Clinical Policy: Nivolumab (Opdivo)

Reference Number: CP.PHAR.121
Effective Date: 07.15
Last Review Date: 01.18
Line of Business: Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Nivolumab (Opdivo®) is a programmed death receptor-1 (PD-1) blocking antibody.

FDA Approved Indication(s)
Opdivo is indicated for the treatment of:

- Patients with BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent.
- Patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent.
- Patients with unresectable or metastatic melanoma, in combination with ipilimumab.
- Patients with metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Opdivo.
- Patients with advanced renal cell carcinoma who have received prior antiangiogenic therapy.
- Adult patients with classical Hodgkin lymphoma that has relapsed or progressed after:
  - autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
  - 3 or more lines of systemic therapy that includes autologous HSCT.
- Patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy.
- Patients with locally advanced or metastatic urothelial carcinoma who:
  - have disease progression during or following platinum-containing chemotherapy;
  - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- Adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.
- Patients with hepatocellular carcinoma who have been previously treated with sorafenib.

Policy/Criteria
Provider must submit documentation (which may include office chart notes and lab results) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Opdivo is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria
A. Melanoma (must meet all)**:**

1. Diagnosis of unresectable or metastatic melanoma;
2. Age ≥ 18 years;
3. Dose does not exceed (a or b):
   a. As a single agent: 240 mg every 2 weeks;
   b. In combination with ipilimumab: 1 mg/kg for 4 doses, followed by 240 mg every 2 weeks.

Approval duration: 6 months

B. Non-Small Cell Lung Cancer (must meet all)**:**
1. Diagnosis of metastatic non-small cell lung cancer (NSCLC);
2. Age ≥ 18 years;
3. Member has experienced disease progression on or after platinum-based chemotherapy;
   a. If known epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations, disease progression on one of the following (1 or 2):
      i. FDA-approved therapy if EGFR mutation status is positive (e.g., erlotinib, afatinib, gefitinib, osimertinib);
      ii. FDA-approved therapy if ALK mutation status is positive (e.g., crizotinib, ceritinib, alectinib, brigatinib);
4. Dose does not exceed 240 mg every 2 weeks.

Approval duration: 6 months

C. Renal Cell Carcinoma (must meet all)**:**
1. Diagnosis of renal cell carcinoma (RCC);
2. Age ≥ 18 years;
3. Meets a or b:
   a. FDA approved use: advanced RCC and has received prior anti-angiogenic therapy;
   b. Off-label NCCN recommended use:
      i. Systemic therapy as a single agent for non-clear cell histology;
4. Request meets one of the following (a or b):
   a. Dose does not exceed 240 mg every 2 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

Approval duration: 6 months

D. Classical Hodgkin Lymphoma (must meet all):
1. Diagnosis of classical Hodgkin lymphoma;
2. Age ≥ 18 years;
3. Meets a or b:
   a. FDA approved use meets one of the following (i or ii):
      i. Disease has relapsed or progressed after autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin;
      ii. Disease has relapsed or progressed after 3 or more lines of systemic therapy that includes autologous hematopoietic stem cell transplantation;

   b. Off-label NCCN recommended use, as a single agent for one of the following:
      i. Palliative treatment for age > 60 years if previously treated with brentuximab vedotin;
      ii. Treatment of relapsed disease or refractory disease for age ≥ 18 years if one of the following (1 or 2);
         1. Deauville 4-5;
         2. Previously treated with brentuximab vedotin;
4. Request meets one of the following (a or b):
   a. Dose does not exceed 3 mg/kg every 2 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

Approval duration: 6 months

E. Squamous Cell Carcinoma of the Head and Neck (must meet all):
1. Diagnosis of squamous cell carcinoma of the head or neck;
2. Age ≥ 18 years;
3. Disease is recurrent or metastatic;
4. Disease has progressed on or after platinum-based chemotherapy;
5. Request meets one of the following (a or b):
   a. Dose does not exceed 3 mg/kg every 2 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

Approval duration: 6 months

F. Urothelial Carcinoma (must meet all):
1. Diagnosis of urothelial carcinoma;
2. Age ≥ 18 years;
3. Meets a or b:
   a. FDA approved use:
      i. Disease is locally advanced or metastatic and (a or b):
         a) Disease has progressed during or following platinum-based chemotherapy;
         b) Disease has progressed within 12 months of neoadjuvant or adjuvant treatment with platinum-based chemotherapy;
   b. Off-label NCCN recommended use:
      i. As a single agent for the treatment of bladder cancer recurrence post cystectomy;
4. Request meets one of the following (a or b):
   a. Dose does not exceed 240 mg every 2 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

Approval duration: 6 months

G. Colorectal Cancer (must meet all):
1. Diagnosis of MSI-H or defective mismatch repair (dMMR) colorectal cancer;
2. Age ≥ 12 years;

3. Disease is unresectable or metastatic;
4. Member has had disease progression following treatment with a fluoropyrimidine (e.g., fluorouracil, capecitabine), oxaliplatin, and irinotecan;
5. Dose does not exceed 240 mg every 2 weeks.

Approval duration: 6 months

H. Hepatocellular Carcinoma (must meet all):
1. Diagnosis of hepatocellular carcinoma;
2. Age ≥ 18 years;
3. Member has had disease progression following treatment with sorafenib;
4. Dose does not exceed 240 mg every 2 weeks.

Approval duration: 6 months

I. Malignant Pleural Mesothelioma (off-label) (must meet all)**:**
1. Diagnosis of malignant pleural mesothelioma;
2. Age ≥ 18 years;
3. Member has failed initial treatment (i.e., platinum [cisplatin, carboplatin]-based chemotherapy, pemetrexed or vinorelbine);
4. Request is for use as a single agent or in combination with ipilimumab;
5. Dose is supported by practice guidelines or peer-reviewed literature for malignant pleural mesothelioma *(prescriber must submit supporting evidence).*

Approval duration: 6 months

J. Small Cell Lung Cancer (off-label) (must meet all):
1. Diagnosis of small cell lung cancer;
2. Age ≥ 18 years;
3. Member meets a or b:
   a. Member is experiencing a relapse within 6 months following complete or partial response or stable disease with initial treatment (i.e., platinum [cisplatin, carboplatin]-based chemotherapy);
   b. Member has primary progressive disease;
4. Request is for use as a single agent or in combination with ipilimumab;
5. Dose is supported by practice guidelines or peer-reviewed literature for small cell lung cancer *(prescriber must submit supporting evidence).*

Approval duration: 6 months

K. Other diagnoses/indications
1. Refer to CP.PHAR.57 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;

2. Member is responding positively to therapy (e.g., no disease progression or significant toxicity);
3. If request is for a dose increase, request meets one of the following (a or b):
   a. New dose does not exceed 3 mg/kg every 2 weeks;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to CP.PHAR.57 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy – CP.PHAR.57 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALK: anaplastic lymphoma kinase
BRAF: B-Raf proto-oncogene, serine/threonine kinase
dMMR: mismatch repair deficient
EGFR: epidermal growth factor receptor
FDA: Food and Drug Administration
HSCT: hematopoietic stem cell transplantation
MSI-H: microsatellite instability-high
NSCLC: non-small cell lung cancer
PD-1: programmed death receptor-1
ULN: upper limit of normal

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Melanoma	Monotherapy: 240 mg intravenously every 2 weeks With ipilimumab: 1 mg/kg, followed by ipilimumab on the same day, every 3 weeks for 4 doses, then Opdivo 240 mg every 2 weeks	240 mg
NSCLC, renal cell carcinoma, urothelial carcinoma, MSI-H or dMMR colorectal cancer, hepatocellular carcinoma	240 mg intravenously every 2 weeks	240 mg

Classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck	3 mg/kg intravenously every 2 weeks	3 mg/kg

VI. Product Availability

Injection: 40 mg/4 mL and 100 mg/10 mL

VII. References

1. Opdivo Prescribing Information. Princeton, NJ: Bristol-Myers Squibb; September 2017. Available at http://packageinserts.bms.com/pi/pi_opdivo.pdf. Accessed September 28, 2017.
2. Nivolumab. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at nccn.org. Accessed August 28, 2017.
3. Melanoma (Version 1.2017). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed August 28, 2017.
4. Non-small cell lung cancer (Version 8.2017). In: National Comprehensive Cancer Network Guidelines. Available at nccn.org.Accessed August 28, 2017.
5. Kidney cancer (Version 2.2017). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed August 28, 2017.
6. Hodgkin lymphoma (Version 1.2017). In: National Comprehensive Cancer Network Guidelines. Available at nccn.org. Accessed August 28, 2017.
7. Head and neck cancers (Version 2.2017). In: National Comprehensive Cancer Network Guidelines. Available at nccn.org. Accessed August 28, 2017.
8. Bladder cancer (Version 5.2017). In: National Comprehensive Cancer Network Guidelines. Available at nccn.org. Accessed August 28, 2017.
9. Malignant pleural mesothelioma (Version 2.2017). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed August 28, 2017.
10. Small cell lung cancer (Version 3.2017). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed August 28, 2017.
11. Hepatobiliary cancers (Version 3.2017) In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed September 28, 2017.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy developed.	07.15	07.15
Policy converted to new template. Melanoma: removed BRAF mutation requirement and previous trial/failure requirement of ipilimumab/BRAF inhibitor therapy per FDA labeling. NSCLC: removed squamous histologic type requirement and added requirement for previous trial/failure of targeted therapy for patients with EGFR or ALK mutations per FDA labeling; broadened previous trial/failure requirement from platinum-based chemo to first-line	05.16	06.16

Reviews, Revisions, and Approvals	Date	P&T Approval Date
cytotoxic therapy per NCCN guidelines. Created criteria for advanced RCC and Hodgkin lymphoma per FDA labeling and per NCCN guidelines/compendia. Updated reasons to discontinue per FDA labeling.		
Two new labeled indications added: head and neck cancer and urothelial carcinoma (NCCN compendial uses added for both indications and for colorectal and small cell lung cancer). RCC NCCN recommended uses edited to include non-clear histology; for clear cell, "after tyrosine kinase inhibitor therapy" deleted. Safety criteria removed if not a contraindication or black box warning not covered by a REMS program. Reference to performance status removed.	03.17	04.17
Consolidated the criteria under Melanoma as the FDA labeled use aligns with off-label NCCN use. Added new indication for Hodgkin lymphoma for disease that has relapsed or progressed after 3 or more lines of systemic therapy that includes autologous hematopoietic stem cell transplantation.	05.17	06.17
- Updated off-label usage requirements for NSCLC, RCC, Classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck and urothelial carcinoma to reflect off-label NCCN recommendations for use. - Added age limit ≥ 12 years for MSI-H/dMMR colorectal cancer and ≥ 18 years for all other indications. - Added coverage criteria for the new FDA-approved indication of MSI-H/dMMR colorectal cancer and for the NCCN-recommended off-label usages of malignant pleural mesothelioma and small cell lung cancer.	09.05.17	11.17
New indication addition: - Added coverage criteria for the new FDA-approved indication of hepatocellular carcinoma.	12.05.17	11.17

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical

practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.