

Clinical Policy: Nivolumab (Opdivo)

Reference Number: CP.PHAR.121

Effective Date: 07.01.15

Last Review Date: 02.19

Line of Business: HIM-Medical Benefit, Medicaid

[Coding Implications](#)[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 melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting.
- Patients with metastatic non-small cell lung cancer (NSCLC) and progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Opdivo.
- Patients with metastatic small cell lung cancer (SCLC) with progression after platinum based chemotherapy and at least one other line of therapy.
- Patients with advanced renal cell carcinoma (RCC) who have received prior antiangiogenic therapy.
- Patients with intermediate or poor risk, previously untreated advanced RCC, in combination with ipilimumab.
- Adult patients with classical [classic] Hodgkin lymphoma (CHL) 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 (SCCHN) with disease progression on or after a platinum-based therapy.
- Patients with locally advanced or metastatic urothelial carcinoma (UC) who
 - have disease progression during or following platinum-containing chemotherapy, or
 - 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 (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab.

- Patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

Policy/Criteria

Provider must submit documentation (including such as office chart notes, lab results or other clinical information) 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 melanoma;
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 18 years;
4. Request meets one of the following (a, b, or c):
 - a. Monotherapy: Dose does not exceed 240 mg every 2 weeks or 480 mg every 4 weeks;
 - b. In combination with Yervoy[®]: Dose does not exceed 1 mg/kg every 3 weeks for 4 doses, followed by 240 mg every 2 weeks or 480 mg every 4 weeks;
 - c. 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

B. Non-Small Cell Lung Cancer (must meet all):

1. Diagnosis of metastatic NSCLC;
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 18 years;
4. Disease has progressed on or after systemic therapy ;
5. Request meets one of the following (a or b):
 - a. Dose does not exceed 240 mg every 2 weeks or 480 mg every 4 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

C. Small Cell Lung Cancer (must meet all):

1. Diagnosis of SCLC;
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 18 years;
4. Failure of platinum-containing regimen (e.g. cisplatin, carboplatin), unless contraindicated or clinically significant adverse effects are experienced;
5. 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. Renal Cell Carcinoma (must meet all):

1. Diagnosis of RCC;
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 18 years;
4. Request meets one of the following (a, b, or c):
 - a. Monotherapy: Dose does not exceed 240 mg every 2 weeks or 480 mg every 4 weeks;
 - b. In combination with Yervoy: Dose does not exceed 3 mg/kg every 3 weeks for 4 doses, followed by 240 mg every 2 weeks or 480 mg every 4 weeks;
 - c. 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. Classical Hodgkin Lymphoma (must meet all):

1. Diagnosis of cHL;
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 18 years;
4. Disease has relapsed or progressed after autologous hematopoietic stem cell transplantation;
5. Request meets one of the following (a or b):
 - a. Dose does not exceed 240 mg every 2 weeks or 480 mg every 4 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. Squamous Cell Carcinoma of the Head and Neck (must meet all):

1. Diagnosis of SCCHN;
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 18 years;
4. Disease has progressed on or after a platinum-containing regimen (e.g., cisplatin, carboplatin);
5. Request meets one of the following (a or b):
 - a. Dose does not exceed 240 mg every 2 weeks or 480 mg every 4 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. Urothelial Carcinoma (must meet all):

1. Diagnosis of UC;
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 18 years;
4. Failure of a platinum-containing regimen (e.g., cisplatin, carboplatin), unless contraindicated or clinically significant adverse effects are experienced;
5. Request meets one of the following (a or b):
 - a. Dose does not exceed 240 mg every 2 weeks or 480 mg every 4 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

H. Colorectal Cancer (must meet all):

1. Diagnosis of unresectable or metastatic CRC;
2. Tumor is characterized as MSI-H or dMMR;
3. Prescribed by or in consultation with an oncologist;
4. Age \geq 12 years;
5. Dose does not exceed one of the following (a, b, or c):
 - a. Monotherapy: 240 mg every 2 weeks;
 - b. In combination with Yervoy: 3 mg/kg every 3 weeks for 4 doses, then 240 mg every 2 weeks;
 - c. 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

I. Hepatocellular Carcinoma (must meet all):

1. Diagnosis of HCC;
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 18 years;
4. Member has had disease progression following treatment with Nexavar[®];
**Prior authorization may be required for Nexavar.*
5. Request meets one of the following (a or b):
 - a. Dose does not exceed 240 mg every 2 weeks or 480 mg every 4 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

J. Off-label NCCN Compendium Recommended Indications (must meet all):

1. Diagnosis of one of the following (a, b, or c):
 - a. Metastatic squamous cell anal carcinoma;
 - b. Metastatic Merkel cell carcinoma;;
 - c. Gestational trophoblastic neoplasia;
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 18 years;
4. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

K. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.PMN.53 for Medicaid and HIM-Medical Benefit.

II. Continued Therapy

A. All Indications in Section I (must meet all):

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Opdivo for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a or b):
 - a. New dose does not exceed 480 mg every 4 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 the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.PMN.53 for Medicaid and HIM-Medical Benefit.

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 policies – CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALK: anaplastic lymphoma kinase	HCC: hepatocellular carcinoma
BRAF: B-Raf proto-oncogene, serine/threonine kinase	HSCT: hematopoietic stem cell transplantation
CHL: classic Hodgkin lymphoma	MSI-H: microsatellite instability-high
CRC: colorectal cancer	NSCLC: non-small cell lung cancer
dMMR: mismatch repair deficient	PD-1: programmed death receptor-1
EGFR: epidermal growth factor receptor	RCC: renal cell carcinoma
FDA: Food and Drug Administration	SCLC: small cell lung cancer
	UC: urothelial carcinoma

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Nexavar (sorafenib)	HCC: 400 mg PO BID until clinical benefit cease or unacceptable toxicity occurs	800 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Cisplatin- or carboplatin-containing chemotherapy	SCLC, UC, SCCHN: Varies	Varies

Therapeutic alternatives are listed as Brand name[®] (generic) when the drug is available by brand name only and generic (Brand name[®]) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings
None reported

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Melanoma - unresectable or metastatic	Monotherapy: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks With ipilimumab: 1 mg/kg IV, followed by ipilimumab on the same day, every 3 weeks for 4 doses, then nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks	480 mg/dose
Melanoma - adjuvant treatment NSCLC RCC - advanced with previous anti-angiogenic therapy CHL, SCCHN, UC, HCC	240 mg IV every 2 weeks or 480 mg IV every 4 weeks	480 mg/dose
MSI-H or dMMR CRC	Monotherapy: 240 mg IV every 2 weeks With ipilimumab: 3 mg/kg IV, followed by ipilimumab 1 mg/kg on the same day every 3 weeks for 4 doses, then nivolumab 240 mg IV every 2 weeks	Monotherapy: 240 mg/dose With ipilimumab: 3 mg/kg/dose
RCC - advanced previously untreated	Monotherapy: 240 mg IV every 2 weeks or 480 mg every 4 weeks With ipilimumab: 3 mg/kg IV, followed by ipilimumab 1 mg/kg IV on the same day every 3 weeks for 4 doses, then nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks	480 mg/dose

VI. Product Availability

Single-dose vials: 40 mg/4 mL, 100 mg/10 mL, 240 mg/24 mL

VII. References

1. Opdivo Prescribing Information. Princeton, NJ: Bristol-Myers Squibb; August 2018. Available at <https://www.opdivo.com/>. Accessed September 26, 2018.
2. Bavencio Prescribing Information. Rockland, MD: EMD Serono, Inc.; October 2017. Available at <https://www.emdserono.com/content/dam/web/corporate/non-images/country-specifics/us/pi/bavencio-pi.pdf>. Accessed September 26, 2018.
3. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at <http://www.nccn.org>. Accessed September 26, 2018.
4. Small cell lung cancer (Version 2.2018). National Comprehensive Cancer Network Guidelines. Available at <http://www.nccn.org>. Accessed September 26, 2018.
5. Non-small cell lung cancer (Version 6.2018) National Comprehensive Cancer Network. Available at <http://www.nccn.org>. Accessed September 26, 2018.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J9299	Injection, nivolumab, 1 mg

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 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.	05.16	06.16
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

Reviews, Revisions, and Approvals	Date	P&T Approval Date
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
Added coverage criteria for the new FDA-approved indication of hepatocellular carcinoma.	09.29.17	11.17
Added requirement for being prescribed by or in consultation with an oncologist; added requirement for Child-Pugh classification to for HCC indication; updated melanoma criteria set to reflect expanded indication for the adjuvant treatment of patients with melanoma: removed “unresectable or metastatic” from the diagnosis.	01.25.18	02.18
Criteria added for new FDA indication: advanced renal cell carcinoma in combination with ipilimumab; lowered age limit from 18 years to 12 years for all indications; removed distinction between FDA-approved and NCCN-recommended off-label uses since both clear cell and non-clear cell histology are indicated for relapse or surgically unresectable stage IV kidney cancer; summarized NCCN and FDA-approved uses for improved clarity; removed malignant pleural mesothelioma due to NCCN 2B recommendation status; for small cell lung cancer, added failure of platinum-containing chemotx, removed requirement for relapse or primary progressive disease, and removed its use as single agent or with Yervoy; for colon cancer, removed requirement for FOLFOX since initial therapy recommended by NCCN with 2A rating for those who are not appropriate for intensive tx; for head and neck cancer, removed requirement for recurrent or metastatic disease since NCCN also recommends tx for newly diagnosed with no metastases with 1/2A; for NSCLC, removed conditional requirement for EGFR/ALK therapies; allowed continuity of care for continued approval; added HIM-medical benefit line of business; references reviewed and updated.	05.22.18	08.18

Reviews, Revisions, and Approvals	Date	P&T Approval Date
No significant changes: Updated FDA approved indication, dosing requirement, and dosage/administration section for MSI-H or dMMR metastatic colorectal cancer to include Opdivo in combination with ipilimumab (previously approved as monotherapy for this same indication).	08.07.18	
No significant changes: Updated FDA approved indication section with new indication for SCLC; SCLC: removed ‘off-label’ language from existing usage criteria and revised max dose requirement per PI.	08.28.18	
1Q 2019 annual review; ages adjusted per PI to 18 and older for all indications except CRC; melanoma - brain metastasis is deleted and incorporated under a diagnosis of melanoma; for NSCLC, progression on platinum therapy changed to progression on systemic therapy to encompass progression on first-line targeted therapy per PI and NCCN; off-label NCCN recommended trophoblastic tumor is added; dMMR/MSI-H metastatic rectal cancer removed from off-label section as it is represented under the CRC labeled use; for RCC, combination dosing with Yervoy added per PI; references reviewed and updated.	11.13.18	02.19

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.

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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

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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.

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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.

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