member’s health plan must be reviewed. If there is a conflict between the Medical Policy and a health plan, the express terms of the health plan will govern.

ADDITIONAL INFORMATION

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).

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