Clinical Policy: Nivolumab (Opdivo)

Reference Number: LA.PHAR.121
Effective Date: 01.21
Last Review Date: ~~06.23~~05.07.24 Coding Implications
Line of Business: Medicaid Revision Log

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

****Please note: This policy is for medical benefit****

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**
  - Adult and pediatric (12 years and older) patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab.
  - Adult and pediatric (12 years and older) patients with ~~melanoma with lymph node involvement or metastatic disease who have undergone complete resection~~completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma, in the adjuvant setting.
- **Non-small cell lung cancer (NSCLC)**
  - Adult patients with resectable (tumors ≥ 4 cm or node positive) NSCLC in the neoadjuvant setting, in combination with platinum-doublet chemotherapy.
  - Adult patients with metastatic NSCLC 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 NSCLC with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy.
  - Adult 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)**
  - Adult patients with advanced renal cell carcinoma (RCC) who have received prior antiangiogenic therapy.
  - Adult patients with advanced renal cell carcinoma, as a first-line treatment in combination with cabozantinib.
  - Adult patients with intermediate or poor risk advanced RCC, as a first-line treatment 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)**
  - Adult patients with recurrent or metastatic SCCHN with disease progression on or after a platinum-based therapy.
- **Urothelial carcinoma (UC)**
  - Adjuvant treatment of adult patients with UC who are at high risk of recurrence after undergoing radical resection of UC.
  - Adult patients with ~~locally advanced~~unresectable or metastatic UC~~ who:*~~, as first-line treatment in combination with cisplatin and gemcitabine.
  - Adult 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)**
  - Adult patients with HCC who have been previously treated with sorafenib in combination with ipilimumab.*
- **Esophageal cancer**
  - As adjuvant treatment in adult patients with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease who have received neoadjuvant chemoradiotherapy (CRT).
  - In combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).
  - In combination with ipilimumab for the first-line treatment of adult patients with unresectable advanced or metastatic ESCC.
  - Adult patients with unresectable advanced, recurrent, or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy.
- **Gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma**
  - Adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing 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 Louisiana Healthcare Connections that Opdivo is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Melanoma (must meet all)**:**

1. Diagnosis of unresectable, metastatic, or lymph node positive melanoma; that is either (a or b):
   a. Unresectable or metastatic;
   b. Resected stage IIB, IIC, or III;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 12 years;
4. Request meets one of the following (a, b, or c):*
   a. If prescribed as monotherapy (unresectable or metastatic disease, or adjuvant treatment), dose does not exceed any of the following (i or ii):
      i. Adult and pediatric members weighing ≥ ≥ 40 kg: 240 mg every 2 weeks or 480 mg every 4 weeks;
      ii. Pediatric members weighing < 40 kg: 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks (*see Appendix E for dose rounding guidelines*);
   b. If prescribed in combination with Yervoy® (unresectable or metastatic disease), dose does not exceed any of the following (i or ii; *see Appendix E for dose rounding guidelines*):
      i. Adult and pediatric members weighing ≥ ≥ 40 kg: 1 mg/kg every 3 weeks for 4 doses, followingfollowed by 240 mg every 2 weeks or 480 mg every 4 weeks;
      ii. Pediatric members weightingweighing < 40 kg: 1 mg/kg every 3 weeks for 4 doses, followed by 3 mg/kg every 2 weeks or 6 mg/kg 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).

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

Approval duration: 6 months

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

1. Diagnosis of resectable, 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. For resectable NSCLC: Both of the following are met (a and b):
   a. Opdivo is prescribed as neoadjuvant treatment;
   b. Tumors ≥ 4 cm or node positive disease;
6. For recurrent, advanced, or metastatic NSCLC: Opdivo is prescribed in one of the following ways (a, b, or cb):

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.~~b. 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*

7. Request meets one of the following (a, b, c, d, or e):*
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~~360 mg~~/kg~~ every ~~2~~3 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. In combination with platinum-doublet chemotherapy, both of the following are met (i and ii):
i. Dose does not exceed 360 mg every 3 weeks;
ii. Request does not exceed 3 cycles;
e. 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 *(9 weeks for neoadjuvant NSCLC)*

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~~;~~ *(off-label)*;
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

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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~~;~~ or palliative therapy (*off-label*);
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. ~~Prescribed~~Opdivo is prescribed in one of the following ways (a, b, or c):
~~4.~~ For use as a single agent~~;~~
   ~~5.~~a. ~~Disease~~, and disease has progressed on or after a platinum-containing regimen (e.g., cisplatin, carboplatin);
   b. For use in combination with cisplatin and gemcitabine (*off-label*);
   c. For use in combination with Erbitux® as first-line therapy (*off-label*);
~~6.~~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;

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2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. One of the following (a, b, c, or ~~e~~d):
   a. Failure of a platinum-containing regimen (e.g., cisplatin, carboplatin), unless clinically significant adverse effects are experienced or all are contraindicated;
   b. Prescribed as adjuvant treatment and member is at high risk of recurrence after undergoing resection of UC;
   c. Member is at high risk of recurrence and did not previously receive a platinum-containing regimen;
   d. Prescribed as first-line treatment in combination with cisplatin and gemcitabine;
5. Request meets one of the following (a, b, or ~~b~~c):*
   a. Monotherapy: Dose does not exceed 240 mg every 2 weeks or 480 mg every 4 weeks;
   b. In combination with cisplatin and gemcitabine: Dose does not exceed 360 mg every 3 weeks (for up to 6 cycles), followed by 240 mg every 2 weeks or 480 mg every 4 weeks;
   ~~b.~~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

H. Colorectal Cancer (must meet all)**:**

1. Diagnosis of unresectable ~~or,~~ metastatic, or advanced CRC;
2. Tumor is characterized as MSI-H, dMMR, or ~~dMMR;~~*(off-label)* polymerase epsilon/delta (POLE/POLD1);
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~~If prescribed as monotherapy, dose does not exceed either of the following (i or ii):
      ~~a.~~i. Adult and pediatric members weighing ≥ 40 kg: 240 mg every 2 weeks~~;~~ or 480 mg every 4 weeks;
      ii. ~~In~~Pediatric members weighing < 40 kg: 3 mg/kg every 2 weeks (*see Appendix E for dose rounding guidelines*);
   b. If prescribed in combination with Yervoy, dose does not exceed either of the following (i or ii; *see Appendix E for dose rounding guidelines*):
      ~~b.~~i. Adult and pediatric members weighing ≥ 40 kg: 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);~~;
      ii. Pediatric members weighing < 40 kg: 3 mg/kg every 3 weeks for 4 doses, followed by 3 mg/kg 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)*.

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

Approval duration: 6 months

I. Hepatocellular Carcinoma (must meet all)**:**

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1. Diagnosis of HCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. One of the following (a or b):
   a. Documentation of Child-Pugh Class A status and both of the following (i and ii):
      ~~4.~~i. Member has had disease progression following treatment with Nexavar®, Lenvima®, Tecentriq® + bevacizumab (*Mvasi® and Zirabev™ are preferred*), or Imfinzi®;
      **Prior authorization may be required for Nexavar, Lenvima, Tecentriq, bevacizumab, and Imfinzi.*
      ~~5.~~ii. Prescribed in combination with Yervoy;
   ~~6.~~b. Documentation of Child-Pugh Class ~~A~~B status~~;~~ and prescribed as a single agent *(off-label)*;
~~7.~~5. Dose does not exceed one of the following (a or b):*
   a. 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*);
   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

J. Esophageal Cancer (must meet all)**:**

1. Diagnosis of one of the following (a, b, or ~~b~~c):
   a. Completely resected esophageal cancer or gastroesophageal junction (esophagogastric junction; EGJ) cancer;
   b. Unresectable advanced, recurrent, or metastatic ESCC;
   c. MSI-H or dMMR esophageal cancer or EGJ cancer (*off-label*);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. For completely resected esophageal cancer or EGJ cancer, member meets both of the following (a and b):
   a. Member has residual pathologic disease;
   b. Member has previously received CRT;
5. For ESCC, one of the following (a or b):
   a. For unresectable advanced or metastatic disease: Prescribed in combination with Yervoy or with fluoropyrimidine- and platinum-containing chemotherapy;
   b. For unresectable advanced, recurrent, or metastatic disease: Member has had previous treatment with a fluoropyrimidine-based (e.g., 5-fluorouracil, capecitabine) and platinum-based (e.g., carboplatin, cisplatin, oxaliplatin) chemotherapy;
6. For MSI-H or dMMR cancers, prescribed in combination with Yervoy or with fluoropyrimidine-containing chemotherapy (e.g., 5-fluorouracil, capecitabine) and oxaliplatin;
~~6.~~7. Request meets one of the following (a, b, or c):*
   a. ESCC in combination with Yervoy: Dose does not exceed 3 mg/kg every 2 weeks or 360 mg every 3 weeks;

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b. Other indications: Dose does not exceed 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)*.

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

Approval duration: 6 months

K. Gastric and Esophageal Adenocarcinomas (must meet all)**:**

1. Diagnosis of gastric cancer, EGJ cancer, or esophageal adenocarcinoma;
2. Member meets one of the following (a, b, or ~~b~~c):
   a. Disease is advanced, recurrent, or metastatic;
   b. For EGJ cancer or esophageal adenocarcinoma: ~~member~~Member meets one of the following (i or ii):
      i. Member is post-operative following chemoradiation;
      ii. Disease is advanced, recurrent, or metastatic;
   c. Tumor is characterized as MSI-H or dMMR (*off-label*);
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. For advanced, recurrent, or metastatic disease~~:~~, both of the following ~~are met~~ (a and b):
   a. Prescribed in combination with a fluoropyrimidine- (e.g., 5-fluorouracil, capecitabine) and platinum-containing (e.g., carboplatin, cisplatin, oxaliplatin) chemotherapy;
   b. Disease is HER2-negative;
6. For MSI-H or dMMR cancers, prescribed in combination with Yervoy or with fluoropyrimidine-containing chemotherapy (e.g., 5-fluorouracil, capecitabine) and oxaliplatin;
~~6.~~7. Request meets one of the following (a or b):*
   a. Dose does not exceed 240 mg every 2 weeks or 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

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

1. Diagnosis of one of the following (a-~~o~~t):
   a. Squamous cell anal carcinoma that is recurrent or metastatic;
   b. Merkel cell carcinoma;
   c. Gestational trophoblastic neoplasia;
   d. Uveal melanoma that is metastatic or unresectable;
   ~~e. Small bowel adenocarcinoma that is advanced or metastatic;~~
   ~~f.~~e. Extranodal NK/T-cell lymphoma, nasal type, that is relapsed or refractory;
   ~~g.~~f. Pediatric Hodgkin lymphoma, as subsequent therapy;
   ~~h.~~g. Vulvar cancer ~~–~~ HPV-related advanced, recurrent, or metastatic disease, as second-line treatment;
   ~~i.~~h. Cervical cancer;
   ~~j.~~i. Endometrial carcinoma that is recurrent or metastatic;

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~~k.~~j. Small cell lung cancer, as subsequent therapy;
~~l.~~k. Bone cancer (e.g., Ewing Sarcoma, chordoma, osteosarcoma, chondrosarcoma);
~~m.~~l. Central nervous system (CNS) cancer (e.g., brain metastases);
~~n.~~m. ~~Pediatric primary~~Primary mediastinal large B-cell lymphoma that is relapsed or refractory;
~~o.~~n. Pediatric diffuse high-grade gliomas;
o. One of the following MSI-H or dMMR cancers (i, ii, or iii):
   i. Ampullary adenocarcinoma;
   ii. Small bowel adenocarcinoma that is unresectable or metastatic;
   iii. Endometrial carcinoma that is recurrent or metastatic, as subsequent therapy;
p. Small bowel adenocarcinoma with POLE/POLD1 mutation;
q. One of the following biliary tract cancers that is unresectable, resected gross residual (R2), or metastatic (i, ii, or iii):
   i. Extrahepatic cholangiocarcinoma;
   ii. Intrahepatic cholangiocarcinoma;
   iii. Gallbladder cancer;
r. Classic Kaposi sarcoma, as subsequent therapy;
s. One of the following unresectable or metastatic soft tissue sarcomas (i – vii):
   i. Tumor classified as TMB high (TMB-H) (i.e., ≥ 10 mutations/megabase [mut/Mb]);
   ii. Angiosarcoma;
   iii. Myxofibrosarcoma;
   iv. Undifferentiated pleomorphic sarcoma;
   v. Dedifferentiated liposarcoma;
   vi. Undifferentiated sarcomas;
   vii. Pleomorphic rhabdomyosarcoma, as subsequent therapy;
t. Anaplastic thyroid carcinoma that is metastatic;

2. Prescribed by or in consultation with an oncologist;
3. For anal carcinoma: prescribed prior to resection or as second line or subsequent therapy (examples of prior therapy include 5-FU/cisplatin, carboplatin/paclitaxel, FOLFOX, FOLFCIS);
4. For gestational trophoblastic neoplasia: prescribed as a single agent for multi-agent chemotherapy-resistant disease (*see Appendix B*) in one of the following settings (a or b):
   a. Recurrent or progressive intermediate trophoblastic tumor following treatment with a platinum-containing regimen (e.g., cisplatin, carboplatin);
   b. High-risk disease (*see Appendix D*);
5. For ~~pediatric~~ primary mediastinal large B-cell lymphoma: prescribed as one of the following (a or b):
   a. As a single agent ~~as second line therapy after failure of induction therapy/initial treatment (*see appendix B*);~~ ;
   b. Combination with brentuximab vedotin as consolidation/additional therapy;
6. For pediatric diffuse high-grade gliomas: prescribed as a single agent for adjuvant therapy or for recurrent/progressive disease;

7. For Merkel cell carcinoma, uveal melanoma, ~~bone cancer,~~ CNS cancer, hepatobiliary cancer, small bowel adenocarcinoma, soft tissue sarcoma: prescribed as a single agent or in combination with Yervoy;
   **Prior authorization may be required for Yervoy.*
8. For bone cancer, ampullary adenocarcinoma, Kaposi sarcoma: prescribed in combination with Yervoy;
9. For endometrial carcinoma, anaplastic thyroid carcinoma: prescribed as a single agent;
~~8.~~10. For cervical cancer: prescribed as second line or subsequent therapy for PD-L1 tumor expression of ≥ 1%;
~~9.~~11. 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

M. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to LA.PMN.255
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy LA.PMN.53

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via Louisiana Healthcare Connections 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, c, d, e, or f~~ - h):*
   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, and gastric and esophageal adenocarcinomas: New dose does not exceed 360 mg every 3 weeks;
   c. ESCC in combination with Yervoy: New dose does not exceed 3 mg/kg every 2 weeks or 360 mg every 3 weeks;
   d. Melanoma (i or ii):
      i. If prescribed as monotherapy (unresectable or metastatic disease, or adjuvant treatment), new dose does not exceed any of the following (a or b):
         a) Adult and pediatric members weighing ≥ 40 kg: 240 mg every 2 weeks or 480 mg every 4 weeks;
         b) Pediatric members weighing < 40 kg: 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks;
      ii. If prescribed in combination with Yervoy (unresectable or metastatic disease), new dose does not exceed any of the following (a or b):

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a) Adult and pediatric members weighing ≥ ~~40kg~~40 kg: 1 mg/kg every 3 weeks for 4 doses, followed by 240 mg every 2 weeks or 480 mg every 4 weeks;
b) Pediatric members weighing < 40 kg: 1 mg/kg every 3 weeks for 4 doses, followed by 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks;

e. UC (i or ii):
i. If prescribed as monotherapy, new dose does not exceed 240 mg every 2 weeks or 480 mg every 4 weeks;
ii. If prescribed in combination with cisplatin and gemcitabine, new dose does not exceed 360 mg every 3 weeks (for up to 6 cycles), followed by 240 mg every 2 weeks or 480 mg every 4 weeks;

f. CRC (i or ii):
i. If prescribed as monotherapy, new dose does not exceed either of the following (a or b):
a) Adult and pediatric members weighing ≥ 40 kg: 240 mg every 2 weeks or 480 mg every 4 weeks;
b) Pediatric members weighing < 40 kg: 3 mg/kg every 2 weeks (*see Appendix E for dose rounding guidelines*);
ii. If prescribed in combination with Yervoy, new dose does not exceed either of the following (a or b; *see Appendix E for dose rounding guidelines*):
a) Adult and pediatric members weighing ≥ 40 kg: 3 mg/kg every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks;
b) Pediatric members weighing < 40 kg: 3 mg/kg every 3 weeks for 4 doses, followed by 3 mg/kg every 2 weeks;

~~e.~~g. Other indications: New dose does not exceed 240 mg every 2 weeks or 480 mg every 4 weeks;

~~f.~~h. 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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to LA.PMN.255
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy LA.PMN.53

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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 LA.PMN.53

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
CNS: central nervous system
CRC: colorectal cancer
dMMR: mismatch repair deficient
EGFR: epidermal growth factor receptor
EGJ: esophagogastric junction
ESCC: esophageal squamous cell carcinoma
FDA: Food and Drug Administration
HCC: hepatocellular carcinoma
HER-2: human epidermal growth factor receptor-2
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
POLE: polymerase epsilon
POLD: polymerase delta
RCC: renal cell carcinoma
ROS1: ROS proto-oncogene 1
SCLC: small cell lung cancer
TMB: ~~Tumor Mutational Burden~~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 (Nexavar)	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
Tecentriq (atezolizumab) + bevacizumab (Avastin®, Mvasi, Zirabev)	HCC Tecentriq: 840 mg IV every 2 weeks, 1,200 mg IV every 3 weeks, or 1,680 mg IV every 4 weeks Bevacizumab: 15 mg/kg IV every 3 weeks	See regimen
Imfinzi (durvalumab)*	HCC 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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
platinum-containing regimens	NSCLC – squamous cell carcinoma: paclitaxel + carboplatin dose varies NSCLC – nonsquamous cell carcinoma: pemetrexed + [carboplatin or cisplatin] dose varies UC, SCCHN: Varies	Varies
Multiagent chemotherapy regimens examples: EMA/CO (etoposide, methotrexate, dactinomycin/cyclophosphamide, vincristine), EMA/EP (etoposide, methotrexate, dactinomycin/etoposide, cisplatin)	Gestational Trophoblastic Neoplasia: Varies	Varies
~~Dose-adjusted EPOCH-R, R-CHOP with radiation therapy, or LMB-modified B/C chemotherapy with rituximab~~	~~Pediatric primary mediastinal large B-cell lymphoma: Varies~~	~~Varies~~
Yervoy (ipilimumab)	Melanoma, HCC: 3 mg/kg IV every 3 weeks for a maximum of 4 doses RCC, CRC: 1 mg/kg IV every 3 weeks for a maximum of 4 doses NSCLC, malignant pleural mesothelioma, ESCC: 1 mg/kg IV every 6 weeks	See regimen

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.
**Off-label*

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 IV ~~-~~or a prognostic score ≥ 7~~.~~
  - FIGO staging system:

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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
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: • Adult and pediatric patients weighing ≥ 40 kg: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks • Pediatric patients weighing < 40 kg: 3 mg/kg IV every 2 weeks or 6 mg/kg IV every 4 weeks With ipilimumab: • Adult and pediatric patients weighing ≥ 40 kg: 1 mg/kg IV, followed by ipilimumab 3 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 • Pediatric patients weighing < 40 kg: 1 mg/kg IV, followed by ipilimumab 3 mg/kg on the same day, every 3 weeks for 4 doses, then nivolumab 3 mg/kg IV every 3 weeks or 6 mg/kg mg IV every 6 weeks	See regimen
Melanoma (adjuvant treatment)	• Adult and pediatric patients weighing ≥ 40 kg: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks • Pediatric patients weighing < 40 kg: 3 mg/kg IV every 2 weeks or 6 mg/kg IV every 4 weeks Until disease recurrence or unacceptable toxicity for up to 1 year	See regimen
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~~RCC – advanced previously untreated	Monotherapy or with cabozantinib: 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 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	See regimen~~Monotherapy: 480 mg/dose~~ ~~With ipilimumab: 3 mg/kg/dose~~

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Indication	Dosing Regimen	Maximum Dose
~~RCC – advanced previously untreated~~UC	Monotherapy~~ or with cabozantinib: ~~: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks With ~~ipilimumab: 3~~cisplatin and gemcitabine: 360 mg~~/kg~~ IV every 3 weeks, followed by ~~ipilimumab 1 mg/kg IV~~ cisplatin and gemcitabine on the same day every 3 weeks for ~~4 doses~~up to 6 cycles, then nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks until disease progression, unacceptable toxicity, or up to 2 years from first dose	~~480 mg/dose~~See regimen
~~HCC~~MSI-H/dMMR CRC	Monotherapy: • Adult and pediatric patients weighing ≥ 40 kg: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks • Pediatric patients weighing < 40 kg: 3 mg/kg IV every 2 weeks With ipilimumab: ~~nivolumab 1 mg/kg~~ • Adult and pediatric patients weighing ≥ 40 kg: 3 mg/kg IV, followed by ipilimumab ~~3~~1 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 • Pediatric patients weighing < 40 kg: 3 mg/kg IV, followed by ipilimumab 1 mg/kg on the same day, every 3 weeks for 4 doses, then nivolumab ~~240~~3 mg/kg IV every 2 weeks ~~or 480 mg IV every 4 weeks until disease progression or unacceptable toxicity~~	~~480 mg/dose~~See regimen
HCC	With ipilimumab: 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 nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks	See regimen
NSCLC	Monotherapy: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks ~~until disease progression or unacceptable toxicity~~	~~Monotherapy: 480 mg/dose~~

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Indication	Dosing Regimen	Maximum Dose
	With ipilimumab: ~~nivolumab 3~~360 mg~~/kg~~ IV every ~~2~~3 weeks and ipilimumab 1 mg/kg IV every 6 weeks until disease progression, unacceptable 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 platinum-doublet chemotherapy: ~~nivolumab~~ 360 mg IV every 3 weeks with platinum-doublet chemotherapy on the same day every 3 weeks for 3 cycles	~~With ipilimumab: 3 mg/kg/dose~~ ~~With platinum doublet with or without ipilimumab: 360 mg/dose~~See regimen
Esophageal cancer	Adjuvant treatment of resected esophageal or GEJ cancer: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks for a total treatment duration of 1 year ESCC: until disease progression, unacceptable toxicity, or up to 2 years: • As a single agent or in combination with fluoropyrimidine- and platinum-containing chemotherapy: 240 mg every 2 weeks or 480 mg every 4 weeks • In combination with ipilimumab: ~~nivolumab~~ 3 mg/kg every 2 weeks or 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks	See regimen
Gastric cancer, EGJ cancer, and esophageal adenocarcinoma	With fluoropyrimidine- and platinum-containing chemotherapy: 240 mg every 2 weeks or 360 mg every 3 weeks	360 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

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VI. Product Availability

Single-dose vials: 40 mg/4 mL, 100 mg/10 mL, 120 mg/12 mL, 240 mg/24 mL

VII. References

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Coding Implications

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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	LDH Approval Date
Converted corporate to local policy	01.21	04.21
FDA approved malignant pleural mesothelioma added. 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; added new FDA approved indication of use in combination with cabozantinib as first-line therapy for advanced RCC; Added new FDA-approved indications of gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma; Added new FDA-approved indication of completely resected esophageal or gastroesophageal junction cancer;	04.22	07.23.22

Reviews, Revisions, and Approvals	Date	LDH Approval Date
Per updated prescribing information removed use in HCC as a single agent; for UC added indication for adjuvant treatment; updates made per NCCN: for urothelial carcinoma removed requirement for resection to be radical as NCCN also supports partial resection prior to adjuvant therapy and added treatment option of highrisk recurrence as an optional criterion; added cervical cancer as off-label indication; updated gestational trophoblastic neoplasia treatment settings; added criterion for use as singleagent therapy for SCCHN; clarified uveal melanoma to be metastatic; removed "metastatic" designation for Merkel cell carcinoma; clarified small bowel adenocarcinoma be advanced or metastatic; small cell lung cancer indication added; clarified extranodal NK/T-cell lymphoma to be relapsed or refractory.		
Added new FDA-approved indication of neoadjuvant use in NSCLC. Criteria added for new FDA approved indication for first-line use in ESCC in combination with Yervoy or with fluoropyrimidine- and platinum-containing chemotherapy; for HCC, added additional options for prior use of Tecentriq+bevacizumab or Imfinzi and removed requirement for no previous treatment with a checkpoint inhibitor per latest NCCN guidelines. Added off-label criteria for bone cancer, central nervous system cancers, pediatric primary mediastinal large Bcell lymphoma, pediatric diffuse high-grade gliomas per NCCN 2A recommendations; removed age restriction from off-label criteria; updated Appendix D to simplify definition of high-risk disease in GTN to mirror the 2023 NCCN GTN guidelines. Template changes applied to other diagnoses/indications. References reviewed and updated. Added blurb this for medical benefit only. Updated criteria for melanoma to reflect FDA approved pediatric age extension; updated Appendix B.	06.27.23	01.03.24
Annual review: updated indication and criteria for the treatment of melanoma in the adjuvant setting. HCC, added option for Child-Pugh Class B and prescribed as a single agent per NCCN 2A recommendation; references reviewed and updated.	05.07.24	

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. LHCC makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing

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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 LHCC administrative policies and procedures.

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