Opdivo (nivolumab)

Override(s)	Approval Duration
Prior Authorization	1 year

Medications
Opdivo (nivolumab)

APPROVAL CRITERIA

Requests for Opdivo (nivolumab) may be approved if the following criteria are met:

I. Individual has a diagnosis of Ampullary Adenocarcinoma (NCCN 2A):**AND**
   A. Using in one of the following ways:
      1. As first-line therapy for metastatic intestinal type disease; **OR**
      2. For disease progression; **AND**
   B. Individual has deficient mismatch repair or microsatellite instability-high [dMMR or MSI-H] disease; **AND**
   C. Individual is using in combination with ipilimumab; **AND**
   D. Individual has an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; **AND**
   E. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
   F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

II. Individual has a diagnosis of Anal carcinoma (NCCN 2A); **AND**
   A. Individual is using as second-line and subsequent therapy; **AND**
   B. Individual is using in metastatic disease; **AND**
   C. Individual is using as a single agent; **AND**
   D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
   E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

III. Individual is using for the treatment of Bone cancer, including osteosarcoma, Ewing Sarcoma, chondrosarcoma, and chordoma (NCCN 2A); **AND**
   A. Individual is using in combination with ipilimumab for unresectable or metastatic disease; **AND**
   B. Individual has failed and progressed on prior treatment; **AND**
   C. Individual has no satisfactory alternative treatment options for tissue tumor mutation burden-high (TMB-H) tumors with 10 or more mutations per megabase; **AND**
   D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
   E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

IV. Individual has a diagnosis of Biliary Tract Cancers (NCCN 2A); **AND**
   A. Individual is using in combination with ipilimumab; **AND**
   B. Meets one of the following:
      1. Individual is using for progression on or after systemic treatment for unresectable or resected gross residual (R2) disease, or metastatic disease that is tumor mutational burden-high (TMB-H); **OR**
      2. Individual is using as neoadjuvant systemic therapy for resectable locoregionally advanced disease and does not have jaundice;

   AND
   C. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
   D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

V. Individual has a diagnosis of Cervical Cancer (NCCN 2A); **AND**
   A. Individual is using as a single agent; **AND**
   B. Individual is using for second-line or subsequent therapy; **AND**
   C. Individual has CPS ≥ 1 for local/regional recurrence or stage IVB or recurrence with distant metastases; **AND**
   D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
   E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

VI. Individual has a diagnosis of Colorectal Cancer, including advanced Appendiceal Adenocarcinoma (NCCN 2A); **AND**
   A. Individual is using as monotherapy or in combination with ipilimumab; **AND**
   B. Meets one of the following:
      1. Individual has resectable disease for neoadjuvant or initial treatment (NCCN 2A); **AND**
      2. Individual has deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation) (NCCN 2A);

      OR
      3. Individual has disease progression from prior treatment for advanced or metastatic disease (NCCN 2A); **AND**
      4. Individual has deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation) (NCCN 2A);

      OR
      5. Individual is using as neoadjuvant therapy in clinical T4b disease (NCCN 2A); **AND**
      6. Individual has deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H];

   AND
   C. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**

D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

VII. Individual has a diagnosis of Colorectal Cancer, including advanced Appendiceal Adenocarcinoma (Label, NCCN 2A); **AND**

A. Meets one of the following:
    1. Individual is using as monotherapy or in combination with ipilimumab in primary treatment for unresectable metachronous metastases (defective mismatch repair/high microsatellite instability [dMMR/MSIH] or polymerase epsilon/delta [POLE/POLD1] mutation) and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months; **OR**
    2. Individual is using as monotherapy or in combination with ipilimumab as subsequent therapy for unresectable advanced or metastatic disease (defective mismatch repair/high microsatellite instability [dMMR/MSIH] or polymerase epsilon/delta [POLE/POLD1] mutation) following previous treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan- based chemotherapy (Label, NCCN 2A);

AND

B. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
C. Individual has a current Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

VIII. Individual has a diagnosis of Endometrial carcinoma (NCCN 2A); **AND**

A. Individual has a diagnosis of recurrent MSI-H/dMMR disease; **AND**
B. Individual is using as a single agent; **AND**
C. Individual is using as second-line or subsequent therapy; **AND**
D. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

IX. Individual has Esophageal and Esophagogastric junction cancer (NCCN 1, 2A); **AND**

A. Individual is using for induction systemic therapy; **AND**
B. Individual is using to relieve dysphagia; **AND**
C. Individual is medically fit and planned for esophagectomy; **AND**
D. Meets one of the following:
    1. Using in combination with platinum-containing chemotherapy and capecitabine or fluorouracil; **OR**
    2. Using in combination with ipilimumab; **OR**
    3. If positive MSI-H/dMMR tumor, using in combination with ipilimumab OR in combination with oxaliplatin and capecitabine or fluorouracil;

AND

E. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**

F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

X. Individual has a diagnosis of unresectable locally advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) (Label); **AND**
   A. Individual is using in one of the following ways:
      1. In combination with ipilmumab (Yervoy); **OR**
      2. In combination with fluoropyrimidine- and platinum-containing chemotherapy;

   AND
   B. Individual is using as first-line treatment; **AND**
   C. Individual has a current ECOG performance status of 0-1; **AND**
   D. Individual has not received prior treatment with anti-PD-1, anti-PD-L1, any antibody or drug specifically targeting T-cell co-stimulation, or checkpoint pathways; **AND**
   E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XI. Individual has a diagnosis of unresectable locally advanced, recurrent, or metastatic Esophageal Squamous Cell Carcinoma (ESCC) (Label); **AND**
   A. Individual is using as single agent or in combination with ipilimumab for second line or subsequent therapy; **AND**
   B. Individual has confirmation of disease progression on or had intolerance to fluoropyrimidine- and platinum-based chemotherapy; **AND**
   C. Individual has a current ECOG performance status of 0-2 or Karnofsky performance score of 60-100; **AND**
   D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XII. Individual has a diagnosis of *completely resected* Esophageal and Esophagogastric Junction Cancer (Label); **AND**
   A. Individual is using as single agent for residual pathologic disease; **AND**
   B. Individual has received neoadjuvant chemoradiotherapy (CRT); **AND**
   C. Individual has a current ECOG performance status of 0-2; **AND**
   D. Individual has not received treatment with another anti-PD-1, anti-PD-L1 agent, or other checkpoint inhibitor; **AND**
   E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XIII. Individual has a diagnosis of Gastric or Esophageal and Esophagogastric Junction Cancers and has microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumor (NCCN 2A); **AND**
   A. One of the following:
      1. Individual is using as a single agent for adenocarcinoma as postoperative management following completely resected disease in those who received preoperative therapy with intravenous nivolumab (Opdivo) + ipilimumab; **OR**
      2. Individual is using in combination with ipilimumab for primary treatment of adenocarcinoma as neoadjuvant or perioperative immunotherapy;

   AND

B. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XIV. Individual has a diagnosis of advanced or metastatic Gastric, or Esophageal and Esophagogastric Junction Cancers (Label); **AND**

A. Individual is using in combination with fluoropyrimidine and platinum-containing chemotherapy; **AND**
B. Individual has HER2 negative disease; **AND**
C. Individual has a current ECOG performance status of 0-2; **AND**
D. Individual has not received treatment with another anti-PD-1, anti-PD-L1 agent, or other checkpoint inhibitor; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XV. Individual has a diagnosis of Esophageal and Esophagogastric Junction Cancers; **AND**

A. Individual is using for palliative care (NCCN 1, 2A); **AND**
B. Individual is not a surgical candidate OR has unresectable locally advanced, recurrent, or metastatic disease;

AND

C. Meets one of the following:
    1. Has HER2 negative disease; **AND**
    2. Using as first-line therapy in combination with fluoropyrimidine- and oxaliplatin;

    AND

    3. Individual has PD-L1 CPS ≥ 5;

    OR

    4. Has MSI-H/dMMR tumors; **AND**
    5. Using as first-line therapy in combination with ipilimumab or in combination with fluoropyrimidine- and oxaliplatin;

    OR

    6. Has Squamous cell carcinoma; **AND**
    7. Using as first-line therapy in combination with ipilimumab OR fluoropyrimide and platinum-containing chemotherapy;

    OR

    8. Using as second-line or subsequent therapy; **AND**
    9. Using as a single agent or in combination with ipilimumab;

AND

D. Individual has a current ECOG performance status of 0-2 or Karnofsky performance score of 60-100; **AND**
E. Individual does not have prior tumor progression while on therapy with a checkpoint inhibitor; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XVI. Individual has a diagnosis of Gastric Cancer (NCCN 1); **AND**

A. Individual is medically fit for surgery but with surgically unresectable disease; **AND**
B. Meets one of the following:

1. Has HER2 negative disease; **AND**
2. Individual is using in combination with fluoropyrimidine and oxaliplatin.

OR

3. Has MSI-H or dMMR tumors; **AND**
4. Individual is using in combination with ipilimumab or in combination with fluoropyrimidine and oxaliplatin;

AND

C. Individual has a PD-L1 CPS ≥ 5; **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XVII. Individual has a diagnosis of multi-agent chemotherapy-resistant gestational trophoblastic neoplasia (NCCN 2A); **AND**

A. Individual has intermediate trophoblastic tumor or high-risk disease; **AND**
B. Individual is using as single-agent therapy or in combination with ipilimumab; **AND**
C. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XVIII. Individual has a diagnosis of advanced Hepatocellular Carcinoma (Label, NCCN 2A); **AND**

A. Individual is using in one of the following ways:
    1. Individual is using as a single agent in those classified as Child-Pugh Class B; **OR**
    2. Individual is using in combination with ipilimumab for subsequent therapy; **OR**
    3. Individual is using in combination with ipilimumab for progressive disease and classified as Child-Pugh Class A;

AND

B. Individual has a current ECOG performance status of 0-2; **AND**
C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XIX. Individual has a diagnosis of Hodgkin Lymphoma (Label, NCCN 1, 2A); **AND**

A. Individual is using for relapsed or refractory Hodgkin lymphoma except for those with lymphocyte-predominant Hodgkin lymphoma; **AND**
B. Using in one of the following ways:
    1. Individual is using as a single agent; **OR**
    2. Individual is using in combination with brentuximab vedotin or with ifosfamide, carboplatin, etoposide (ICE) as primary systemic therapy or second-line therapy; **OR**
    3. Individual is using in combination with AVD (doxorubicin, vinblastine, dacarbazine) for primary treatment;

AND

C. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XX. Individual has a diagnosis of Pediatric Classic Hodgkin Lymphoma (NCCN 2A); **AND**

A. Individual is using for relapsed or refractory Hodgkin lymphoma except for those with lymphocyte-predominant Hodgkin lymphoma; **AND**
B. Using in one of the following ways:
    1. Individual is as a single agent; **OR**
    2. Individual is using in combination with brentuximab vedotin or with ifosfamide, carboplatin, etoposide (ICE);

AND

C. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXI. Individual has a diagnosis of relapsed/refractory advanced classic Kaposi Sarcoma (NCCN 2A); **AND**

A. Individual is using as a single agent or in combination with ipilimumab (Yervoy); **AND**
B. Individual is using as subsequent systemic therapy; **AND**
C. Individual does not have multicentric Castleman Disease (MCD) or KSHV-associated inflammatory cytokine syndrome (KICS);

OR

XXII. Individual has a diagnosis of unresectable Malignant Pleural or Peritoneal Mesothelioma and using as first line therapy (Label, NCCN 1, 2A); **AND**

A. Individual is using in combination with ipilimumab (Yervoy); **AND**
B. Individual has a ECOG performance status of 0-2; **AND**
C. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXIII. Individual has a diagnosis of Malignant Pleural or Peritoneal Mesothelioma (NCCN 2A); **AND**

A. Individual is using as a single agent, or in combination with ipilimumab (Yervoy) for subsequent therapy; **AND**
B. Individual has a ECOG performance status of 0-2; **AND**
C. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXIV. Individual has a diagnosis of Malignant Pleural Mesothelioma (NCCN 1); **AND**

A. Individual has epithelioid histology; **AND**
B. Individual is using as induction systemic therapy; **AND**

C. Individual is using in combination with ipilimumab; **AND**
D. Individual uses prior to surgical exploration for stage I disease; **AND**
E. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXV. Individual has a diagnosis of Melanoma (Cutaneous or Uveal); **AND**
A. Individual has unresectable or metastatic melanoma (Label, NCCN 1, 2A); **AND**
1. Individual is using as a single agent, or in combination with ipilimumab; **AND**
2. Individual has a current ECOG performance status of 0-2; **AND**
3. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
4. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

B. Individual has resected advanced melanoma (Label, NCCN 1, 2A); **AND**
1. Individual is using as a single agent for adjuvant therapy; **AND**
2. Individual has resected stage IIB, stage IIC, stage III, or stage IV disease; **AND**
3. Individual has a current ECOG performance status of 0-2; **AND**
4. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
5. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

C. Individual has Melanoma (Cutaneous or Uveal) (Label, NCCN 1, 2A); **AND**
1. Meets one of the following:
a. Individual has melanoma with involvement of lymph nodes; **OR**
b. Individual has metastatic melanoma and has undergone complete resection;

AND

2. Individual is using as a single agent for adjuvant therapy;

OR

D. Individual has metastatic or unresectable melanoma (Cutaneous or Uveal) (NCCN 1, 2A); **AND**
1. Individual is using as second-line or subsequent systemic therapy; **AND**
2. Using in combination with ipilimumab for disease progression on single-agent anti-PD-1 therapy; **OR**
3. Using as a single agent or in combination with ipilimumab if disease control occurred with prior anti-PD-1 immunotherapy as re-induction therapy;

OR

XXVI. Individual has a diagnosis of metastatic Melanoma with brain metastases (NCCN 2A); **AND**
A. Individual has a primary diagnosis of melanoma; **AND**
B. Using in one of the following ways:
1. Individual has asymptomatic brain metastases (Long 2017, 2018, Tawbi 2017); **OR**
2. Individual has BRAF non-specific asymptomatic brain metastases; **AND**

3. Individual is using as monotherapy or in combination with ipilimumab;

AND

4. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
5. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXVII. Individual has a diagnosis of Merkel Cell Carcinoma (Label, NCCN 2A); **AND**

A. Individual is using as a single agent; **AND**
B. Individual has presence of metastatic or recurrent locoregional MCC determined to be not amenable to definitive surgery or radiation therapy; **AND**
C. Individual has a current ECOG performance status of 0-2; **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

F. Individual is using as a single agent or in combination with ipilimumab (NCCN 2A); **AND**
G. Individual has M1 disseminated disease if anti-PD-L1 or anti-PD-1 therapy is contraindicated or disease has progressed on anti-PD-L1 or anti-PD-1 monotherapy; **AND**
H. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXVIII. Individual has a diagnosis of Non-Small Cell Lung Cancer (NSCLC) (Label, NCCN 2A); **AND**

A. Individual has recurrent, advanced, or metastatic NSCLC; **AND**
    1. Individual is using as a single agent; **AND**
    2. Individual has confirmation of disease progression on or after platinum-containing chemotherapy; **AND**
    3. Individual has a current ECOG performance status of 0-2; **AND**
    4. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
    5. Individual is not receiving therapy for an autoimmune disease, chronic condition or interstitial lung disease with a systemic immunosuppressant;

OR

B. Individual has recurrent, advanced, or metastatic NSCLC and using as first-line therapy (Label, NCCN 1, 2A); **AND**
    1. Individual is using in combination with ipilimumab; **AND**
    2. Individual does not have presence of actionable molecular markers*; **AND**
    3. Current ECOG performance status of 0-2; **AND**
    4. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
    5. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

C. Individual has recurrent, advanced, or metastatic NSCLC and using as first-line therapy (Label, NCCN 1, 2A); **AND**
   1. Individual is using in combination with ipilimumab *and* 2 (two) cycles of platinum-doublet chemotherapy (i.e., platinum-based chemotherapy with pemetrexed, or carboplatin with paclitaxel); **AND**
   2. Individual does not have presence of actionable molecular markers*; **AND**
   3. Current ECOG performance status of 0-2; **AND**
   4. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
   5. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

D. Individual is using for continuation treatment of recurrent, advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) (NCCN 1, 2A); **AND**
   1. Individual is using in combination with ipilimumab (Yervoy); **AND**
   2. Individual achieved a response or has stable disease following first line therapy of intravenous nivolumab (Opdivo) + ipilimumab +/- chemotherapy given; **AND**
   3. Individual does not have presence of actionable molecular markers*; **AND**
   4. Current ECOG performance status of 0-2; **AND**
   5. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

E. Individual has resectable NSCLC and using as neoadjuvant therapy (Label, NCCN 2A); **AND**
   1. Individual is using in combination with platinum-doublet chemotherapy (e.g. paclitaxel and carboplatin); **AND**
   2. Resectable is defined as tumors ≥ 4 cm or node positive; **AND**
   3. Current ECOG performance status of 0-2; **AND**
   4. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
   5. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

F. Individual has resectable NSCLC (Label, NCCN 1); **AND**
   1. Resectable is defined as tumors ≥ 4 cm and/or node positive; **AND**
   2. Individual has no known EGFR mutations or ALK rearrangements; **AND**
   3. Using as adjuvant therapy post-surgery; **AND**
   4. Individual is using Opdivo as a single agent after prior combination use of Opdivo and platinum-doublet chemotherapy; **AND**
   5. Current ECOG performance status of 0-2; **AND**
   6. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
   7. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXIX. Individual has a diagnosis of metastatic NSCLC with brain metastases (NCCN 2A); **AND**

A. Individual has a primary diagnosis of non-small cell lung cancer; **AND**
B. Individual is using as single agent for brain metastases; **AND**
C. Individual has PD-L1 expression positive (≥ 1%) tumors; **AND**

D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXX. Individual has a diagnosis of Primary Mediastinal Large B-Cell Lymphoma (NCCN 2A); **AND**

A. Individual is using for pediatric aggressive mature B-cell lymphoma; **AND**
    1. Individual is using for relapsed or refractory disease as a single agent; **OR**
    2. Individual is using for consolidation/additional therapy in combination with brentuximab vedotin after partial response achieved after therapy for relapsed or refractory disease;

AND

B. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXI. Individual has a diagnosis of Renal Cell Carcinoma (RCC) (Label, NCCN 2A); **AND**

A. Individual has advanced or metastatic RCC; **AND**
    1. Individual is using as monotherapy; **AND**
    2. Histologic confirmation of RCC with clear-cell component; **AND**
    3. Individual has confirmation of disease progression after one or two prior anti-angiogenic regimens (for example, axitinib, bevacizumab [or its biosimilar], pazopanib, sorafenib, sunitinib, etc.) for treatment of advanced or metastatic disease; **AND**
    4. Individual has a current ECOG performance status 0-2; **AND**
    5. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
    6. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with an immunosuppressant;

OR

B. Individual has intermediate- or poor-risk, advanced RCC (Label, NCCN 1, 2A); **AND**
    1. Individual is using in combination with ipilimumab, for four cycles followed by single agent Opdivo (nivolumab) as first-line therapy for previously untreated RCC; **OR**
    2. Individual is using in combination with ipilimumab for four cycles followed by single agent Opdivo (nivolumab), as subsequent therapy, if no checkpoint blockade (PD-1, PD-L1, or CTLA-4) antibody treatment has been previously administered (NCCN 2A); **AND**
    3. Histologic confirmation of RCC with clear-cell component; **AND**
    4. Individual has a current ECOG performance status 0-2; **AND**
    5. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
    6. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

C. Individual has relapsed, recurrent, or advanced RCC (Label, NCCN 1, 2A); **AND**
    1. Individual is using as first-line therapy or subsequent therapy in combination with cabozantinib tablets; **AND**
    2. Current ECOG performance status of 0-2; **AND**
    3. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
    4. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

D. Individual has relapsed, recurrent, or advanced RCC (NCCN 2A); **AND**
    1. Individual is using as subsequent therapy in combination with cabozantinib or ipilimumab; **AND**
    2. Individual has a current ECOG performance status of 0-2; **AND**
    3. Individual has had prior immune-oncology therapy (e.g. pembrolizumab); **AND**
    4. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

E. Individual has relapse or metastatic non-clear cell RCC (nccRCC) [including hereditary leiomyomatosis and renal cell carcinoma (HLRCC)] (NCCN 2A); **AND**
    1. Individual is using as systemic therapy as a single agent or in combination with cabozantinib; **AND**
    2. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
    3. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXII. Individual has a diagnosis of Small Bowel Adenocarcinoma (SBA) including Ampullary Adenocarcinoma (NCCN 2A); **AND**

A. Individual has advanced or metastatic disease (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation); **AND**
B. Individual is using as monotherapy or in combination with ipilimumab; **AND**
C. Current ECOG performance status of 0-2; **AND**
D. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXIII. Individual has a diagnosis of Extranodal NK/T-cell lymphomas (NCCN 2A); **AND**

A. Individual has relapsed/refractory disease; **AND**
B. Individual is using following treatment with asparaginase-based regimen; **AND**
C. Individual is using as monotherapy; **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual has a current ECOG performance status of 0-2; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXIV. Individual has a diagnosis of advanced or metastatic Soft Tissue Sarcoma and Aggressive Soft Tissue Neoplasms (NCCN 2A); **AND**

A. Individual is using in combination with ipilimumab; **OR**
B. Individual is using as a single agent; **AND**
C. Has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXV. Individual has a diagnosis of Squamous Cell Carcinoma of the Head and Neck (SCCHN) (Label, NCCN 1); **AND**

A. Individual has recurrent, unresectable, or metastatic SCCHN; **AND**
   1. Individual is using as monotherapy; **AND**
   2. Individual has confirmation of disease progression on or after platinum-containing chemotherapy; **AND**
   3. Individual has a current ECOG performance status of 0-2; **AND**
   4. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
   5. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXVI. Individual has a diagnosis of Head and Neck cancers (NCCN 1, 2A); **AND**

A. Using for one of the following types of cancers:
   1. Individual has recurrent, unresectable, oligometastatic, or metastatic Nasopharyngeal Cancers (NCCN 2A); **AND**
   2. Individual has no surgery or radiotherapy (RT) options; **AND**
      a. Individual is using nivolumab in combination with cisplatin and gemcitabine; **OR**
      b. Individual is using nivolumab as monotherapy for first-line or systemic therapy if previously treated;

      AND
   3. Has not received another anti-PD-1 or anti-PD-L1 agent; **OR**
B. Individual has squamous recurrent, unresectable, or metastatic non-nasopharyngeal cancer; **AND**
   1. Individual has no surgery or radiotherapy options; **AND**
   2. Individual is using as monotherapy or in combination with cetuximab;

OR

XXXVII. Individual has metastatic Anaplastic Thyroid carcinoma (NCCN 2A); **AND**

A. Individual is using as a single agent; **AND**
B. Current ECOG performance status of 0-2; **AND**
C. Has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXVIII. Individual has Urothelial carcinoma (Label, NCCN 1, 2A); **AND**

A. Individual has locally advanced, recurrent, or metastatic disease; **AND**
   1. Individual is using as a single agent; **AND**
   2. Individual meets the following criteria:

a. Confirmation of disease progression on or after platinum or other chemotherapy; **OR**
b. Confirmation of disease progression within 12 months of receiving neoadjuvant or adjuvant treatment with platinum-containing chemotherapy;

OR

B. Individual is using as single agent for adjuvant therapy; **AND**
1. Individual is at high risk of recurrence after having radical resection;

AND

C. Individual has a current ECOG performance status of 0-2; **AND**
D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXIX. Individual has urothelial carcinoma (Label, NCCN 1, 2A); **AND**
A. Individual has unresectable, recurrent or metastatic disease; **AND**
B. Individual is using in combination with cisplatin and gemcitabine; **AND**
C. Individual is using as first-line treatment; **AND**
D. Current ECOG performance status of 0-2; **AND**
E. Has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XL. Individual has a diagnosis of Urothelial Carcinoma of the Prostate (NCCN 2A); **AND**
A. Individual is using as adjuvant therapy; **AND**
B. Individual is using for tumors with stromal invasion if platinum-based neoadjuvant chemotherapy not given and pT3, pT4a, pN+; **AND**
C. Individual is using as a single agent;

OR

XLI. Individual has a diagnosis of Central Nervous System Cancers- Pediatric Diffuse High-Grade Gliomas (NCCN 2A); **AND**
A. Individual is using as single agent for hypermutant tumor; **AND**
B. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XLII. Individual has a diagnosis of recurrent or metastatic Vaginal Cancer (NCCN 2A); **AND**
A. Individual is using a single agent; **AND**
B. Individual is using as second-line or subsequent therapy; **AND**
C. Individual has PD-L1 expression positive (CPS ≥ 1%) tumor; **AND**
D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XLIII. Individual has a diagnosis of recurrent or metastatic Vulvar Cancer (NCCN 2A); **AND**
A. Individual is using as a single agent; **AND**

B. Individual is using as second-line or subsequent therapy; **AND**
C. Individual has HPV-related tumor; **AND**
D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant.

***Note:** Actionable molecular markers include EGFR, ALK, KRAS, ROS1, BRAF, NTRK, MET, RET, ERBB2 (HER2) and NRG1 mutations. The NCCN panel recommends testing prior to initiating therapy to help guide appropriate treatment. If there is insufficient tissue to allow testing for all of these markers, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes (NCCN 1, 2A).

Opdivo (nivolumab) may not be approved when the above criteria are not met and for all other indications.

Key References:

1. Apolo AB, da Motta Girardi D, Niglio SA, et al. Final results from a phase I trial and expansion cohorts of cabozantinib and nivolumab (CaboNivo) alone or with ipilimumab (CaboNivoIpi) for metastatic genitourinary tumors. ASCO; 2021. Available at: https://meetinglibrary.asco.org/record/194730/abstract.
2. Azad NS, Gray RJ, Overman MJ, et al. Nivolumab Is Effective in Mismatch Repair-Deficient Noncolorectal Cancers: Results From Arm Z1D-A Subprotocol of the NCI-MATCH (EAY131) Study. *J Clin Oncol*. 2020;38(3):214-222. doi:10.1200/JCO.19.00818 Available at: https://ascopubs.org/doi/10.1200/JCO.19.00818.
3. Chan TSY, Li J, Loong F, Khong PL, Tse E, Kwong YL. PD1 blockade with low-dose nivolumab in NK/T cell lymphoma failing L-asparaginase: efficacy and safety. *Ann Hematol*. 2018;97(1):193-196. doi:10.1007/s00277-017-3127-2.
4. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2022. URL: http://www.clinicalpharmacology.com. Updated periodically.
5. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Updated periodically.
6. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
7. Gauvain C, Vauléon E, Chouaid C, et al. Intracerebral efficacy and tolerance of nivolumab in non-small-cell lung cancer patients with brain metastases [published correction appears in Lung Cancer. 2019 Oct;136:159]. Lung Cancer. 2018;116:62-66. doi:10.1016/j.lungcan.
8. Ghorani E, Kaur B, Fisher RA, et al. Pembrolizumab is effective for drug-resistant gestational trophoblastic neoplasia. Lancet 2017;390:2343- 2345. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29185430.
9. Goldman JW, Crino L, Vokes EE, et al. Nivolumab (nivo) in patients (pts) with advanced (adv) NSCLC and central nervous system (CNS) metastases (mets). J Thorac Oncol. 2016;34(15):9038. Doi:10.1200/JCO.2016.34.15_supple.9038. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.9038.
10. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med. 2018; 378(22):2093-2104.
11. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Eng J Med.* 2019;381:2020-31.
12. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2021; Updated periodically.
13. Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicenter randomized phase 2 study. *Lancet Oncol.* 2018;19:672-81.
14. Long GV, Atkinson V, Menzies AM, et al. A randomized phase II study of nivolumab or nivolumab combined with ipilimumab in patients with melanoma brain metastases: the Anti-PD1 Brain Collaboration. *J Clin Oncol.* 2017;35:9508[abstract]. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.9508.
15. Morris VK, Salem ME, Nimeiri H, et al. Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicentre, single-arm, phase 2 study. Lancet Oncol 2017;18:446-453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28223062.

16. Moehler M, Shitara K, Garrido M, et al. Nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: first results of the CheckMate 649 study. [abstract]. Presented at the Oral Presentation presented at the ESMO 2020 Annual Meeting; September 19-21, 2020; Virtual Meeting. Available at: https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/nivolumab-nivo-plus-chemotherapy-chemo-versus-chemo-as-first-line-1l-treatment-for-advanced-gastric-cancer-gastroesophageal-junction-cancer.
17. Naumann RW, Hollebecque A, Meyer T, et al. Safety and Efficacy of Nivolumab Monotherapy in Recurrent or Metastatic Cervical, Vaginal, or Vulvar Carcinoma: Results From the Phase I/II CheckMate 358 Trial. *J Clin Oncol*. 2019;37(31):2825-2834. doi:10.1200/JCO.19.00739 Available at: https://ascopubs.org/doi/full/10.1200/JCO.19.00739.
18. NCCN Clinical Practice Guidelines in Oncology™. © 2025 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. January 17, 2025.
    a. Ampullary adenocarcinoma. V2.2025. Revised January 10, 2025.
    b. Anal Carcinoma. V1.2025. Revised December 4, 2024.
    c. Biliary Tract Cancers. V6.2024. Revised January 10, 2024.
    d. B-Cell Lymphomas. V1.2025. Revised December 20, 2024.
    e. Bladder cancer. V5.2024. Revised October 28, 2024.
    f. Bone cancer. V1.2025. Revised August 20, 2024.
    g. Central Nervous System Cancers V3.2024. Revised September 30, 2024.
    h. Cervical Cancer. V1.2025. Revised December 19, 2024.
    i. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. V1.2025. Revised October 1, 2024.
    j. Colon Cancer V6.2024. Revised January 17, 2025.
    k. Cutaneous Melanoma. V1.2025. December 20. 2024.
    l. Esophageal and esophagogastric junction cancers. V5.2024. Revised December 20, 2024.
    m. Gastric cancer. V5.2024. Revised December 20, 2024.
    n. Gestational Trophoblastic Neoplastic. V1.2025. Revised December 17, 2024.
    o. Head and neck cancers. V1.2025. Revised November 26, 2024
    p. Hepatocellular Carcinoma. V4.2024. Revised January 10, 2025.
    q. Hodgkin Lymphoma V1.2024. Revised October 12, 2023.
    r. Kaposi Sarcoma. V2.2025. Revised January 14, 2025.
    s. Kidney Cancer. V3.2025. Revised January 9, 2025
    t. Merkel Cell Carcinoma. V1.2024. Revised November 22, 2023.
    u. Malignant Pleural Mesothelioma V2.2025. Revised January 14, 2025.
    v. Malignant Peritoneal Mesothelioma. V2.2025. Revised January 14, 2025.
    w. Cutaneous Melanoma V3.2023. Revised October 27, 2023.
    x. Neuroendocrine and Adrenal Tumors. V1.2023. Revised August 2, 2023.
    y. Non-Small Cell Lung Cancer. V3.2025. Revised January 14, 2025.
    z. Pediatric Aggressive Mature B-Cell Lymphomas. V2.2024. Revised September 3, 2024.
    aa. Pediatric Central Nervous System Cancers. V1.2025. Revised November 8, 2024.
    bb. Pediatric Hodgkin Lymphoma. V1.2024. Revised May 14, 2024.
    cc. Rectal Cancer V4.2024. Revised August 22, 2024.
    dd. Small Bowel Adenocarcinoma. V1.2025. Revised December 4, 2024.
    ee. Small cell lung cancer. V4.2025. Revised January 13, 2025.
    ff. Soft Tissue Sarcoma. V4.2024. Revised November 21, 2024.
    gg. T-Cell Lymphomas. V1.2025. Revised November 11, 2024.
    hh. Thyroid Carcinoma. V5.2024. Revised January 15, 2025.
    ii. Uterine neoplasms. V1.2025. Revised December 16, 2024.
    jj. Vaginal Cancer V3.2025. Revised December 16, 2024.
    kk. Uveal Melanoma. V1.2024. Revised May 23, 2024.
    ll. Vulvar Cancer. V4.2024. Revised May 1, 2024.
19. Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. *J Clin Oncol.* 2018;36:773-9. Available at: https://ascopubs.org/doi/pdf/10.1200/JCO.2017.76.9901.
20. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicenter, phase 2 study. *Lancet Oncol.* 2017;18:1182-91.
21. Rizvi NA, Mazières J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol. 2015;16(3):257-265. doi:10.1016/S1470-2045(15)70054-9 Available at: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)70054-9/fulltext.
22. Tawbi HA, Forsyth AJ, Algazi AP, et al. Efficacy and safety of nivolumab (NIVO) plus ipilimumab (IPI) in patients with melanoma (MEL) metastatic to the brain: results of the phase II study CheckMate 204. *J Clin Oncol.* 2017;35:9507-9507[abstract]. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.9507.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.