

SPECIALTY GUIDELINE 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 adult 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 (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer**
Yervoy, in combination with nivolumab, is indicated for the treatment of adult and pediatric patients 12 years of age and older 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.
5. **Hepatocellular Carcinoma**
Yervoy, in combination with nivolumab, is indicated for the treatment of adult patients with hepatocellular carcinoma 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 ($\geq 1\%$) 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 with no EGFR or ALK genomic tumor aberrations.
7. **Malignant Pleural Mesothelioma**
Yervoy, in combination with nivolumab, is indicated for the 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. Non-small cell lung cancer
5. Renal cell carcinoma
6. Colorectal cancer, including appendiceal adenocarcinoma and anal adenocarcinoma
7. Pleural mesothelioma
8. Peritoneal mesothelioma
9. Hepatocellular carcinoma
10. Small bowel adenocarcinoma
11. Ampullary adenocarcinoma
12. Esophageal/Esophagogastric Junction Cancers
13. Kaposi Sarcoma
14. Bone Cancer
15. Biliary Tract Cancers
 - a. Cholangiocarcinoma
 - b. Gallbladder Cancer
16. Soft Tissue Sarcoma
 - a. Extremity/body wall sarcoma
 - b. Head/neck sarcoma
 - c. Retroperitoneal/intra-abdominal sarcoma
 - d. Rhabdomyosarcoma
 - e. Angiosarcoma
17. Merkel Cell Carcinoma
18. Gastric Cancer

All other indications are considered experimental/investigational and not medically necessary.

II. DOCUMENTATION

Submission of the following information is necessary to initiate the prior authorization review:

- A. Documentation of laboratory report confirming MSI-H, mismatch repair deficient (dMMR), or polymerase epsilon/delta (POLE/POLD1) 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**

Authorization of 6 months may be granted for treatment of cutaneous melanoma in any of the following settings:

1. The requested medication will be used as a single agent (for up to 4 doses) or in combination with nivolumab (for 4 doses followed by nivolumab as a single agent) for metastatic or unresectable disease.
2. The requested medication will be used as a single agent (for up to 4 doses) or in combination with nivolumab (for 4 doses followed by nivolumab as a single agent) as adjuvant treatment if no evidence of disease following metastasis-directed therapy (e.g., complete resection).

3. The requested medication will be used at a low dose in combination with pembrolizumab for disease progression following single-agent anti-PD-1 therapy as subsequent therapy for metastatic or unresectable disease.
4. The requested medication will be used as a single agent for limited resectable local recurrence after prior anti-PD-1 therapy.
5. The requested medication will be used in combination with nivolumab (for 4 doses followed by nivolumab as a single agent) as neoadjuvant treatment of resectable disease.

B. Uveal Melanoma

Authorization of 6 months may be granted as a single agent or in combination with nivolumab (for 4 doses followed by nivolumab as a single agent) for treatment of uveal melanoma for unresectable or metastatic disease.

C. CNS Brain Metastases

Authorization of 6 months may be granted as a single agent or in combination with nivolumab (for 4 doses followed by nivolumab as a single agent) for treatment of CNS brain metastases in members with melanoma.

D. Non-Small Cell Lung Cancer (NSCLC)

Authorization of 6 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.

E. Renal Cell Carcinoma

Authorization of 6 months may be granted for treatment of renal cell carcinoma in combination with nivolumab (for 4 doses, followed by single agent nivolumab) for relapsed, advanced, or stage IV disease with clear cell histology.

F. Colorectal Cancer

Authorization of 6 months may be granted for treatment of colorectal cancer, including appendiceal adenocarcinoma and anal adenocarcinoma, for microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR) or polymerase epsilon/delta (POLE/POLD1) tumors when used in combination with nivolumab (for 4 doses followed by nivolumab as a single agent).

G. Pleural or Peritoneal Mesothelioma

Authorization of 6 months may be granted in combination with nivolumab for treatment of pleural or peritoneal mesothelioma, including pericardial mesothelioma and tunica vaginalis testis mesothelioma.

H. Hepatocellular Carcinoma

Authorization of 6 months may be granted in combination with nivolumab (for 4 doses followed by nivolumab as a single agent) for treatment of hepatocellular carcinoma.

I. Small Bowel Adenocarcinoma

Authorization of 6 months may be granted in combination with nivolumab (for 4 doses followed by nivolumab as a single agent) for treatment of advanced or metastatic small bowel adenocarcinoma for microsatellite-instability high (MSI-H), mismatch repair deficient (dMMR) or polymerase epsilon/delta (POLE/POLD1) tumors.

J. Ampullary Adenocarcinoma

Authorization of 6 months may be granted in combination with nivolumab (for 4 doses followed by nivolumab as a single agent) for treatment of progressive, unresectable, or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) ampullary adenocarcinoma.

K. Esophageal and Esophagogastric Junction Cancers

1. Authorization of 6 months may be granted in combination with nivolumab for the treatment of esophageal or esophagogastric junction cancer in members who are not surgical candidates or have unresectable locally advanced, recurrent or metastatic disease.
2. Authorization of 6 months may be granted in combination with nivolumab for neoadjuvant or perioperative treatment of esophageal or esophagogastric junction adenocarcinoma if tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) and member is medically fit for surgery.

L. Gastric Cancer

1. Authorization of 6 months may be granted in combination with nivolumab for treatment of gastric adenocarcinoma in members with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors who are not surgical candidates or have unresectable, recurrent or metastatic disease.
2. Authorization of 6 months may be granted in combination with nivolumab for neoadjuvant or perioperative treatment of gastric adenocarcinoma if tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) and member is medically fit for surgery.
3. When the requested medication will be used in combination with nivolumab in members with early stage microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors and completed endoscopic resection.

M. Kaposi Sarcoma

Authorization of 6 months may be granted in combination with nivolumab for subsequent treatment of relapsed/refractory classic Kaposi Sarcoma.

N. Bone Cancer

Authorization of 6 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

O. Biliary Tract Cancer (Cholangiocarcinoma and Gallbladder Cancer)

Authorization of 6 months may be granted as subsequent treatment in combination with nivolumab for unresectable or resected gross residual (R2) disease, or metastatic disease that is tumor mutation burden-high (TMB-H).

P. Soft Tissue Sarcoma

Authorization of 6 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.

Q. Merkel Cell Carcinoma

Authorization of 6 months may be granted as a single agent or in combination with nivolumab (for 4 doses followed by nivolumab as a single agent) for treatment of unresectable, recurrent, or stage IV Merkel cell carcinoma.

IV. CONTINUATION OF THERAPY

A. Adjuvant Treatment of Melanoma

Authorization of 6 months may be granted (up to 3 years) for continued treatment in members requesting reauthorization for adjuvant melanoma when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

B. Cutaneous Melanoma, Renal Cell Carcinoma, Colorectal Cancer, Hepatocellular Cancer

Authorization of 6 months may be granted (up to 4 doses maximum, if member has not already received 4 doses) for continued treatment in members requesting reauthorization for cutaneous melanoma, renal cell carcinoma, colorectal cancer, and hepatocellular cancer when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

C. Non-Small Cell Lung Cancer, Gastric/ Esophageal/Esophagogastric Junction Cancers, or Pleural Mesothelioma

Authorization of 6 months may be granted (up to 24 months total) for continued treatment in members requesting reauthorization for non-small cell lung cancer, esophageal cancer, or pleural mesothelioma, including pericardial mesothelioma and tunica vaginalis testis mesothelioma subtypes, when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

D. All Other Indications

Authorization of 6 months may be granted for continued treatment in members requesting reauthorization for all other indications listed in Section III when treatment guidelines do not specify a limited number of total doses (see above) and there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

V. REFERENCES

1. Yervoy [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; February 2023.
2. The NCCN Drugs & Biologics Compendium 2024 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed March 6, 2024.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Anal Carcinoma. Version 1.2024. https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf Accessed March 6, 2024.
4. Lexicomp [database online]. Hudson, OH: Lexi-Comp, Inc.; <https://online.lexi.com/lco/action/home> [available with subscription]. Accessed March 6, 2024.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer Version 3.2023. https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf Accessed March 6, 2024.