Reference number(s)
2437-A

STANDARD MEDICARE PART B MANAGEMENT

YERVOY (ipilimumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications

1. Unresectable or Metastatic Melanoma
   Yervoy is indicated as a single agent or in combination with nivolumab for the treatment of unresectable or metastatic melanoma in adults and pediatric patients 12 years and older.

2. Adjuvant Treatment of Melanoma
   Yervoy is indicated for the adjuvant treatment of 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.

3. Advanced Renal Cell Carcinoma
   Yervoy, in combination with nivolumab, is indicated for the first-line treatment of adult patients with intermediate or poor risk advanced renal cell carcinoma (RCC).

4. Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer
   Yervoy, in combination with nivolumab, is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

5. Hepatocellular Carcinoma
   Yervoy, in combination with nivolumab, is indicated for the treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

6. Metastatic Non-Small Cell Lung Cancer
   a. Yervoy, in combination with nivolumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.
   b. Yervoy, in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC) with no EGFR or ALK genomic tumor aberrations.

7. Malignant Pleural Mesothelioma

Yervoy, in combination with nivolumab, is indicated for first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

8. Esophageal Cancer
   Yervoy, in combination with nivolumab, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).

B. Compendial Uses
1. Cutaneous melanoma
2. Uveal melanoma
3. Central nervous system (CNS) brain metastases
4. Colorectal cancer, including appendiceal carcinoma
5. Hepatocellular carcinoma
6. Renal cell carcinoma
7. Non-small cell lung cancer
8. Malignant pleural mesothelioma
9. Malignant peritoneal mesothelioma
10. Small bowel adenocarcinoma
11. Neuroendocrine tumors
    a. Poorly differentiated neuroendocrine carcinoma/large or small cell
    b. Well-differentiated grade 3 neuroendocrine tumors
12. Ampullary adenocarcinoma
13. Esophageal/Esophagogastric Junction Cancers
14. Kaposi Sarcoma
15. Bone Cancer
16. Biliary Tract Cancers
    a. Cholangiocarcinoma
    b. Gallbladder Cancer
17. Soft Tissue Sarcoma
    a. Extremity/body wall sarcoma
    b. Head/neck sarcoma
    c. Retroperitoneal/intra-abdominal sarcoma
    d. Rhabdomyosarcoma
    e. Angiosarcoma
18. Merkel Cell Carcinoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. DOCUMENTATION

The following documentation must be available, upon request, for all submissions:
A. Documentation of laboratory report confirming MSI-H or mismatch repair deficient (dMMR) tumor status, where applicable
B. Documentation of molecular testing for EGFR exon 19 deletions or exon 21 L858R mutations and ALK rearrangements, where applicable

III. CRITERIA FOR INITIAL APPROVAL

A. Cutaneous melanoma

1. Authorization of 12 months may be granted for treatment of progressive, unresectable or metastatic disease.
2. Authorization of 12 months may be granted for adjuvant treatment of stage III or IV disease following complete resection or no evidence of disease.
3. The requested medication will be used as a single agent for limited resectable local recurrence after prior anti-PD-1 therapy.

B. Central nervous system brain metastases

Authorization of 12 months may be granted for treatment of brain metastases with a diagnosis of melanoma.

C. Malignant pleural or peritoneal mesothelioma

Authorization of 12 months may be granted for treatment of malignant pleural or peritoneal mesothelioma, including pericardial mesothelioma and tunica vaginalis testis mesothelioma, in combination with nivolumab.

D. Renal cell carcinoma[1,2]

Authorization of 12 months may be granted for treatment of renal cell carcinoma in combination with nivolumab (for 4 doses followed by nivolumab as a single agent).

E. Colorectal cancer

Authorization of 12 months may be granted for treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer, including appendiceal adenocarcinoma and anal adenocarcinoma, in combination with nivolumab (for 4 doses followed by nivolumab as a single agent).

F. Non-small cell lung cancer

Authorization of 12 months may be granted for treatment of recurrent, advanced, or metastatic non-small cell lung cancer if there are no EGFR exon 19 deletions or exon 21 L858R mutations or ALK rearrangements (unless testing is not feasible due to insufficient tissue) and the requested medication will be used in a regimen containing nivolumab.

G. Uveal melanoma

Authorization of 12 months may be granted for treatment of uveal melanoma for distant metastatic disease.

H. **Hepatocellular carcinoma**

Authorization of 12 months may be granted for treatment of hepatocellular carcinoma as a single agent or in combination with nivolumab (for 4 doses followed by nivolumab as a single agent).

I. Small bowel adenocarcinoma

Authorization of 12 months may be granted for treatment of advanced or metastatic small bowel adenocarcinoma for microsatellite-instability high or mismatch repair deficient tumors, in combination with nivolumab.

J. Ampullary adenocarcinoma
Authorization of 12 months may be granted for treatment of progressive, unresectable, or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) ampullary adenocarcinoma, in combination with nivolumab.

K. Neuroendocrine tumors
Authorization of 12 months may be granted for treatment of neuroendocrine tumors, including poorly differentiated neuroendocrine carcinoma/large or small cell and well-differentiated grade 3 neuroendocrine tumors, in combination with nivolumab.

L. Esophageal and Esophagogastric Junction Cancers
Authorization of 12 months may be granted in combination with nivolumab for the first-line treatment of unresectable locally advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC).

M. Kaposi Sarcoma
Authorization of 12 months may be granted in combination with nivolumab for subsequent treatment of relapsed/refractory classic Kaposi Sarcoma.

A. Bone Cancer
Authorization of 12 months may be granted in combination with nivolumab for unresectable or metastatic disease when all of the following are met:
1. Disease has tumor mutation burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] tumors
2. Disease has progressed following prior treatment and has no satisfactory alternative treatment options

B. Biliary Tract Cancer (Cholangiocarcinoma and Gallbladder Cancer)
Authorization of 12 months may be granted as subsequent treatment in combination with nivolumab for unresectable or resected gross residual (R2) disease, progressive or metastatic disease that is tumor mutation burden-high (TMB-H).

C. Soft Tissue Sarcoma
Authorization of 12 months may be granted in combination with nivolumab for treatment of extremity/body wall sarcomas, head/neck sarcomas and retroperitoneal/intra-abdominal sarcomas, rhabdomyosarcoma and angiosarcoma.

D. Merkel Cell Carcinoma
Authorization of 12 months may be granted in combination with nivolumab for treatment of progressive, unresectable, recurrent, or stage IV Merkel cell carcinoma.

IV. CONTINUATION OF THERAPY

A. Adjuvant treatment of melanoma
Authorization for 12 months (up to 3 years) may be granted for all members (including new members) who are continuing with the requested medication therapy when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used as adjuvant treatment for a member with melanoma.
3. The member is receiving benefit from therapy. Benefit is defined as:
   a. No evidence of unacceptable toxicity while on the current regimen and
   b. No evidence of disease progression while on the current regimen.

B. Cutaneous melanoma, renal cell carcinoma, hepatocellular carcinoma, colorectal cancer
Authorization for 12 months (up to 4 doses maximum, if member has not already received 4 doses) may be granted for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used to treat cutaneous melanoma, renal cell carcinoma, hepatocellular carcinoma, or colorectal cancer.
3. The member is receiving benefit from therapy. Benefit is defined as:
    a. No evidence of unacceptable toxicity while on the current regimen and
    b. No evidence of disease progression while on the current regimen.

C. Non-small cell lung cancer, Esophageal/Esophagogastric Junction Cancers, or malignant pleural mesothelioma
Authorization of 12 months (up to 24 months total) may be granted for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used to treat non-small cell lung cancer, esophageal cancer, or malignant pleural mesothelioma, including pericardial mesothelioma and tunica vaginalis testis mesothelioma subtypes.
3. The member is receiving benefit from therapy. Benefit is defined as:
    a. No evidence of unacceptable toxicity while on the current regimen and
    b. No evidence of disease progression while on the current regimen.

D. All other indications
Authorization of 12 months may be granted for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used to treat any other indication enumerated in Section III.
3. The member is receiving benefit from therapy. Benefit is defined as:
    a. No evidence of unacceptable toxicity while on the current regimen and
    b. No evidence of disease progression while on the current regimen.

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Yervoy.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Neuroendocrine and adrenal tumors
4. NCCN Guideline: Small bowel adenocarcinoma
5. NCCN Guideline: Peritoneal mesothelioma
6. NCCN Guideline: Pleural mesothelioma
7. NCCN Guideline: Cutaneous melanoma

8. NCCN Guideline: Non-small cell lung cancer
9. NCCN Guideline: Hepatocellular carcinoma
10. NCCN Guideline: Uveal melanoma
11. NCCN Guideline: Central nervous system cancers
12. NCCN Guideline: Ampullary adenocarcinoma
13. NCCN Guideline: Colon cancer
14. NCCN Guideline: Rectal cancer
15. NCCN Guideline: Kidney cancer
16. NCCN Guideline: Kaposi sarcoma
17. NCCN Guideline: Biliary tract cancers
18. NCCN Guideline: Soft tissue sarcoma
19. NCCN Guideline: Merkel cell carcinoma

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Yervoy are covered in addition to the following:

1. Cutaneous melanoma
2. Uveal melanoma
3. Central nervous system (CNS) brain metastases
4. Colorectal cancer, including appendiceal carcinoma
5. Hepatocellular carcinoma
6. Renal cell carcinoma
7. Non-small cell lung cancer
8. Malignant pleural mesothelioma
9. Malignant peritoneal mesothelioma
10. Small bowel adenocarcinoma
11. Neuroendocrine tumors
12. Ampullary adenocarcinoma
13. Esophageal/esophagogastric junction cancers
14. Kaposi sarcoma
15. Bone cancer
16. Biliary tract cancers
17. Soft tissue sarcoma
18. Merkel cell carcinoma

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for the following indications can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

1. Cutaneous melanoma
2. Uveal melanoma
3. Central nervous system (CNS) brain metastases
4. Colorectal cancer, including appendiceal carcinoma
5. Hepatocellular carcinoma
6. Renal cell carcinoma

7. Non-small cell lung cancer
8. Malignant pleural mesothelioma
9. Malignant peritoneal mesothelioma
10. Small bowel adenocarcinoma
11. Neuroendocrine tumors
12. Ampullary adenocarcinoma
13. Esophageal/esophagogastric junction cancers
14. Kaposi sarcoma
15. Bone cancer
16. Biliary tract cancers
17. Soft tissue sarcoma
18. Merkel cell carcinoma

Support for using Yervoy to treat Merkel cell carcinoma can be found in the Lexi-Drugs database. Use of information in the Lexi-Drugs database for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

VII. REFERENCES

1. Yervoy [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; February 2023.
2. The NCCN Drugs & Biologics Compendium 2022 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed March 8, 2023.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Anal Carcinoma. Version 3.2022. https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf Accessed March 8, 2023
4. Lexicomp [database online]. Hudson, OH: Lexi-Comp, Inc.; https://online.lexi.com/lco/action/home [available with subscription]. Accessed March 13, 2023.