 **Approved Revision: Do Not Implement until 8/31/21**

# 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, an IgG4 kappa immunoglobulin, is a human monoclonal antibody. It is programmed to block the interaction between PD-1 (programmed death receptor-1) and its ligands, PD-L1 and PD-L2.

T-cells have a PD-1 receptor on their cell surface. When these receptors bind with the PD-L1 and PD-L2 ligands, T-cell proliferation and cytokine production is inhibited. With the increased production of these ligands by some tumors, T-cell immune surveillance of tumors is inhibited. By binding to the T-cell PD-1 receptor, nivolumab blocks PD-1 interaction with the PD-L1 & PD-L2, releasing pathway-mediated inhibition of the immune response, including the anti-tumor immune response, resulting 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 Cancer
  - 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**

- 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, dostarlimab, 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**
    - 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**
  - 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**
  - 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**

- 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 Cancers~~**~~

- Patient is not a surgical candidate or has unresectable, advanced, recurrent, or metastatic disease; **AND**
  - Patient has squamous cell carcinoma (SCC); **AND**
    - Used as a single agent for subsequent therapy; **OR**
  - Patient has adenocarcinoma ~~histology~~; **AND**
    - Used in combination with fluoropyrimidine- and platinum-containing chemotherapy; **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

**Esophagogastric/Gastroesophageal Junction Cancer**

- Patient is not a surgical candidate or has unresectable, advanced, recurrent, or metastatic disease; **AND**
  - Used in combination with fluoropyrimidine- and platinum-containing chemotherapy; OR
- Used as postoperative therapy in patients with an R0 resection and residual disease (i.e., T positive and/or N positive); **AND**
  - Used as a single agent in patients who have received preoperative chemoradiation

**Gastric Cancer**

- Patient is not a surgical candidate or has unresectable, advanced, recurrent, or metastatic disease; **AND**
  - Used in combination with fluoropyrimidine- and platinum-containing chemotherapy

**Endometrial Carcinoma (Uterine Neoplasms)**
- Used as a single agent; **AND**
- 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/CcompanionDiagnostics*

| §Genomic Aberration/Mutational Driver Targeted Therapies (NOTE: ***not all inclusive, refer to guidelines for appropriate use***) |
|---|
| Sensitizing *EGFR* mutation-positive tumors<br>• Afatinib<br>• Dacomitinib<br>• Erlotinib<br>• Gefitinib<br>• Osimertinib |
| *ALK* rearrangement-positive tumors<br>• Alectinib<br>• Brigatinib<br>• Ceritinib<br>• Crizotinib<br>• Lorlatinib |
| *ROS1* rearrangement-positive tumors<br>• Ceritinib<br>• Crizotinib<br>• Entrectinib |

| |
|---|
| *BRAF* V600E-mutation positive tumors<br>• Dabrafenib +Trametinib<br>• Vemurafenib |
| *NTRK* Gene Fusion positive tumors<br>• Larotrectinib<br>• Entrectinib |
| PD-1/PD-L1 expression-positive tumors (≥1%)<br>• Pembrolizumab<br>• Atezolizumab<br>• Nivolumab ± ipilimumab |
| *MET* Exon-14 skipping mutations<br>• Capmatinib<br>• Crizotinib<br>• Tepotinib |
| *RET rearrangement-positive tumors*<br>• Cabozantinib<br>• Selpercatinib<br>• Vandetanib<br>• Pralsetinib |

**RENEWAL CRITERIA**

- 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 the 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 Cancer (single agent postoperative therapy)**
- Patient has not exceeded a maximum of twelve (12) months of therapy

**Gastric Cancer, Esophagogastric Junction Cancer, and Esophageal Adenocarcinoma (in combination with fluoropyrimidine- and platinum-containing chemotherapy)**
- Patient has not exceeded a maximum of two (2) years of therapy

**cHL (in combination with brentuximab vedotin)**
- Coverage may not be renewed

**Cutaneous Melanoma Re-induction**
- Refer to the Initial Approval 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 | Single agent (excluding adjuvant therapy):<br>• Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity<br>In combination with ipilimumab (excluding adjuvant therapy):<br>• Administer 1 mg/kg intravenously, with ipilimumab on the same day, every 3 weeks for 4 doses, then follow with single agent regimen<br>Adjuvant treatment:<br>• 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 | Single agent:<br>• Administer up to 10 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity<br>In combination with ipilimumab:<br>• 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 | Single agent:<br>• Administer 240 mg intravenously every 2 weeks OR 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity<br>In combination with ipilimumab:<br>• 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<br>In combination with ipilimumab and platinum-doublet chemotherapy for metastatic or recurrent disease:<br>• 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 | Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity |

| | |
|---|---|
| Trophoblastic Neoplasia (GTN) | |
| cHL | Single-agent:<br>• Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity<br>In combination with brentuximab vedotin<br>• 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 | Adult patients and for pediatric patients ≥ 12 years and ≥ 40 kg<br>• **As a single agent:** Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity<br>• **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<br>Pediatric patients ≥ 12 years and < 40 kg<br>• **As a single agent:** Administer 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity<br>• **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) | Single-agent:<br>• Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity<br>In combination with ipilimumab:<br>• Administer 3 mg/kg intravenously, with ipilimumab on the same day, every 3 weeks for 4 doses, then follow with single-agent regimen<br>In combination with cabozantinib (Cabometyx):<br>• 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) | Single-agent:<br>• Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity<br>In combination with ipilimumab:<br>• 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) | Single agent:<br>• Administer 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity<br>In combination with ipilimumab:<br>• Subsequent Therapy<br>− 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**<br>− 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<br>• Initial Therapy<br>− 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 | Single agent: |

| | |
|---|---|
| | • Administer 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity<br>In combination with ipilimumab:<br>• 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 | Single agent:<br>• 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<br>In combination with ipilimumab:<br>• 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 | Esophageal Squamous Cell Carcinoma:<br>• Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity<br>Single agent for postoperative therapy:<br>• Administer 240 mg intravenously every 2 weeks for 16 weeks followed by 480 mg intravenously every 4 weeks for up to 1 year<br>In combination with fluoropyrimidine- and platinum-containing chemotherapy:<br>• Administer 360 mg intravenously every 3 weeks or 240 mg intravenously every 2 weeks until disease progression or unacceptable toxicity for up to 2 years |
| Gastric Cancer | Administer 360 mg intravenously every 3 weeks or 240 mg intravenously every 2 weeks until disease progression or unacceptable toxicity for up to 2 years |
| 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 |

Dosing should be calculated using actual body weight and not flat dosing (as applicable) based on the following:

Weight ≥ 74 kg:

- Standard dose 480 mg IV every 4 weeks

Weight is 67 kg to 73 kg:

- Use 440 mg IV every 4 weeks

Weight is ≤ 66kg:

- Use 400 mg IV every 4 weeks

**-OR-**

Weight > 67 kg:

- Standard dose 240 mg IV every 2 weeks

Weight is 53 kg to 67 kg:

- Use 200 mg IV every 2 weeks

Weight is < 53kg:

- Use 160 mg IV every 2 weeks

*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.*

**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.
- 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.
- Use in the treatment of gastric cancer, esophagogastric junction cancer, and esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy can be authorized up to a maximum of 2 years of therapy.

**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 fluoropyrimidine- and platinum-containing chemotherapy), 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 |
| 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).

## SOURCES

1. Opdivo [package insert]. Princeton, NJ; Bristol-Myers Squibb Company; April 2021. Accessed April 2021.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) nivolumab. National Comprehensive Cancer Network, 2020. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed April 2021.
3. Scherpereel A, Mazieres J, Greillier L, et al. Second- or third-line nivolumab (Nivo) versus nivo plus ipilimumab (Ipi) in malignant pleural mesothelioma (MPM) patients: Results of the IFCT-1501 MAPS2 randomized phase II trial. [Abstract]. J Clin Oncol 2017;35: Abstract LBA 8507.
4. Walocko FM, Scheier BY, Harms PW, et al. Metastatic Merkel cell carcinoma response to nivolumab. J Immunother Cancer. 2016 Nov 15;4:79.
5. Tawbi HA-H, Forsyth PAJ, Algazi AP, et al. Efficacy and safety of nivolumab (NIVO) plus ipilimumab (IPI) in patients with melanoma (MEL) metastatic to the brain: Results of the phase II study CheckMate 204. J Clin Oncol 2017;35(15_suppl):abstr 9507.
6. Morris VK, Salem ME, Nimeiri H, et al. Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicentre, single-arm, phase 2 study. Lancet Oncol. 2017 Apr;18(4):446-453. doi: 10.1016/S1470-2045(17)30104-3. Epub 2017 Feb 18.
7. Zhao X, Ivaturi V, Gopalakrishnan M, et al. Abstract CT 101: A model-based exposure-response (E-R) assessment of a nivolumab (NIVO) 4-weekly (Q4W) dosing schedule across multiple tumor types. Cancer Res July 1 2017 (77) (13 Supplement) CT101; DOI: 10.1158/1538-7445.AM2017-CT101.
8. Zhao X, Suryawanshi M, Hruska M, et al. Assessment of nivolumab benefit-risk profile of a 240 mg flat dose relative to a 3 mg/kg dosing regimen in patients with advanced tumors. Ann Oncol2017; 28:2002-2008.
9. Feng Y, Xiaoning W, Bajaj G, et al. Nivolumab exposure-response analyses of efficacy and safety in previously treated squamous or nonsquamous non-small cell lung cancer. ClinCa Res 2017;23(18): 5394-5405.

10. Gupta S, Sonpavde G, Grivas P, et al. Defining “platinum-ineligible” patients with metastatic urothelial cancer (mUC). J Clin Oncol. 2019 Mar 1;37(7_suppl):451.
11. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med 2018; 378:2093-2104.
12. Fahrenbruch R, Kintzel P, Bott AM, et al. Dose Rounding of Biologic and Cytotoxic Anticancer Agents: A Position Statement of the Hematology/Oncology Pharmacy Association. J Oncol Pract. 2018 Mar;14(3):e130-e136.
13. Hematology/Oncology Pharmacy Association (2019). Intravenous Cancer Drug Waste Issue Brief. Retrieved from http://www.hoparx.org/images/hopa/advocacy/Issue-Briefs/Drug_Waste_2019.pdf
14. Bach PB, Conti RM, Muller RJ, et al. Overspending driven by oversized single dose vials of cancer drugs. BMJ. 2016 Feb 29;352:i788.
15. Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2015 Apr;16(4):375-84. doi: 10.1016/S1470-2045(15)70076-8. Epub 2015 Mar 18.
16. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015 Jan 22;372(4):320-30. doi: 10.1056/NEJMoa1412082. Epub 2014 Nov 16.
17. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015 Jul 2;373(1):23-34. doi: 10.1056/NEJMoa1504030. Epub 2015 May 31.
18. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. N Engl J Med. 2017 Nov 9;377(19):1824-1835. doi: 10.1056/NEJMoa1709030. Epub 2017 Sep 10.
19. Algazi AP, Tsai KK, Shoushtari AN, et al. Clinical outcomes in metastatic uveal melanoma treated with PD-1 and PD-L1 antibodies. Cancer. 2016 Nov 15;122(21):3344-3353. doi: 10.1002/cncr.30258. Epub 2016 Aug 17.
20. Piulats JM, Cruz-Merino LDL, Garcia MTC, et al. Phase II multicenter, single arm, open label study of nivolumab in combination with ipilimumab in untreated patients with metastatic uveal melanoma (GEM1402.NCT02626962). J Clin Oncol 2017; 35 Abstr 9533.
21. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017 Jun 24;389(10088):2492-2502. doi: 10.1016/S0140-6736(17)31046-2. Epub 2017 Apr 20.
22. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med. 2015 Jul 9;373(2):123-35. doi: 10.1056/NEJMoa1504627. Epub 2015 May 31.
23. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015 Oct 22;373(17):1627-39. doi: 10.1056/NEJMoa1507643. Epub 2015 Sep 27.
24. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol. 2016 Jul;17(7):883-895. doi: 10.1016/S1470-2045(16)30098-5. Epub 2016 Jun 4.
25. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015 Nov 5;373(19):1803-13. doi: 10.1056/NEJMoa1510665. Epub 2015 Sep 25.
26. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med. 2018 Apr 5;378(14):1277-1290. doi: 10.1056/NEJMoa1712126. Epub 2018 Mar 21.
27. Armand P, Engert A, Younes A, et al. Nivolumab for Relapsed/Refractory Classic Hodgkin Lymphoma After Failure of Autologous Hematopoietic Cell Transplantation: Extended Follow-Up of the Multicohort Single-Arm Phase II CheckMate 205 Trial. J Clin Oncol. 2018 May 10;36(14):1428-1439. doi: 10.1200/JCO.2017.76.0793. Epub 2018 Mar 27.
28. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med. 2015 Jan 22;372(4):311-9. doi: 10.1056/NEJMoa1411087. Epub 2014 Dec 6.
29. Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med. 2016 Nov 10;375(19):1856-1867. Epub 2016 Oct 8.

30. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2017 Mar;18(3):312-322. doi: 10.1016/S1470-2045(17)30065-7. Epub 2017 Jan 26.
31. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol. 2017 Sep;18(9):1182-1191. doi: 10.1016/S1470-2045(17)30422-9. Epub 2017 Jul 19.
32. Overman MJ, Lonardi S, Wong KYM, et al. Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer. J Clin Oncol. 2018 Mar 10;36(8):773-779. doi: 10.1200/JCO.2017.76.9901. Epub 2018 Jan 20.
33. Topalian SL, Bhatia S, Hollebecque A, et al. Non-comparative, open-label, multiple cohort, phase 1/2 study to evaluate nivolumab (NIVO) in patients with virus-associated tumors (CheckMate 358): Efficacy and safety in Merkel cell carcinoma (MCC). DOI: 10.1158/1538-7445.AM2017-CT074 Published July 2017.
34. Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol. 2018 May;19(5):672-681. doi: 10.1016/S1470-2045(18)30139-6. Epub 2018 Mar 27.
35. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Anal Carcinoma. Version 2.2020. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed January 2021.
36. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Gestational Trophoblastic Neoplasia. Version 3.2020. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed January 2021.
37. Scherpereel A, Mazieres J, Greillier L, et al. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial. Lancet Oncol. 2019 Feb;20(2):239-253. doi: 10.1016/S1470-2045(18)30765-4. Epub 2019 Jan 16.
38. Disselhorst MJ, Quispel-Janssen J, Lalezari F, et al. Ipilimumab and nivolumab in the treatment of recurrent malignant pleural mesothelioma (INITIATE): results of a prospective, single-arm, phase 2 trial. Lancet Respir Med. 2019 Mar;7(3):260-270. doi: 10.1016/S2213-2600(18)30420-X. Epub 2019 Jan 16.
39. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Small Bowel Adenocarcinoma. Version 2.2020. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed January 2021.
40. Chan TSY, Li J, Loong F, et al. PD1 blockade with low-dose nivolumab in NK/T cell lymphoma failing L-asparaginase: efficacy and safety. Ann Hematol. 2018 Jan;97(1):193-196. doi: 10.1007/s00277-017-3127-2. Epub 2017 Sep 6.
41. Goldman JW, Crino L, Vokes EE, et al. Nivolumab (nivo) in patients (pts) with advanced (adv) NSCLC and central nervous system (CNS) metastases (mets). J Clin Oncol 34, no. 15_suppl (May 20, 2016) 9038-9038. DOI: 10.1200/JCO.2016.34.15_suppl.9038.
42. Gauvain C, Vauleon E, Chouaid C, et al. Intracerebral efficacy and tolerance of nivolumab in non–small-cell lung cancer patients with brain metastases. Lung Cancer. 2018 Feb; 116:62-66. doi: 10.1016/j.lungcan.2017.12.008.
43. Referenced with permission from the NCCN Clinical Practice Guidelines (NCCN Guidelines®) Non-Small Cell Lung Cancer. Version 2.2021. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®,

and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed January 2021.

44. Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced esophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20(11):1506-1517. doi:10.1016/S1470-2045(19)30626-6.
45. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2019;381(21):2020-2031. doi:10.1056/NEJMoa1910231.
46. Reck M, Ciuleanu T-E, Dols MC, et al. Nivolumab (NIVO) + ipilimumab (IPI) + 2 cycles of platinum-doublet chemotherapy (chemo) vs 4 cycles chemo as first-line (1L) treatment (tx) for stage IV/recurrent non-small cell lung cancer (NSCLC): CheckMate 9LA [abstract]. J Clin Oncol 2020;38:Abstract 9501-9501.
47. Zalcman G, Peters S, Mansfield AS, et al. Checkmate 743: A phase 3, randomized, open-label trial of nivolumab (nivo) plus ipilimumab (ipi) vs pemetrexed plus cisplatin or carboplatin as first-line therapy in unresectable pleural mesothelioma. Journal of Clinical Oncology 2017 35:15_suppl, TPS8581-TPS8581
48. Azad NS, Gray RJ, Overman MJ, et al. Nivolumab Is Effective in Mismatch Repair-Deficient Noncolorectal Cancers: Results From Arm Z1D-A Subprotocol of the NCI-MATCH (EAY131) Study. J Clin Oncol. 2020 Jan 20;38(3):214-222.
49. Naumann RW, Hollebecque A, Meyer T, et al. Safety and Efficacy of Nivolumab Monotherapy in Recurrent or Metastatic Cervical, Vaginal, or Vulvar Carcinoma: Results From the Phase I/II CheckMate 358 Trial. J Clin Oncol. 2019 Nov 1;37(31):2825-2834.
50. Choueiri TK, Powles T, Burotto M, et al. 696O_PR Nivolumab + cabozantinib vs sunitinib in first-line treatment for advanced renal cell carcinoma: First results from the randomized phase III CheckMate 9ER trial. Volume 31, SUPPLEMENT 4, S1159, September 01, 2020.
51. Referenced with permission from the NCCN Clinical Practice Guidelines (NCCN Guidelines®) Bladder Cancer. Version 6.2020. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed January 2021.
52. Referenced with permission from the NCCN Clinical Practice Guidelines (NCCN Guidelines®) Esophageal and Esophagogastric Junction Cancers. Version 5.2020. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed January 2021.
53. Referenced with permission from the NCCN Clinical Practice Guidelines (NCCN Guidelines®) Gastric Cancer. Version 4.2020. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed January 2021.
54. Herrera AF, Moskowitz AJ, Bartlett NL, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractor Hodgkin lymphoma. Blood. 2018 Mar 15;131 (11):1183-1194.
55. Cole PD, Mauz-Körholz C, Mascarin M, et al. HL-032: Nivolumab and Brentuximab Vedotin (BV)–Based, Response-Adapted Treatment in Children, Adolescents, and Young Adults (CAYA) With Standard-Risk Relapsed/Refractory Classical Hodgkin Lymphoma (R/R cHL): Primary Analysis of the Standard-Risk Cohort of the Phase 2 CheckMate 744 Study. Clinical Lymphoma Myeloma and Leukemia. Volume 20, Supplement 1, September 2020, Pages S245-S246.
56. Moehler M, Shitara K, Garrido M, et al. Nivolumab (nivo) plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer (GC/GEJC)/esophageal adenocarcinoma (EAC): First results of the CheckMate 649 study. [abstract]. Presented at the Oral Presentation presented at the ESMO 2020 Annual Meeting; September 19-21, 2020; Virtual Meeting.

57. Lexicomp Online. (2021, February). AHFS DI. *Nivolumab*. Retrieved May 5, 2021 from Lexicomp Online with AHFS.
58. MICROMEDEX Healthcare Series. Drugdex Evaluations. (2021, April). *Nivolumab*. Retrieved May 5, 2021 from MICROMEDEX Healthcare Series

**EFFECTIVE DATE** 8/31/2021

ID_MRx