Clinical Policy: Ipilimumab (Yervoy)

Reference Number: LA.PHAR.319
Effective Date: 11.03.24
Last Review Date: 05.09.25
Line of Business: Medicaid

Coding Implications
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

Ipilimumab (Yervoy®) is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody.

FDA Approved Indication(s)

Yervoy is indicated for:

- **Unresectable or metastatic melanoma**
  - Treatment of unresectable or metastatic melanoma in adults and pediatric patients 12 years and older as a single agent or in combination with nivolumab
- **Adjuvant treatment of melanoma**
  - Adult patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy
- **Renal cell carcinoma (RCC)**
  - Treatment of patients with intermediate or poor risk advanced renal cell carcinoma, as first-line treatment in combination with nivolumab
- **Colorectal cancer (CRC)**
  - Treatment of adult and pediatric patients 12 years of age and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab*
- **Hepatocellular carcinoma (HCC)**
  - In combination with nivolumab, the treatment of adult patients with HCC who have been previously treated with sorafenib*
- **Non-small cell lung cancer (NSCLC)**
  - In combination with nivolumab, for the first-line treatment of adult patients with metastatic NSCLC whose tumors express programmed death-ligand 1 (PD-L1) ≥ 1% as determined by an FDA-approved test, with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations
  - In combination with nivolumab and 2 cycles of platinum-doublet chemotherapy, for the first-line treatment of adult patients with metastatic or recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations
- **Malignant pleural mesothelioma**

- Treatment of adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with nivolumab

- **Esophageal cancer**
  - Treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC), as first line treatment in combination with nivolumab

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*This indication is approved under accelerated approval based on 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 (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 Yervoy is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

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

1. Diagnosis of melanoma, and disease meets one of the following (a or b);
   a. Unresectable or metastatic;
   b. Resectable, limited resectable, or lymph node positive;
2. Prescribed by or in consultation with an oncologist;
3. Age is one of the following (a or b):
   a. For unresectable or metastatic disease: ≥ 12 years;
   b. For adjuvant treatment: ≥ 18 years;
4. Prescribed in one of the following ways (a, b, or c):
   a. As a single agent;
   b. In combination with Opdivo®*;
   c. In combination with Keytruda® or Imlygic* for unresectable or metastatic melanoma (*off-label*);
   **Prior authorization may be required for Opdivo and Keytruda*
5. Request meets one of the following (a, b, or c):*
   a. Unresectable or metastatic disease: Dose does not exceed 3 mg per kg every 3 weeks for a maximum of 4 doses;
   b. Adjuvant treatment: Dose does not exceed 3 mg/kg every 3 weeks for 4 doses, followed by 3 mg/kg every 12 weeks for up to 4 additional doses;
   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. Renal Cell Carcinoma (must meet all)**:**

1. Diagnosis of advanced or metastatic RCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 12 years;
4. Prescribed in combination with Opdivo;*

**Prior authorization may be required for Opdivo*

5. Request meets one of the following (a or b):*
   a. Dose does not exceed 1 mg/kg IV every 3 weeks for a maximum of 4 doses;
   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: 16 weeks (maximum of 4 doses)

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

1. Diagnosis of or CRC with one of the following mutations (a, b, or c):
   a. MSI-H;
   b. dMMR;
   c. Polymerase epsilon/delta (POLE/POLD1);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 12 years;
4. Disease is unresectable or metastatic;
5. Prescribed in combination with Opdivo*;

   **Prior authorization may be required for Opdivo*
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 1 mg/kg IV every 3 weeks for a maximum of 4 doses;
   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: 16 weeks (maximum of 4 doses)

D. 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 previously received Nexavar®, Lenvima®, or Tecentriq® + bevacizumab (*Mvasi® and Zirabev™ are preferred*), or Imfinzi®;

   **Prior authorization may be required for Nexavar, Lenvima, Tecentriq, bevacizumab, and Imfinzi*
5. Prescribed in combination with Opdivo;

   **Prior authorization may be required for Opdivo*
6. Documentation of Child-Pugh Class A status;
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 3 mg/kg IV every 3 weeks for a maximum of 4 doses;
   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: 16 weeks (maximum of 4 doses)

E. 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. Prescribed in combination with Opdivo;*

   **Prior authorization may be required for Opdivo*

5. Member does not have contraindications to PD-1/PD-L1 inhibitor therapy (e.g., Opdivo, Keytruda, Tecentriq, Imfinzi) (*see Appendix D*);
6. Request meets one of the following (a, b, or c):
   a. Disease mutation status is negative for actionable biomarkers (EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET and ERBB2 [HER2]), and member has not received prior systemic therapy for advanced disease;
   b. Disease mutation status is positive for EGFR S768I, L861Q, and/or G719X, and member has received prior afatinib, osimertinib, erlotinib, gefitinib, or dacomitinib;*
   c. Disease mutation status is positive for EGFR exon 20, KRAS G12C, NRTK1/2/3, BRAF V600E, MET exon 14 skipping, NRG1 gene fusion, or ERBB2 (HER2);
   **Prior authorization may be required*
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 1 mg/kg IV every 6 weeks in combination with Opdivo;
   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. Malignant Pleural Mesothelioma (must meet all)**:**
1. Diagnosis of malignant pleural mesothelioma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed in combination with Opdivo;*
   **Prior authorization may be required for Opdivo.*
5. Request meets one of the following (a or b):*
   a. Dose does not exceed 1 mg/kg IV every 6 weeks in combination with Opdivo;
   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. Esophageal Cancer (must meet all)**:**
1. Diagnosis of ESCC and one of the following (a or b):
   a. Disease is unresectable advanced or metastatic;
   b. Prescribed as induction, neoadjuvant, or perioperative therapy (*off-label*);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed in combination with Opdivo;*
   **Prior authorization may be required for Opdivo.*
5. Request meets one of the following (a or b):*
   a. Dose does not exceed 1 mg/kg IV every 6 weeks in combination with Opdivo;
   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. NCCN Compendium Indications (off-label) (must meet all)**:**
1. Diagnosis of one of the following (a-i):
   a. One of the following MSI-H or dMMR tumor cancers (i-iv):
      i. Small bowel adenocarcinoma;
      ii. Ampullary adenocarcinoma;
      iii. Gastric cancer;
      iv. Esophageal adenocarcinoma;
   b. Bone cancer (e.g., chondrosarcoma, osteosarcoma, chordoma, Ewing sarcoma), and both of the following (i and ii):
      i. Disease is unresectable or metastatic with tissue tumor mutation burden-high tumors with 10 or more mutations per megabase;
      ii. Disease has progressed following prior treatment and no satisfactory alternative treatment options exist;
   c. BRAF non-specific melanoma brain metastases;
   d. Biliary tract cancer (e.g., gallbladder, intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma);
   e. Gestational trophoblastic neoplasia;
   f. Classic Kaposi sarcoma as subsequent systemic therapy;
   g. Metastatic or unresectable uveal melanoma;
   h. Merkel cell carcinoma;
   i. Soft tissue sarcoma and one of the following (i or ii):
      i. Disease is angiosarcoma;
      ii. Prescribed as subsequent therapy for advanced or metastatic disease, and disease is one of the following (1-6):
         1) Tumor mutation burden-high (≥ 10 mutations per megabase);
         2) Myxofibrosarcoma;
         3) Undifferentiated pleomorphic sarcoma;
         4) Dedifferentiated liposarcoma;
         5) Cutaneous angiosarcoma;
         6) Undifferentiated sarcomas;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 12 years;
4. Prescribed in combination with Opdivo for all of the following (a-e):*
   a. One of the following MSI-H or dMMR tumor cancers (i-iv):
      i. Small bowel adenocarcinoma;
      ii. Ampullary adenocarcinoma;
      iii. Gastric cancer;
      iv. Esophageal adenocarcinoma;
   b. Bone cancer;
   c. Biliary tract cancer;
   d. Gestational trophoblastic neoplasia;
   e. Classic Kaposi sarcoma;
5. Prescribed as a single agent or in combination with Opdivo for all of the following (a-d):*
   a. Brain metastases;
   b. Uveal melanoma;

c. Merkel cell carcinoma;
d. Soft tissue sarcoma

**Prior authorization may be required for Opdivo*

6. 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

I. 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
   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. Melanoma - Unresectable or Metastatic

1. Reauthorization beyond 16 weeks is not permitted. Members must meet the initial approval criteria, at a minimum of 3 months since initial treatment discontinuation.

Approval duration: Not applicable

B. Renal Cell Carcinoma, Colorectal Cancer, Hepatocellular Carcinoma

1. Reauthorization beyond 16 weeks is not permitted. Members must meet the initial approval criteria.

Approval duration: Not applicable

C. Melanoma (Adjuvant Treatment), Non-Small Cell Lung Cancer, Malignant Pleural Mesothelioma, Esophageal Cancer (must meet all)**:**

1. Currently receiving medication via Louisiana Healthcare Connections benefit, or documentation supports that member is currently receiving Yervoy 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. For melanoma: New dose does not exceed 3 mg/kg every 12 weeks for up to 4 additional doses;
   b. For NSCLC, malignant pleural mesothelioma, and ESCC: New dose does not exceed 1 mg/kg IV every 6 weeks in combination with Opdivo;
   c. 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 or up to 4 additional doses (cutaneous melanoma) or 2 years (NSCLC, malignant pleural mesothelioma, ESCC), whichever is less

D. NCCN Compendium Indications (off-label) (must meet all)**:**

1. Currently receiving medication via Louisiana Healthcare Connections benefit, or documentation supports that member is currently receiving Yervoy for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. 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: 12 months

E. 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
   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

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
CRC: colorectal cancer
CTLA-4: cytotoxic T-lymphocyte antigen 4
dMMR: mismatch repair deficient
EGFR: epidermal growth factor receptor
FDA: Food and Drug Administration
HCC: hepatocellular carcinoma
MET: mesenchymal-epithelial transition
MSI-H: microsatellite instability-high
PD-1: programmed death-1
PD-L1: programmed death-ligand 1
RCC: renal cell carcinoma
ROS1: ROS proto-oncogene 1

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	800 mg/day
Lenvima (lenvatinib)	**HCC** 12 mg PO QD (patients ≥ 60 kg) or 8 mg PO QD (patients < 60 kg)	12 mg/day
Tecentriq (atezolizumab) +	**HCC**	See regimen

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
bevacizumab (Avastin®, Mvasi, Zirabev)	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	
Imfinzi (durvalumab)*	**HCC** Varies	Varies
platinum-containing regimens	**NSCLC – squamous cell carcinoma** paclitaxel + carboplatin dose varies **NSCLC – nonsquamous cell carcinoma** pemetrexed + [carboplatin or cisplatin] dose varies	Varies
EGFR S768I, L861Q, and/or G719X targeted therapies: afatinib, osimertinib, erlotinib, gefitinib, dacomitinib	**NSCLC** 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.
**Off-label*

Appendix C: Contraindications and Boxed Warnings

- Bristol-Myers Squibb was released from the REMS program for Yervoy in March 2015.
- Boxed warning(s): none reported
- Contraindication(s): none reported

Appendix D: General Information

- NCCN no longer recommends the use of Yervoy for the following indications:
  - Small cell lung cancer
  - NSLCLC with tumor mutation burden, RET rearrangement positive tumors, EGFR exon 19 deletion tumors, exon 21 L858R tumors, ALK rearrangement positive tumors, or ROS1 rearrangement positive tumors
  - Cutaneous melanoma, as adjuvant systemic therapy in combination with Opdivo if no evidence of disease following metastasis-directed therapy or systemic therapy for oligometastatic disease
  - Colon cancer for patients who are not appropriate for intensive therapy
  - Hepatocellular carcinoma with tumor mutation burden-high

- Per NCCN, contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents, and some oncogenic drivers (i.e., EGFR exon 19 deletion or exon 21 L858R, ALK, RET, or ROS1 rearrangements have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Melanoma (adjuvant treatment)	3 mg/kg IV every 3 weeks up to a maximum of 4 doses, followed by 3 mg/kg every 12 weeks for up to 4 additional doses.	3 mg/kg/dose
Melanoma (unresectable or metastatic)	Monotherapy: 3 mg/kg IV every 3 weeks for a maximum of 4 doses In combination with nivolumab: 3 mg/kg every 3 weeks with nivolumab 1 mg/kg for a maximum of 4 doses or until unacceptable toxicity, whichever occurs earlier.	3 mg/kg/dose
RCC	1 mg/kg every 3 weeks with nivolumab 3 mg/kg for a maximum of 4 doses.	1 mg/kg/dose
CRC	1 mg/kg every 3 weeks with nivolumab 3 mg/kg	1 mg/kg/dose
HCC	3 mg/kg every 3 weeks with nivolumab 1 mg/kg for 4 doses	3 mg/kg/dose
NSCLC	In combination with nivolumab: 1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression In combination with nivolumab and platinum-doublet chemotherapy: 1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks and 2 cycles of histology-based platinum-doublet chemotherapy every 3 weeks until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression	1 mg/kg/dose
Malignant pleural mesothelioma	1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.	1 mg/kg/dose
ESCC	1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks or 360 mg every 3 weeks until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.	1 mg/kg/dose

VI. Product Availability

Single-use vials: 50 mg/10 mL, 200 mg/40 mL

VII. References

1. Yervoy Prescribing information. Princeton, NJ: Bristol-Myers Squibb Company; January 2025. Available at: https://packageinserts.bms.com/pi/pi_yervoy.pdf. Accessed January 30, 2025.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed January 30, 2025.
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4. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer Version 3.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed January 30, 2025.
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6. National Comprehensive Cancer Network. Hepatocellular Carcinoma, Version 4.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hcc.pdf. Accessed January 30, 2025.
7. National Comprehensive Cancer Network. Esophageal and Esophagogastric Junction Cancers, Version 5.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Accessed January 30, 2025.
8. National Comprehensive Cancer Network. Melanoma: Cutaneous, Version 2.2025. Available at: www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed January 30, 2025.
9. National Comprehensive Cancer Network. Kidney Cancer, Version 3.2025. Available at: www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed January 30, 2025.
10. National Comprehensive Cancer Network. Colon Cancer, Version 6.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed January 30, 2025.
11. National Comprehensive Cancer Network. Rectal Cancer, Version 5.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed January 30, 2025.

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
J9228	Injection, ipilimumab, 1 mg

Reviews, Revisions, and Approvals	Date	LDH Approval Date
Converted corporate to local policy	04.22	07.01.22
Criteria added for new FDA approved indication of ESCC in combination with Opdivo; for HCC, added additional option for prior use of Imfinzi and removed requirement for no previous treatment with a checkpoint inhibitor per latest NCCN guidelines. For melanoma clarified combination use with Keytruda and removed combination use with Imlygic per NCCN 2B recommendation; updated FDA indication for RCC to mirror PI; revised NSCLC criteria to include additional requirements related to mutation status, added off-label use for MSI-H/dMMR ampullary adenocarcinoma, bone cancer, brain metastases, and Kaposi sarcoma per NCCN compendium; Updated criteria for melanoma to reflect FDA approved pediatric age extension for use in combination with Opdivo and updated appendix B; references reviewed and updated.	06.02.23	10.05.23
Annual review: for melanoma, added criteria for resectable and limited resectable per NCCN 2A recommendations, removed specification to use combination Opdivo/Yervoy for only unresectable or metastatic melanoma; for colorectal cancer, added indication of POLE/POLD1 mutation per NCCN; for NSCLC ROS1 rearrangement, added reprotrectinib and lorlatinib as prior use option per NCCN; for malignant pleural mesothelioma, revised criteria to allow both unresectable and resectable disease per NCCN; for off-label NCCN compendium indication, added the following indications: MSI-H or dMMR gastric cancer, MSI-H or dMMR esophageal adenocarcinoma, biliary tract cancers, merkel cell carcinoma, and soft tissue sarcoma; references reviewed and updated.	06.11.24	09.04.24

Reviews, Revisions, and Approvals	Date	LDH Approval Date
Annual review: updated FDA indication for RCC and HCC to mirror PI; for melanoma, clarified combination use with Keytruda is off-label use per NCCN and revised adjuvant treatment maximum dosage per PI; for NSCLC per NCCN, added criteria for NRG1 gene fusion positive; removed criteria for the following mutations: RET rearrangement, EGFR exon 19 deletion, exon 21 L858R, ALK rearrangement, ROS1 rearrangement; for ESCC per NCCN, added off-label indication for prescribed as induction systemic therapy; for off-label NCCN compendium indications, consolidated MSI-H/dMMR cancers, revised biliary tract cancer criteria to allow primary treatment; in Appendix B, removed entries that are not redirections (Opdivo and Keytruda); in Appendix D, added no longer recommended indications; in Section V, clarified dosing regimen wording per PI; references reviewed and updated.	05.09.25	

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 this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

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.

This clinical policy is effective as of the date determined by LHCC. 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. LHCC 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.

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