Reference number(s)
2345-A

STANDARD MEDICARE PART B MANAGEMENT

OPDIVO (nivolumab)

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
   Opdivo (nivolumab), as a single agent or in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic melanoma.

2. Adjuvant Treatment of Melanoma
   Opdivo is indicated for the adjuvant treatment of adult and pediatric patients 12 years and older with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

3. Metastatic Non-Small Cell Lung Cancer
   Opdivo, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

   Opdivo, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations.

   Opdivo is indicated for the treatment of adult patients with metastatic NSCLC with 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.

4. Neoadjuvant Treatment of Resectable Non-Small Cell Lung Cancer
   Opdivo, in combination with platinum-doublet chemotherapy, is indicated as neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer (NSCLC).

5. Malignant Pleural Mesothelioma
   Opdivo, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

6. Advanced Renal Cell Carcinoma
   a. Opdivo as a single agent is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.
   b. Opdivo, in combination with ipilimumab, is indicated for the first-line treatment of patients with intermediate or poor risk advanced RCC.

c. Opdivo, in combination with cabozantinib, is indicated for the first-line treatment of patients with advanced RCC.

7. Classical Hodgkin Lymphoma
   Opdivo is indicated for the treatment of adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after:
   a. Autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
   b. Three or more lines of systemic therapy that includes autologous HSCT.

8. Squamous Cell Carcinoma of the Head and Neck
   Opdivo (nivolumab) is indicated for the treatment of adult patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

9. Urothelial Carcinoma
   a. Opdivo is indicated for the adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC.
   b. Opdivo is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who:
      i. Have disease progression during or following platinum-containing chemotherapy
      ii. Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

10. Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer
    Opdivo, as a single agent or in combination with ipilimumab, 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 (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

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

12. Esophageal Cancer
    a. Opdivo is indicated for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in patients who have received neoadjuvant chemoradiotherapy (CRT).
    b. Opdivo, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).
    c. Opdivo, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).
    d. Opdivo is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

13. Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma
    Opdivo, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the treatment of patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

B. <u>Compendial Uses</u>
   1. Cutaneous melanoma

2. Non-small cell lung cancer
3. Colorectal cancer, including appendiceal adenocarcinoma
4. Urothelial carcinoma
    a. Bladder cancer
    b. Primary carcinoma of the urethra
    c. Upper genitourinary tract tumors
    d. Urothelial carcinoma of the prostate
5. Renal cell carcinoma
6. Head and neck cancers
    a. Very advanced head and neck cancer
    b. Mucosal melanoma
    c. Cancer of the nasopharynx
7. Classical Hodgkin lymphoma
8. Hepatocellular carcinoma
9. Uveal melanoma
10. Anal carcinoma
11. Merkel cell carcinoma
12. Central nervous system (CNS) brain metastases
13. Malignant pleural mesothelioma
14. Malignant peritoneal mesothelioma
15. Gestational trophoblastic neoplasia
16. Diffuse large B-cell lymphoma
    a. Primary mediastinal large B-cell lymphoma
    b. Histologic (Richter's) transformation to diffuse large B-cell lymphoma
17. Small bowel adenocarcinoma
18. Ampullary adenocarcinoma
19. Extranodal NK/T-cell lymphoma
20. Neuroendocrine tumors
    a. Poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma
    b. Well-differentiated grade 3 neuroendocrine tumors
21. Endometrial carcinoma
22. Vulvar Cancer
23. Gastric cancer
24. Esophageal and esophagogastric junction cancers
25. Hepatobiliary cancers – Biliary tract cancers
    a. Gallbladder cancer
    b. Intrahepatic cholangiocarcinoma
    c. Extrahepatic cholangiocarcinoma
26. Cervical cancer
27. Small cell lung cancer
28. Kaposi Sarcoma
29. Bone Cancer
30. Pediatric Diffuse High-Grade Gliomas
31. Biliary Tract Cancers
    a. Cholangiocarcinoma
    b. Gallbladder Cancer
32. Soft Tissue Sarcoma
    a. Extremity/body wall sarcoma
    b. Head/neck sarcoma
    c. Retroperitoneal/intra-abdominal sarcoma
    d. Rhabdomyosarcoma
    e. Angiosarcoma

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:
1. Documentation of laboratory report confirming microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumor status, where applicable.
2. Documentation of the presence of EGFR exon 19 deletions or exon 21 L858R mutations or ALK rearrangements, where applicable.

III. CRITERIA FOR INITIAL APPROVAL

A. Cutaneous melanoma

Authorization of 12 months may be granted for treatment of cutaneous melanoma in either of the following settings:
1. For treatment of locally recurrent, unresectable, progressive or metastatic disease.
2. The requested medication will be used as adjuvant treatment of stage III or IV disease following complete resection or no evidence of disease.

B. Non-small cell lung cancer

1. Authorization of 12 months may be granted for treatment of recurrent, advanced, or metastatic NSCLC when either of the following conditions is met:
   a. 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 ipilimumab.
   b. The requested medication will be used as a single agent as subsequent therapy.
2. Authorization of 3 months (for up to 3 cycles total) may be granted for neoadjuvant treatment of resectable non-small cell lung cancer (NSCLC) in combination with platinum-doublet chemotherapy.

C. Colorectal cancer

Authorization of 12 months may be granted for treatment of colorectal cancer, including appendiceal adenocarcinoma and anal adenocarcinoma, when both of the following criteria are met:
1. Disease is unresectable, advanced, metastatic, or inoperable.
2. Tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).

D. Urothelial carcinoma

Authorization of 12 months may be granted for treatment of urothelial carcinoma, including bladder cancer, upper genitourinary tract tumors, urothelial carcinoma of the prostate, and primary carcinoma of the urethra.

E. Renal cell carcinoma

Authorization of 12 months may be granted for treatment of renal cell carcinoma for relapsed, advanced or stage IV disease.

F. Head and neck cancers

Authorization of 12 months may be granted for treatment of head and neck cancers, including very advanced head and neck cancer, mucosal melanoma, and cancer of the nasopharynx.

G. Classical Hodgkin lymphoma (cHL)

Authorization of 12 months may be granted for the treatment of classical Hodgkin lymphoma.

H. Hepatocellular carcinoma
Authorization of 12 months may be granted for treatment of hepatocellular carcinoma.

I. Uveal melanoma
Authorization of 12 months may be granted for treatment of uveal melanoma.

J. Anal carcinoma
Authorization of 12 months may be granted for treatment of anal carcinoma.

K. Merkel cell carcinoma
Authorization of 12 months may be granted for treatment of Merkel cell carcinoma.

L. CNS brain metastases
Authorization of 12 months may be granted for treatment of CNS brain metastases in patients with melanoma or NSCLC.

M. 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 either of the following settings:
1. The requested medication will be used as first-line therapy in combination with ipilimumab.
2. The requested medication will be used as subsequent therapy as a single agent or in combination with ipilimumab.

N. Gestational Trophoblastic Neoplasia
Authorization of 12 months may be granted for treatment of gestational trophoblastic neoplasia.

O. Diffuse large B-cell lymphoma
Authorization of 12 months may be granted for treatment of either of the following:
1. Primary mediastinal large B-cell lymphoma
2. Histologic (Richter's) transformation to diffuse large B-cell lymphoma.

P. Esophageal and esophagogastric junction carcinoma
1. Authorization of 12 months may be granted for treatment of esophageal and esophagogastric junction carcinoma when any of the following criteria are met:
   a. As first-line treatment of unresectable advanced or metastatic squamous cell carcinoma in combination with ipilimumab or fluoropyrimidine- and platinum-containing chemotherapy.
   b. As subsequent therapy for treatment of unresectable advanced, recurrent or metastatic squamous cell carcinoma.
   c. For treatment of adenocarcinoma in members who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease when the requested medication will be used in combination with chemotherapy.
2. Authorization of 6 months may be granted for adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease.

Q. Small bowel adenocarcinoma
Authorization of 12 months may be granted for treatment of advanced or metastatic small bowel adenocarcinoma for microsatellite-instability high (MSI-H) or mismatch repair deficient tumors (dMMR), as a single agent or in combination with ipilimumab.

R. 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 ipilimumab.

S. Extranodal NK/T-cell lymphoma
Authorization of 12 months may be granted for treatment of extranodal NK/T-cell lymphoma.

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

U. Endometrial carcinoma
Authorization of 12 months may be granted for treatment of endometrial carcinoma with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors.

V. Vulvar cancer
Authorization of 12 months may be granted for treatment of human papillomavirus (HPV)-related vulvar cancer.

W. Gastric cancer
Authorization of 12 months may be granted for treatment of gastric cancer in members who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease when the requested medication will be used in combination with chemotherapy.

X. Hepatobiliary cancers – biliary tract cancers
Authorization of 12 months may be granted for treatment of biliary tract cancers, including gallbladder cancer, intrahepatic cholangiocarcinoma, and extrahepatic cholangiocarcinoma.

Y. Cervical cancer
Authorization of 12 months may be granted for subsequent treatment of recurrent, or metastatic cervical cancer.

Z. Small cell lung cancer
Authorization of 12 months may be granted for subsequent treatment of relapsed or progressive small cell lung cancer.

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

BB. Bone Cancer
Authorization of 12 months may be granted in combination with ipilimumab for unresectable or metastatic bone cancer with tumor mutation burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] tumors.

CC. Pediatric Diffuse High-Grade Gliomas
Authorization of 12 months may be granted for hypermutant tumor pediatric diffuse high-grade glioma as adjuvant treatment or for recurrent or progressive disease.

DD. Biliary Tract Cancers (Cholangiocarcinoma and Gallbladder Cancer)

Authorization of 12 months may be granted as subsequent treatment in combination with ipilimumab for unresectable or resected gross residual (R2) disease, or metastatic disease that is tumor mutation burden-high (TMB-H).

EE. Soft Tissue Sarcoma

Authorization of 12 months may be granted for treatment of soft tissue sarcoma in the following settings:

1. The requested medication will be used as a single agent or in combination with ipilimumab for treatment of extremity/body wall sarcomas, head/neck sarcomas and retroperitoneal/intra-abdominal sarcomas and rhabdomyosarcoma.
2. The requested medication will be used in combination with ipilimumab for the treatment of angiosarcoma.

IV. CONTINUATION OF THERAPY

A. Adjuvant treatment of melanoma

Authorization for 12 months total therapy 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 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 recurrence while on the current regimen.

B. Non-small cell lung cancer or malignant pleural mesothelioma

1. Authorization for 12 months may be granted (up to 24 months total when used in combination with ipilimumab) for all members (including new members) who are continuing with the requested therapy when all of the following criteria are met:
    a. The member is currently receiving therapy with the requested medication.
    b. The requested medication is being used to treat non-small cell lung cancer or malignant pleural, including pericardial mesothelioma and tunica vaginalis testis mesothelioma subtypes.
    c. The member is receiving benefit from therapy. Benefit is defined as:
        i. No evidence of unacceptable toxicity while on the current regimen AND
        ii. No evidence of disease progression while on the current regimen.
2. Neoadjuvant treatment of NSCLC will be approved for a total of 3 months of therapy.

C. Renal cell carcinoma

Authorization for 12 months may be granted (up to 24 months total when used in combination with cabozantinib) 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 renal cell carcinoma.
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. Gastric cancer, esophageal cancer, and esophagogastric junction carcinoma

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 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.

Therapy durations will be limited to the following:
1. Esophageal squamous cell carcinoma in combination with ipilimumab or chemotherapy for up to 24 months
2. Unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma as a single agent until disease progression or unacceptable toxicity
3. Adjuvant treatment of resected esophageal or esophagogastric junction cancer as a single agent for up to 12 months
4. Gastric cancer, esophagogastric junction cancer, and esophageal adenocarcinoma in combination with chemotherapy for up to 24 months

E. All other indications

Authorization for 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 diagnosis or condition 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 Opdivo.
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: Hodgkin lymphoma
4. NCCN Guideline: Small cell lung cancer
5. NCCN Guideline: Vulvar cancer
6. NCCN Guideline: Cervical cancer
7. NCCN Guideline: Gestational trophoblastic neoplasia
8. NCCN Guideline: Small bowel adenocarcinoma
9. NCCN Guideline: Peritoneal mesothelioma
10. NCCN Guideline: Pleural mesothelioma
11. NCCN Guideline: T-cell lymphomas
12. NCCN Guideline: Pediatric Hodgkin lymphoma
13. NCCN Guideline: Cutaneous melanoma
14. NCCN Guideline: Merkel cell carcinoma
15. NCCN Guideline: Non-small cell lung cancer
16. NCCN Guideline: Hepatocellular carcinoma
17. NCCN Guideline: Anal carcinoma
18. NCCN Guideline: Uveal melanoma
19. NCCN Guideline: Gastric cancer
20. NCCN Guideline: Esophageal and esophagogastric junction
21. NCCN Guideline: Central nervous system cancers
22. NCCN Guideline: Biliary tract cancers

23. NCCN Guideline: Ampullary adenocarcinoma
24. NCCN Guideline: Bladder cancer
25. NCCN Guideline: Colon cancer
26. NCCN Guideline: Rectal cancer
27. NCCN Guideline: Head and neck cancers
28. NCCN Guideline: Kidney cancer
29. NCCN Guideline: Pediatric central nervous system cancers

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

A. Cutaneous melanoma
B. Non-small cell lung cancer
C. Colorectal cancer, including appendiceal adenocarcinoma
D. Urothelial carcinoma
E. Renal cell carcinoma
F. Head and neck cancers
G. Classical Hodgkin lymphoma
H. Hepatocellular carcinoma
I. Uveal melanoma
J. Anal carcinoma
K. Merkel cell carcinoma
L. Central nervous system (CNS) brain metastases
M. Malignant pleural mesothelioma
N. Malignant peritoneal mesothelioma
O. Gestational trophoblastic neoplasia
P. Diffuse large B-cell lymphoma
Q. Small bowel adenocarcinoma
R. Ampullary adenocarcinoma
S. Extranodal natural killer (NK)/T-cell lymphoma
T. Neuroendocrine tumors
U. Endometrial carcinoma
V. Vulvar carcinoma
W. Gastric cancer
X. Esophageal and esophagogastric junction cancers
Y. Hepatobiliary cancers
Z. Cervical cancer
AA. Small cell lung cancer
BB. Kaposi sarcoma
CC. Bone cancer
DD. Pediatric diffuse high-grade gliomas
EE. Biliary tract cancers
FF. Soft tissue sarcoma

VI. EXPLANATION OF RATIONALE

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

Support for using Opdivo to treat the indications in section V 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).

VII. REFERENCES

1. Opdivo [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; February 2023.
2. The NCCN Drugs & Biologics Compendium® © 2023 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed March 8, 2023.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Anal Carcinoma. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf Accessed March 7, 2023.