Reference number(s)
1894-A

SPECIALTY GUIDELINE 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 patients with unresectable or metastatic melanoma.

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

3. Metastatic Non-Small Cell Lung Cancer
   a. Opdivo, in combination with ipilimumab, 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. 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.
   c. Opdivo is indicated for the treatment of 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. Malignant Pleural Mesothelioma
   Opdivo, in combination with ipilimumab, is indicated for the treatment of adult patients with unresectable malignant pleural mesothelioma, as first-line treatment.

5. 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.

6. 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. 3 or more lines of systemic therapy that includes autologous HSCT.

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

8. Urothelial Carcinoma
   a. Opdivo is indicated for the adjuvant treatment of 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 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.

9. 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.

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

11. Esophageal Carcinoma
    a. Opdivo is indicated for the treatment of patients with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy.
    b. Opdivo is indicated for the treatment of patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

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

B. <u>Compendial Uses</u>
   1. Cutaneous melanoma
   2. Non-small cell lung cancer
   3. Renal cell carcinoma
   4. Classical Hodgkin lymphoma
   5. Squamous cell carcinoma of the head and neck
   6. Urothelial carcinoma
      a. Bladder cancer
      b. Primary carcinoma of the urethra
      c. Upper genitourinary tract tumors
      d. Urothelial carcinoma of the prostate
   7. Colorectal cancer, including appendiceal carcinoma and anal adenocarcinoma
   8. Hepatocellular carcinoma
   9. Uveal Melanoma

10. Anal Carcinoma
11. Merkel Cell Carcinoma
12. Central Nervous System (CNS) brain metastases
13. Gestational trophoblastic neoplasia
14. Malignant pleural mesothelioma
15. Small bowel adenocarcinoma, including advanced ampullary cancer
16. Extranodal NK/T-cell lymphoma, nasal type
17. Endometrial Carcinoma
18. Vulvar squamous cell carcinoma
19. Gastric Cancer
20. Esophageal/Esophagogastric Junction Cancers
21. Small cell lung cancer
22. Cervical Cancer
23. Nasopharyngeal Carcinoma (NPC)

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 or mismatch repair deficient (dMMR) tumor status, where applicable.
B. Documentation of programmed death ligand 1 (PD-L1) tumor expression, where applicable.
C. Documentation of the presence of EGFR exon 19 deletions or L858R mutations or ALK rearrangements, where applicable.

III. EXCLUSIONS

Coverage will not be provided for members who have experienced disease progression while on programmed death receptor-1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitor therapy (other than when used as second-line or subsequent therapy for metastatic or unresectable melanoma in combination with ipilimumab following progression on single agent anti-PD-1 immunotherapy).

IV. CRITERIA FOR INITIAL APPROVAL

A. Cutaneous Melanoma

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

1. Opdivo will be used as a single agent or in combination with ipilimumab (4 doses of ipilimumab, followed by Opdivo as a single agent) for unresectable or metastatic disease.
2. Opdivo will be used as a single agent as adjuvant treatment of stage III or IV disease following complete resection or no evidence of disease

B. 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 either of the following criteria are met:

1. There are no EGFR exon 19 deletions or 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.
2. The requested medication will be used as single agent subsequent therapy.

C. Renal Cell Carcinoma

Authorization of 6 months may be granted for treatment of relapsed, advanced, or stage IV renal cell carcinoma, in any of the following settings:

1. Opdivo will be used as a single agent for clear cell histology as subsequent therapy.
2. Opdivo will be used as a single agent for non-clear cell histology.
3. Opdivo will be used in combination with ipilimumab (4 doses of ipilimumab, followed by Opdivo as a single agent) for:
   i. First-line therapy for poor or intermediate risk.
   ii. First-line therapy for clear cell histology and favorable risk.
   iii. Subsequent therapy for clear cell histology.
4. Opdivo will be used in combination with cabozantinib as:
   i. First-line treatment.
   ii. Subsequent therapy for clear cell histology.

D. Classical Hodgkin Lymphoma (cHL)

Authorization of 6 months may be granted for treatment of classical Hodgkin lymphoma when either of the following criteria is met:

1. Opdivo will be used as a single agent and the member meets one of the following criteria:
   i. Member has relapsed or progressed after 2 or more prior lines of therapy or following hematopoietic stem cell transplant.
   ii. Member has relapsed or refractory disease and is transplant-ineligible.
   iii. Member has relapsed or refractory disease and was heavily pretreated or there was a decrease in cardiac function
2. Opdivo will be used in combination with brentuximab vedotin for relapsed or refractory disease.

E. Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Authorization of 6 months may be granted as a single agent for subsequent treatment of very advanced SCCHN in members with disease progression on or after platinum-containing chemotherapy.

F. Nasopharyngeal Carcinoma (NPC)

Authorization of 6 months may be granted for treatment of unresectable, recurrent or metastatic NPC when used in combination with cisplatin and gemcitabine.

G. Urothelial Carcinoma – Bladder Cancer

Authorization of 6 months may be granted as a single agent for treatment of bladder cancer when any of the following conditions are met:

1. As subsequent therapy for locally advanced or metastatic disease.
2. As subsequent therapy for metastatic disease or local recurrence post-cystectomy.
3. As subsequent therapy for muscle invasive local recurrence or persistent disease in a preserved bladder.
4. As subsequent therapy for stage II or IIIA disease and tumor is present following primary bladder preserving chemoradiation.
5. As adjuvant therapy in members who are at high risk of recurrence after undergoing radical resection.

H. Urothelial Carcinoma – Primary Carcinoma of the Urethra

Authorization of 6 months may be granted as a single agent for treatment of primary carcinoma of the urethra when either of the following are met:

1. As subsequent therapy for recurrent, locally advanced, or metastatic disease.
2. As adjuvant therapy in members who are at high risk of recurrence after undergoing radical resection.

I. Urothelial Carcinoma – Upper Genitourinary Tract Tumors or Urothelial Carcinoma of the Prostate

Authorization of 6 months may be granted as a single agent for treatment of upper genitourinary (GU) tract tumors or urothelial carcinoma of the prostate when either of the following are met:
1. As subsequent therapy for locally advanced or metastatic disease.
2. As adjuvant therapy in members who are at high risk of recurrence after undergoing radical resection.

J. Colorectal Cancer
Authorization of 6 months may be granted for treatment of colorectal cancer, including appendiceal carcinoma and anal adenocarcinoma, for microsatellite-instability high or mismatch repair deficient tumors when used as a single agent or in combination with ipilimumab (4 doses of ipilimumab, followed by Opdivo as a single agent) for advanced, metastatic, unresectable, or inoperable disease.

K. Small Bowel Adenocarcinoma
Authorization of 6 months may be granted as a single agent or in combination with ipilimumab for treatment of advanced or metastatic small bowel adenocarcinoma, including advanced ampullary cancer, for microsatellite-instability high or mismatch repair deficient tumors

L. Hepatocellular Carcinoma
Authorization of 6 months may be granted in combination with ipilimumab (4 doses of ipilimumab, followed by Opdivo as a single agent) for subsequent treatment of hepatocellular carcinoma.

M. Uveal Melanoma
Authorization of 6 months may be granted as a single agent or in combination with ipilimumab for treatment of uveal melanoma for distant metastatic disease.

N. Anal Carcinoma
Authorization of 6 months may be granted as a single agent for second-line or subsequent treatment of metastatic anal carcinoma.

O. Merkel Cell Carcinoma
Authorization of 6 months may be granted for treatment of Merkel cell carcinoma in either of the following settings:
1. Recurrent disseminated or metastatic disease.
2. As neoadjuvant treatment.

P. CNS Brain Metastases
Authorization of 6 months may be granted for treatment of CNS brain metastases when either of the following criteria are met:
1. Opdivo will be used as a single agent or in combination with ipilimumab in members with melanoma.
2. Opdivo will be used as a single agent in members with PD-L1 positive non-small cell lung cancer.

Q. Gestational Trophoblastic Neoplasia
Authorization of 6 months may be granted as a single agent for treatment of gestational trophoblastic neoplasia for multiagent chemotherapy-resistant disease when either of the following criteria is met:
1. Member has recurrent or progressive intermediate trophoblastic tumor (placental site trophoblastic tumor or epithelioid trophoblastic tumor) following treatment with a platinum/etoposide-containing regimen.
2. Member has high-risk disease.

R. Malignant Pleural Mesothelioma
Authorization of 6 months may be granted for the treatment of malignant pleural mesothelioma in either of the following settings:
1. Opdivo will be used as first line therapy in combination with ipilimumab.

2. Opdivo will be used as subsequent therapy as a single agent or in combination with ipilimumab.

S. Esophageal and Esophagogastric Junction Carcinoma
Authorization of 6 months may be granted for treatment of esophageal or esophagogastric junction carcinoma in any of the following settings:
1. As subsequent therapy as a single agent for treatment of unresectable locally advanced, recurrent or metastatic squamous cell carcinoma.
2. As postoperative therapy following preoperative chemoradiation and complete tumor resection, when there is residual pathologic disease.
3. As 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.

T. Extranodal NK/T-Cell Lymphoma, Nasal Type
Authorization of 6 months may be granted for treatment of relapsed or refractory extranodal NK/T-cell lymphoma, nasal type.

U. Endometrial Carcinoma
Authorization of 6 months may be granted for treatment of recurrent, metastatic, or high risk mismatch repair deficient (dMMR) endometrial carcinoma as subsequent therapy as a single agent.

V. Vulvar Squamous Cell Carcinoma
Authorization of 6 months may be granted for treatment of HPV-related advanced, recurrent, or metastatic vulvar squamous cell carcinoma as subsequent therapy as a single agent.

W. Gastric Cancer
Authorization of 6 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. Small Cell Lung Cancer
Authorization of 6 months may be granted for subsequent treatment of relapsed or progressive small cell lung cancer as a single agent.

Y. Cervical Cancer
Authorization of 6 months may be granted for second-line or subsequent treatment of recurrent or metastatic cervical cancer as a single agent if PD-L1 positive (combined positive score [CPS] ≥1).

V. CONTINUATION OF THERAPY

A. Adjuvant treatment of melanoma or urothelial carcinoma
Authorization of 6 months may be granted (up to 12 months total) for continued treatment in members requesting reauthorization for cutaneous melanoma or urothelial carcinoma who have not experienced disease recurrence or an unacceptable toxicity.

B. Non-small cell lung cancer or Malignant pleural mesothelioma
Authorization of 6 months may be granted (up to 24 months total when used in combination with ipilimumab) for continued treatment in members requesting reauthorization for non-small cell lung cancer or malignant pleural mesothelioma when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

C. Renal Cell Carcinoma
Authorization of 6 months may be granted (up to 24 months total when used in combination with cabozantinib) for continued treatment in members requesting reauthorization for renal cell carcinoma when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

D. Gastric Cancer, Esophageal Cancer, and Esophagogastric Junction Carcinoma
Authorization of 6 months may be granted (up to 24 months total when used in combination with chemotherapy; up to 12 months total when used as postoperative therapy for completely resected esophageal cancer or esophagogastric junction carcinoma) for continued treatment in members requesting reauthorization for gastric cancer, esophageal cancer, and esophagogastric junction carcinoma when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

E. All other indications
Authorization of 6 months may be granted for continued treatment in members requesting reauthorization for all other indications listed in Section IV when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

VI. REFERENCES

1. Opdivo [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; August 2021.
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3. The Clinical NCCN Practice Guidelines in Oncology® Colon Cancer (Version 2.2021) © 2021 National Comprehensive Cancer Network, Inc. Available at http://www.nccn.org. Accessed January 29, 2021.
4. The Clinical NCCN Practice Guidelines in Oncology® Rectal Cancer (Version 1.2021) © 2021 National Comprehensive Cancer Network, Inc. Available at http://www.nccn.org. Accessed January 29, 2021.