Policy Title:	Opdivo (nivolumab) Intravenous		
		Department:	PHA
Effective Date:	01/01/2020		
Review Date:	06/07/2019, 12/20/2019		
Revision Date:	06/07/2019, 12/20/2019		

Purpose: To support safe, effective and appropriate use of Opdivo (nivolumab).

Scope: Medicaid, Exchange, Medicare-Medicaid Plan (MMP)

Policy Statement: Opdivo (nivolumab) is covered under the Medical Benefit when used within the following guidelines. Use outside of these guidelines may result in non-payment unless approved under an exception process.

Procedure: Coverage of Opdivo (nivolumab) will be reviewed prospectively via the prior authorization process based on criteria below.

Initial Criteria:

- Patient must be 18 years of age or older (unless otherwise specified); AND
- Patient has not received previous therapy with a programmed death (PD-1/PD-L1)-directed therapy (e.g., cemiplimab, avelumab, pembrolizumab, atezolizumab, durvalumab, etc.) unless otherwise specified; AND

Melanoma *

- Patient's disease is unresectable or metastatic; AND
  - Used as a single agent or in combination with ipilimumab; OR
- Patient has unresectable or metastatic uveal melanoma; AND
  - Used as a single agent or in combination with ipilimumab; OR
- Used as adjuvant treatment as a single agent; AND
  - Patient has lymph node involvement or metastatic disease and has undergone complete resection; OR
- Used for retreatment of disease; AND
  - Used as re-induction therapy as a single agent or in combination with ipilimumab in patients who experienced disease control (i.e., complete or partial response or stable disease), but subsequently have disease progression/relapse > 3 months after treatment discontinuation; OR
  - Used as subsequent therapy, in combination with ipilimumab, in patients who experienced disease progression after monotherapy with an immune checkpoint-inhibitor.

Hepatocellular Carcinoma (HCC) *

- Used as a single agent; AND
- Patient progressed on or was intolerant to sorafenib; AND
- Patient has a laboratory confirmed diagnosis of hepatocellular carcinoma; AND
- Patient has Child-Pugh Class A or B7 disease.

Non-Small Cell Lung Cancer (NSCLC) *

- Patient has disease with a high tumor mutational burden (TMB) (i.e., ≥10 mutations per megabase); AND
  - Used as a single-agent or in combination with ipilimumab; OR
- Used as subsequent therapy in patients with recurrent, advanced, or metastatic disease; AND
  - Must be used as a single agent; AND
  - Disease has progressed during or following cytotoxic (e.g., platinum-based) therapy; AND
  - Patients with genomic tumor aberrations must have progressed following systemic therapy for those aberrations (i.e., EGFR, ALK, etc.) **∝(**See chart below).

Renal Cell Carcinoma (RCC) *

- Used in combination with ipilimumab; AND
  - Used as initial therapy in patients with advanced or metastatic disease with intermediate or poor risk; OR
  - Used as first-line therapy for clear cell histology and favorable risk; OR
  - Used as subsequent therapy in patients with relapsed or stage IV disease with clear cell histology; OR
- Used as a single agent; AND
  - Patient has advanced disease and received prior antiangiogenic therapy (e.g., everolimus); OR
  - Patient has relapsed or stage IV disease; AND
    - Used as subsequent therapy for clear cell histology; OR
    - Patient has non-clear cell histology.

Classical Hodgkin Lymphoma (cHL) *

- Must be used as a single agent; AND
- Patient has relapsed or progressive disease; AND
  - Patient had an autologous hematopoietic stem cell transplantation (HSCT) and posttransplantation brentuximab vedotin; OR
  - Patient has received 3 or more lines of systemic therapy that includes autologous HSCT.

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.

Urothelial Carcinoma *

- Must be used as a single agent; AND
- Must be used as subsequent systemic therapy after previous platinum treatment*; AND
- Patient has one of the following:
    - Locally advanced or metastatic disease; OR
    - Disease 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 GU Tract Tumors **; OR
- Metastatic Urothelial Carcinoma of the Prostate **

*If platinum treatment occurred greater than 12 months ago, the patient should be re-treated with platinum-based therapy. Patients with comorbidities (e.g., hearing loss, neuropathy, poor performance status [PS], renal insufficiency, etc.) may not be eligible for cisplatin. Carboplatin may be substituted for cisplatin particularly in those patients with a GFR<60mL/min or a PS of 2.

Small Cell Lung Cancer (SCLC) *

- Used as subsequent systemic therapy; AND
    - Used as single agent therapy for metastatic disease after previous platinum-based treatment and at least one other line of therapy *; OR
    - Used as single agent or in combination with ipilimumab in patients with a ECOG PS score of 0-2 ** AND
        - Primary progressive disease; OR
        - Relapsed within 6 months following complete response, partial response, or stable disease following initial treatment.

Colorectal Cancer *

- Patient must be at least 12 years old; AND
- Patient's disease must be microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND
- Patients must not have a diagnosis of MSI-H central nervous system metastases; AND
- Patient has one of the following:
    - Patient has unresectable advanced or metastatic disease that progressed following treatment with a fluoropyrimidine-, oxaliplatin-, and/or irinotecan based chemotherapy; AND
        - Used as a single agent or in combination with ipilimumab; OR
    - Used as primary treatment for patients with previous adjuvant FOLFOX (fluorouracil, leucovorin and oxaliplatin) or CapeOX (capecitabine-oxaliplatin) in the past 12 months **; AND
        - Used as a single agent or in combination with ipilimumab for unresectable metastatic disease; OR
    - Used as initial therapy for patients who are not candidates for intensive therapy **; AND

- Used as a single agent for unresectable advanced or metastatic disease.

Merkel Cell Carcinoma **

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

Central Nervous System Cancer **

- Used for the treatment of brain metastases in patients with melanoma; AND
- Used in combination with ipilimumab.

Anal Carcinoma **

- Patient has metastatic squamous cell disease; AND
- Used as a single agent for second-line therapy.

Gestational Trophoblastic Neoplasia **

- Used as single-agent therapy; AND
  - Patient has recurrent or progressive disease; AND
    - Patient has intermediate placental or epithelioid trophoblastic tumor; AND
    - Patient was previously treated with a platinum/etoposide containing regimen; OR
  - Patient has methotrexate-resistant high risk disease.

Malignant Pleural Mesothelioma **

- Used as a single agent or in combination with ipilimumab as subsequent therapy.

* FDA Approved Indication(s); ** Compendia recommended indication(s)

***Continuation of Therapy Criteria:*:**

- Patient continues to meet initial criteria; AND
- Tumor response with stabilization of disease or decrease in size of tumor or tumor spread; AND
- Patient is tolerating treatment with absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: severe infusion reactions, complications of allogeneic HSCT, severe immunemediated adverse reactions such as pneumonitis, colitis, hepatitis, endocrinopathies, nephritis/renal dysfunction, rash, encephalitis, etc.; AND
- For patients being treated for adjuvant treatment of melanoma, the patient has not exceeded 12 months of therapy.

Genomic Aberration Targeted Therapies (not all inclusive) ∝
Sensitizing EGFR mutation-positive tumors – Erlotinib – Afatinib – Gefitinib – Osimertinib – Dacomitinib
ALK rearrangement-positive tumors – Crizotinib – Ceritinib – Brigatinib – Alectinib – Lorlatinib
ROS1 rearrangement-positive tumors – Crizotinib – Ceritinib
BRAF V600E-mutation positive tumors – Dabrafenib/Trametinib
PD-L1 expression-positive tumors (≥50%) – Pembrolizumab – Atezolizumab

Coverage durations:

- Initial & Renewal coverage = 6 months

*** Requests will also be reviewed to National Coverage Determination (NCD) and Local Coverage Determinations (LCDs) if applicable.***

Dosage/Administration:

Indication	Dose (1 billable unit = 1mg)
Merkel Cell	3 mg/kg every 2 weeks

CRC	Single agent: 240 mg every 2 weeks, until disease progression or unacceptable toxicity. In combination with ipilimumab: 3 mg/kg every 3 weeks for 4 doses, then 240 mg every 2 weeks until disease progression or unacceptable toxicity
Anal Cancer	240 mg every 2 weeks or 3 mg/kg every 2 weeks, until disease progression or unacceptable toxicity.
Melanoma	Single agent: 240 mg every 2 weeks OR 480 mg every 4 weeks Adjuvant single-agent treatment: 240 mg every 2 weeks or 480 mg every 4 weeks, until disease recurrence or unacceptable toxicity for up to 1 year. In combination with ipilimumab: 1 mg/kg, followed by ipilimumab on the same day, every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks
NSCLC, MSI-H/dMMR, cHL, SCCHN, HCC and Urothelial Carcinoma	240 mg every 2 weeks or 480 mg every 4 weeks, until disease progression or unacceptable toxicity.
SCLC	Single agent: 240 mg every 2 weeks until disease progression or unacceptable toxicity In combination with ipilimumab: 1 mg/kg to 3 mg/kg, followed by ipilimumab on the same day, every 3 weeks for 4 doses, then 3 mg/kg every 2 weeks
Renal Cell Carcinoma	Single-agent: 240 mg every 2 weeks or 480 mg every 4 weeks, until disease progression or unacceptable toxicity In combination with ipilimumab: 3 mg/kg, followed by ipilimumab on the same day, every 3 weeks for 4 doses, then follow single-agent regimen
Malignant Pleural Mesothelioma (MPM)	Single agent:

	3 mg/kg every 2 weeks In combination with ipilimumab: 3 mg/kg every 2 weeks, followed by ipilimumab 1mg/kg every 6 weeks, until disease progression or unacceptable toxicity
Gestational Trophoblastic Neoplasia (GTN)	240 mg on days 1, 15, 29 (every 2 weeks) of a 42 day cycle repeated until disease progression or unacceptable toxicity
CNS Metastases	1 mg/kg, followed by ipilimumab on the same day, every 3 weeks for 4 doses, then 3 mg/kg every 2 weeks
Dosing should be calculated using actual body weight or flat dosing to minimize drug waste and consolidate the number of vials used. Flat dosing (as applicable) is based on weight and is indicated below: **Weight ≥ 74 kg:** • Standard dose 240 mg IV every 2 weeks OR 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	

Dosing Limits:

Maximum Units (per dose and over time):

Indication	Billable units (BU)	Per unit time (days)
Merkel Cell, Anal Carcinoma	340 BU	14 days
Melanoma (in combination with ipilimumab)	Initial: 140BU	21 days x 4 doses
	Followed by: 480 BU	28 days
Melanoma/RCC (as a single agent), NSCLC, cHL, SCCHN, MSI-H/dMMR, HCC & Urothelial Carcinoma	480 BU	28 days
Gestational Trophoblastic Tumor	240 BU	14 days
CRC and SCLC (as a single agent)	240 BU	14 days

CRC (in combination with ipilimumab)	Initial: 340 BU	21 days x 4 doses
	Followed by: 240 BU	14 days
RCC (in combination with ipilimumab)	Initial: 340 BU	21 days x 4 doses
	Followed by: 480 BU	28 days
SCLC (in combination with ipilimumab)	Initial: 340 BU	21 days x 4 doses
	Followed by: 340 BU	14 days
MPM (as a single agent or in combination with ipilimumab)	340 BU	14 days
CNS Metastases (in combination with ipilimumab)	Initial: 140 BU	21 days x 4 doses
	Followed by: 340 BU	14 days

Investigational Use: All therapies are considered investigational when used at a dose or for a condition other than those that are recognized as medically accepted indications as defined in any one of the following standard reference compendia: American Hospital Formulary Service Drug Information (AHFS-DI), Thomson Micromedex DrugDex, Clinical Pharmacology, Wolters Kluwer Lexi-Drugs, or Peer-reviewed published medical literature indicating that sufficient evidence exists to support use. Neighborhood does not provide coverage for drugs when used for investigational purposes.

Applicable Codes: Below is a list of billing codes applicable for covered treatment options. The below tables are provided for reference purposes and may not be all inclusive. Requests received with codes from tables below do not guarantee coverage. Requests must meet all criteria provided in the procedure section.

The following HCPCS/CPT codes are:

HCPCS/CPT Code	Description
J9299	Injection, nivolumab, 1mg

References:

1. Opdivo [package insert]. Princeton, NJ; Bristol-Myers Squibb Company; May 2019.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) nivolumab. National Comprehensive Cancer Network, 2019. 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 2019.
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 exposureresponse (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. National Government Services, Inc. Local Coverage Article: Nivolumab – Related to LCD L33394 (A54862). Centers for Medicare & Medicaid Services, Inc. Updated on 9/21/2018 with effective date 10/1/2018. Accessed January 2019.