Clinical Policy: Nivolumab (Opdivo)

Reference Number: CP.PHAR.121
Effective Date: 08.01.15
Last Review Date: 02.21
Line of Business: Commercial, HIM, 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:

- **Melanoma**
  - Patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab.
  - Patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting.
- **Non-small cell lung cancer (NSCLC)**
  - Adult patients with metastatic non-small cell lung cancer expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with ipilimumab.
  - Adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy.
  - Patients with metastatic NSCLC 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.
- **Malignant pleural mesothelioma**
  - Adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with ipilimumab.
- **Renal cell carcinoma (RCC)**
  - Patients with advanced renal cell carcinoma (RCC) who have received prior antiangiogenic therapy.
  - Patients with advanced renal cell carcinoma, as a first-line treatment in combination with cabozantinib.
  - Patients with intermediate or poor risk, previously untreated advanced RCC, in combination with ipilimumab.
- **Classical Hodgkin lymphoma (cHL)**
  - Adult patients with 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.
- **Squamous cell carcinoma of the head and neck (SCCHN)**

- Patients with recurrent or metastatic SCCHN with disease progression on or after a platinum-based therapy.

- **Urothelial carcinoma (UC)**
  - Patients with locally advanced or metastatic 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.
- **Colorectal cancer**
  - 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.*
- **Hepatocellular carcinoma (HCC)**
  - Patients with HCC who have been previously treated with sorafenib, as a single agent or in combination with ipilimumab.*
- **Esophageal squamous cell carcinoma (ESCC)**
  - Patients with unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy.*

*This indication is approved under accelerated approval based on overall or tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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 unresectable, metatstatic, or lymph node positive melanoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Request meets one of the following (a, b, or c):*
   a. Monotherapy (unresectable or metastatic disease, or adjuvant treatment): Dose does not exceed 240 mg every 2 weeks or 480 mg every 4 weeks;
   b. In combination with Yervoy® (unresectable or metastatic disease): 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 (*see Appendix E for dose rounding guidelines*);
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 6 months

B. Non-Small Cell Lung Cancer (must meet all)**:**
1. Diagnosis of recurrent, advanced, or metastatic NSCLC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Member has not previously progressed on a PD-1/PD-L1 inhibitor (e.g., Keytruda®, Tecentriq®, Imfinzi®);
5. Opdivo is prescribed in one of the following ways (a, b, or c):
   a. For use as a single agent, and disease has progressed on or after systemic therapy;
   b. For use as a single agent or in combination with Yervoy for tumors positive for the Tumor Mutation Burden (TMB) biomarker;
   c. For use in combination with Yervoy, and both of the following (i and ii):
      i. Request meets one of the following (a, b, or c):
         a) Disease mutation status is unknown or negative for EGFR, ALK, ROS1, BRAF, MET exon 14 skipping, and RET, and member has not received prior systemic therapy for advanced disease;
         b) Disease mutation status is positive for EGFR, ALK, ROS1, BRAF, MET exon 14 skipping, RET, or NTRK gene fusion, and member has received mutation-specific treatment;
         c) Disease is positive for a RET rearrangement;
      ii. Request meets one of the following (a or b):
         a) Member has PD-L1 tumor expression of ≥ 1%;
         b) Opdivo is being used in combination with Yervoy ± a platinum-based regimen (*see Appendix B*);

   **Prior authorization may be required for Yervoy*
6. Request meets one of the following (a, b, c, or d):*
   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 2 weeks (*see Appendix E for dose rounding guidelines*);
   c. In combination with Yervoy and platinum-doublet chemotherapy: Dose does not exceed 360 mg every 3 weeks;
   d. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 6 months

C. Malignant Pleural Mesothelioma (must meet all)**:**
1. Diagnosis of unresectable malignant pleural mesothelioma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed in one of the following ways (a or b):
   a. As first-line therapy in combination with Yervoy;
   b. If not administered first-line, as subsequent therapy in combination with Yervoy or as a single agent;
5. Request meets one of the following (a or b):*
   a. Dose does not exceed 360 mg every 3 weeks;

b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

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 ≥ 18 years;
4. Request meets one of the following (a, b, or c):*
   a. Monotherapy or in combination with cabozantinib: 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 (*see Appendix E for dose rounding guidelines*);
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 6 months

E. Classical Hodgkin Lymphoma (must meet all)**:**

1. Diagnosis of relapsed, refractory or progressive cHL;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed as subsequent 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).*

**Prescribed regimen must be FDA-approved or recommended by NCCN*

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 ≥ 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).*

**Prescribed regimen must be FDA-approved or recommended by NCCN*

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 ≥ 18 years;
4. Failure of a platinum-containing regimen (e.g., cisplatin, carboplatin), unless clinically significant adverse effects are experienced or all are contraindicated;
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).*

**Prescribed regimen must be FDA-approved or recommended by NCCN*

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 ≥ 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 or 480 mg every 4 weeks (*see Appendix E for dose rounding guidelines*);
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

**Prescribed regimen must be FDA-approved or recommended by NCCN*

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 ≥ 18 years;
4. Member has had disease progression following treatment with Nexavar® or Lenvima®;
   **Prior authorization may be required for Nexavar and Lenvima.*
5. Member has not had previous treatment with a checkpoint inhibitor (e.g., Yervoy, Keytruda, Tecentriq, Imfinzi);
6. Member meets one of the following (a or b):
   a. Request is for monotherapy and documentation supports Child-Pugh Class A or B status;
   b. Request is for use in combination Yervoy and documentation supports Child-Pugh Class A status;
7. Dose does not exceed one of the following (a, b, or c):*
   a. Monotherapy: 240 mg every 2 weeks or 480 mg every 4 weeks;
   b. In combination with Yervoy: 1 mg/kg every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks (*see Appendix E for dose rounding guidelines*);
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 6 months

J. Esophageal Squamous Cell Carcinoma (must meet all)**:**
1. Diagnosis of unresectable advanced, recurrent, or metastatic ESCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Member has had previous treatment with a fluoropyrimidine-based (e.g., 5-fluorouracil, capecitabine) and platinum-based (e.g., carboplatin, cisplatin, oxaliplatin) chemotherapy;
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).*

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 6 months

K. Off-label NCCN Compendium Recommended Indications (must meet all)**:**
1. Diagnosis of one of the following (a, b, c, d, e, f, or g):
   a. Metastatic squamous cell anal carcinoma;
   b. Metastatic Merkel cell carcinoma;
   c. Gestational trophoblastic neoplasia;
   d. Uveal melanoma;
   e. Small bowel adenocarcinoma;
   f. Extranodal NK/T-cell lymphoma, nasal type;
   g. Pediatric Hodgkin lymphoma;
   h. Vulvar cancer - HPV-related advanced, recurrent, or metastatic disease;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. For anal carcinoma: prescribed as second line or subsequent therapy (examples of prior therapy include 5-FU/cisplatin, carboplatin/paclitaxel, FOLFOX, FOLFCIS);
5. For gestational trophoblastic neoplasia: prescribed as one of the following (a or b):
   a. Following treatment with a platinum/etoposide-containing regimen;
   b. Disease is methotrexate-resistant and high-risk (*see Appendix D*);
6. For uveal melanoma: prescribed as a single agent or in combination with Yervoy;
   **Prior authorization may be required for Yervoy.*
7. For pediatric Hodgkin lymphoma and vulvar cancer: prescribed as subsequent therapy;
8. 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).*

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 6 months

L. 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.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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, b, or c):*
   a. NSCLC in combination with Yervoy: New dose does not exceed 3 mg/kg every 2 weeks;
   b. Malignant pleural mesothelioma in combination with Yervoy: New dose does not exceed 360 mg every 3 weeks;
   c. Other indications: New dose does not exceed 480 mg every 4 weeks;
   d. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

**Prescribed regimen must be FDA-approved or recommended by NCCN*

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.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, 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
CHL: classic Hodgkin lymphoma
CRC: colorectal cancer
dMMR: mismatch repair deficient
EGFR: epidermal growth factor receptor
ESCC: esophageal squamous cell carcinoma
FDA: Food and Drug Administration
HCC: hepatocellular carcinoma
HSCT: hematopoietic stem cell transplantation
MET: mesenchymal-epithelial transition
MSI-H: microsatellite instability-high
NSCLC: non-small cell lung cancer
PD-1: programmed death receptor-1
PD-L1: programmed death-ligand 1

RCC: renal cell carcinoma
ROS1: ROS proto-oncogene 1
TMB: Tumor Mutational Burden
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 ceases or unacceptable toxicity occurs	800 mg/day
Lenvima (lenvatinib)	HCC: 12 mg PO QD (patients ≥ 60 kg) or 8 mg PO QD (patients < 60 kg) until disease progression or unacceptable toxicity	12 mg/day
Cisplatin- or carboplatin-containing chemotherapy	UC, SCCHN: Varies	Varies
First-line therapies (e.g., 5-FU/cisplatin, carboplatin/paclitaxel, FOLFOX, FOLFCIS)	Metastatic anal carcinoma: Varies	Varies
First-line therapies (e.g., platinum/etoposide-containing regimen)	Gestational trophoblastic neoplasia: Varies	Varies
platinum-containing regimens	NSCLC – squamous cell carcinoma: paclitaxel + carboplatin dose varies NSCLC – nonsquamous cell carcinoma: pemetrexed + [carboplatin or cisplatin] dose 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

Appendix D: General Information
- High-risk disease in gestational trophoblastic neoplasia is defined as having a FIGO stage II to III and ≥ 7 prognostic score or stage IV
  - FIGO staging system:

Stage	Criteria
I	Tumor confined to uterus
II	Tumor extends to other genital structures (ovary, tube, vagina, broad ligaments) by metastasis or direct extension
III	Lung metastasis

Stage	Criteria
IV	All other distant metastases

- Prognostic Scoring Index
  - The total score is obtained by adding the individual scores for each prognostic factor (low risk is indicated by a score < 7 and high risk is indicated by a score ≥ 7)

Prognostic factor	Risk score			
	0	1	2	4
Age (years)	< 40	≥ 40	--	--
Antecedent pregnancy	Hydatidiform mole	Abortion	Term pregnancy	--
Interval from index pregnancy (months)	< 4	4 to 6	7 to 12	>12
Pretreatment hCG (IU/L)	$< 10^3$	10^3 to $< 10^4$	10^4 to 10^5	$\geq 10^5$
Largest tumor size, including uterus (cm)	< 3	3 to 5	> 5	
Site of metastases	Lung	Spleen, kidney	Gastrointestinal tract	Brain, liver
Number of metastases identified	0	1 to 4	5 to 8	> 8
Previous failed chemotherapy	--	--	Single drug	Two or more drugs
Total score	--	--	--	--

*Appendix E: Dose Rounding Guidelines**

Weight-based Dose Range	Vial Quantity Recommendation
≤ 41.99 mg	1 vial of 40 mg/4 mL
42 mg-104.99 mg	1 vial of 100 mg/10 mL
105 mg-146.99 mg	1 vial of 40 mg/4 mL and 100 mg/10 mL
147 mg-209.99 mg	2 vials of 100 mg/10 mL
210 mg-251.99 mg	1 vial of 240 mg/24 mL
260 mg-293.99 mg	1 vial of 40 mg/4 mL and 240 mg/24 mL
294 mg-356.99 mg	1 vial of 100 mg/4 mL and 240 mg/24 mL
357 mg-503.99 mg	2 vials of 240 mg/24 mL

**This is part of a dose rounding guideline on select drug classes as part of an initiative conducted on a larger scale with multiple references and prescriber feedback.*

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) RCC - advanced with previous anti-angiogenic therapy, cHL, SCCHN, UC	240 mg IV every 2 weeks or 480 mg IV every 4 weeks	480 mg/dose
MSI-H/dMMR CRC	Monotherapy: 240 mg IV every 2 weeks or 480 mg IV every 4 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 or 480 mg IV every 4 weeks	Monotherapy: 480 mg/dose With ipilimumab: 3 mg/kg/dose
RCC - advanced previously untreated	Monotherapy or with cabozantinib: 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
HCC	Monotherapy: 240 mg IV every 2 weeks or 480 mg every 4 weeks until disease progression or unacceptable toxicity With ipilimumab: nivolumab 1 mg/kg IV, followed by ipilimumab 3 mg/kg IV on the same day, every 3 weeks for a maximum of 4 doses, then as single-agent nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks until disease progression or unacceptable toxicity	480 mg/dose
NSCLC	Monotherapy: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks until disease progression or unacceptable toxicity With ipilimumab: nivolumab 3 mg/kg IV every 2 weeks and ipilimumab 1 mg/kg IV every 6 weeks until disease progression, unacceptable	Monotherapy: 480 mg/dose With ipilimumab: 3 mg/kg/dose

Indication	Dosing Regimen	Maximum Dose
	toxicity, or for up to 2 years in patients without disease progression With ipilimumab and platinum-doublet chemotherapy: nivolumab 360 mg IV every 3 weeks and ipilimumab 1 mg/kg IV every 6 weeks and histology-based platinum-doublet chemotherapy every 3 weeks for 2 cycles until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression	With ipilimumab and platinum-doublet: 360 mg/dose
ESCC	240 mg IV every 2 weeks or 480 mg IV every 4 weeks until disease progression or unacceptable toxicity	480 mg/dose
Malignant pleural mesothelioma	With ipilimumab: nivolumab 360 mg every 3 weeks and ipilimumab 1 mg/kg every 6 weeks	With ipilimumab: 360 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; January 2021. Available at https://www.opdivo.com/. Accessed February 3, 2021.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at http://www.nccn.org. Accessed November 17, 2020.
3. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer Version 8.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed November 17, 2020.
4. National Comprehensive Cancer Network. Kidney Cancer, Version 2.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed February 3, 2021.
5. Hellman MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. N Engl J Med. 2019 November; 381(21):2020-2031.

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
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
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	05.22.18	08.18

Reviews, Revisions, and Approvals	Date	P&T Approval Date
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.		
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
Added Commercial line of business to policy.	10.08.19	
1Q 2020 annual review: added HIM line of business; added off-label use in malignant pleural mesothelioma per NCCN recommendation update from category 2B to category 2A; added requirement for use in anal carcinoma as second line or subsequent therapy; added requirement for use in gestational trophoblastic neoplasia following a platinum/etoposide-containing regimen or in methotrexate-resistant, high-risk disease; removed HIM NF disclaimer statements; references reviewed and updated.	12.03.19	02.20
Added appendix E: dose rounding guidelines; added reference to appendix E within criteria; added FDA-labeled indication of HCC in combination with Yervoy; added NCCN compendium-supported indication of uveal melanoma as a single agent or in combination with Yervoy.	04.04.20	05.20
Updated HCC criteria to include no previous treatment with a checkpoint inhibitor based on NCCN recommendation; added criteria for FDA-labeled indications of NSCLC & ESCC; updated SCLC indication for optional use in combination with ipilimumab per	06.23.20	08.20

Reviews, Revisions, and Approvals	Date	P&T Approval Date
updated NCCN compendium; added NCCN compendium-supported indications of small bowel adenocarcinoma and T-cell lymphoma.		
RT4: FDA approved malignant pleural mesothelioma added. 1Q 2021 annual review: per FDA/NCCN as follows: for melanoma, unresectable, metastatic, or lymph node positive disease added; for NSCLC, single-agent therapy for TMB positive tumor added, combination therapy for RET rearrangement added, combination therapy changed from Yervoy and platinum doublet therapy to Yervoy plus/minus a platinum based regimen; for cHL, relapsed, refractory or progressive disease added, post HSCT replaced with prescribed as subsequent therapy; for HCC, Lenvima added as a prior therapy option, added documentation of Child-Pugh class status; off-label pediatric Hodgkin lymphoma and vulvar cancer added; SCLC criteria per label update; RT4: added new FDA approved indication of use in combination with cabozantinib as first-line therapy for advanced RCC; references to HIM.PHAR.21 revised to HIM.PA.154; removed references reviewed and updated.	02.03.21	02.21

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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

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.