

Medical Policy Manual **Draft Revised Policy: Do Not Implement**

Nivolumab (Opdivo®)

IMPORTANT REMINDER

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the medical policy and a health plan or government program (e.g., TennCare), the express terms of the health plan or government program will govern.

**The proposal is to add text/statements in red and to delete text/statements with strikethrough:
POLICY**

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.

FDA-Approved Indications

Unresectable or Metastatic Melanoma

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 unresectable or metastatic melanoma.

Adjuvant Treatment of Melanoma

Opdivo is indicated for the adjuvant treatment of adult and pediatric patients 12 years and older with completely resected stage IIB, stage IIC, stage III, or stage IV melanoma.

Metastatic Non-Small Cell Lung Cancer

- 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 ($\geq 1\%$) 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.

Neoadjuvant Treatment of Resectable Non-Small Cell Lung Cancer

Opdivo, in combination with platinum-doublet chemotherapy, is indicated **for the** ~~as~~ neoadjuvant treatment of adult patients with resectable (tumors ≥ 4 cm or node positive) non-small cell lung cancer (NSCLC) **and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements, followed by single-agent Opdivo as adjuvant treatment after surgery.**

Neoadjuvant and Adjuvant 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) and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements, followed by single-agent OPDIVO as adjuvant treatment after surgery.

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Malignant Pleural Mesothelioma

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

Advanced Renal Cell Carcinoma

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

Classical Hodgkin Lymphoma

Opdivo is indicated for the treatment of adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after:

- Autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
- Three or more lines of systemic therapy that includes autologous HSCT.

Squamous Cell Carcinoma of the Head and Neck

Opdivo 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.

Urothelial Carcinoma

- 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.
- Opdivo, in combination with cisplatin and gemcitabine, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.
- Opdivo is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who:
 - Have disease progression during or following platinum-containing chemotherapy
 - Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer

- OPDIVO, in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC).
- Opdivo, as a single agent, 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.

Hepatocellular Carcinoma

- Opdivo, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC).
- Opdivo, in combination with ipilimumab, is indicated for the treatment of adult patients with unresectable or metastatic **hepatocellular carcinoma** (HCC) who have been previously treated with sorafenib.

Esophageal Carcinoma

- Opdivo is indicated for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in adult patients who have received neoadjuvant chemoradiotherapy (CRT).

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- 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) **whose tumors express PD-L1 (≥ 1)**.
- 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) **whose tumors express PD-L1 (≥ 1)**.
- 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.

Gastric Cancer, Gastroesophageal Junction Cancer, Esophageal Adenocarcinoma

Opdivo, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the treatment of adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma **whose tumors express PD-L1 (≥ 1)**.

Compendial Uses

- Cutaneous melanoma
- Non-small cell lung cancer
- Renal cell carcinoma
- Classical Hodgkin lymphoma
- Head and neck cancers
- Urothelial carcinoma
 - Bladder cancer
 - Primary carcinoma of the urethra
 - Upper genitourinary tract tumors
 - Urothelial carcinoma of the prostate
- Colorectal cancer, including appendiceal adenocarcinoma and anal adenocarcinoma
- Hepatocellular carcinoma
- Uveal Melanoma
- Anal Carcinoma
- Merkel Cell Carcinoma
- Central Nervous System (CNS) brain metastases
- Gestational trophoblastic neoplasia
- Pleural mesothelioma
- Peritoneal mesothelioma
- Small bowel adenocarcinoma
- Ampullary Adenocarcinoma
- Extranodal NK/T-cell lymphoma
- Endometrial Carcinoma
- Vulvar Cancer
- Gastric Cancer
- Esophageal/Esophagogastric Junction Cancers
- Small cell lung cancer
- Cervical Cancer
- Pediatric Diffuse High-Grade Gliomas
- Pediatric Primary Mediastinal Large B-cell Lymphoma
- Kaposi Sarcoma
- Bone Cancer
- Biliary Tract Cancers

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- Cholangiocarcinoma
- Gallbladder Cancer
- Soft Tissue Sarcoma
 - Extremity/body wall sarcoma
 - Head/neck sarcoma
 - Retroperitoneal/intra-abdominal sarcoma
 - Rhabdomyosarcoma
 - Angiosarcoma
- Anaplastic Thyroid Carcinoma
- Histologic (Richter) transformation to diffuse large B-cell lymphoma
- Vaginal Cancer
- Squamous Cell Skin **Carcinoma** ~~cancer~~

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

DOCUMENTATION

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

- Documentation of laboratory report confirming MSI-H, mismatch repair deficient (dMMR), or polymerase epsilon/delta (POLE/POLD1) tumor status, where applicable.
- Documentation of programmed death ligand 1 (PD-L1) tumor expression, where applicable.
- Documentation of **molecular testing for the presence of EGFR alterations exon 19 deletions or exon 21 L858R mutations or ALK , RET, and ROS1 rearrangements**, where applicable.

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 **unless any of the following apply:** ~~(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).~~

- **The requested medication will be used for treatment of metastatic or unresectable melanoma**
- **The requested medication will be used for treatment of metastatic or unresectable small bowel adenocarcinoma in combination with ipilimumab following progression on single agent checkpoint inhibitor therapy**
- **The requested medication will be used for treatment of hepatocellular carcinoma following progression on therapy with atezolizumab plus bevacizumab**

COVERAGE CRITERIA

Cutaneous Melanoma

Authorization of 6 months may be granted for treatment of cutaneous melanoma **when any** ~~in either~~ of the following **apply** ~~settings:~~

- The requested medication 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.
- The requested medication will be used as a single agent or in combination with ipilimumab (4 doses of ipilimumab, followed by Opdivo as a single agent) as adjuvant treatment of stage III or IV disease following complete resection or no evidence of disease.

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- The requested medication will be used as ~~a single agent as~~ adjuvant treatment of stage IIB and IIC disease following complete resection.
- The requested medication will be used as a single agent or in combination with ipilimumab (4 doses of ipilimumab, followed by Opdivo as a single agent) as neoadjuvant treatment ~~of resectable disease.~~

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 **when both** ~~if either~~ of the following criteria are met:
 - There are no EGFR exon 19 deletions, ~~or~~ exon 21 L858R mutations, or ALK, **RET, or ROS1** rearrangements (unless testing is not feasible due to insufficient tissue) ~~and the requested medication will be used in a regimen containing ipilimumab.~~
 - The requested medication will be used **in a regimen containing ipilimumab or** as single agent subsequent therapy.
- 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 **when there are no known EGFR mutations or ALK rearrangements (unless testing is not feasible due to insufficient tissue).**
- Authorization of 6 months may be granted for neoadjuvant **and adjuvant** treatment of resectable non-small cell lung cancer (NSCLC) when both of the following conditions are met:
 - There are no EGFR **mutations** ~~exon 19 deletions or exon 21 L858R mutations~~ or ALK rearrangements (unless testing is not feasible due to insufficient tissue)
 - The requested medication is used in combination with platinum-doublet chemotherapy (for up to 4 cycles total), followed by single agent adjuvant therapy (for up to 13 cycles)

Renal Cell Carcinoma

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

- The requested medication will be used as a single agent for clear cell histology as subsequent therapy.
- The requested medication will be used as a single agent for non-clear cell histology.
- The requested medication will be used in combination with ipilimumab (4 doses of ipilimumab, followed by Opdivo as a single agent) for disease with clear cell histology.
- The requested medication will be used in combination with cabozantinib.

Classic Hodgkin Lymphoma (cHL)

Authorization of 6 months may be granted for treatment of classic Hodgkin lymphoma when **the requested regimen will be used in** any of the following **regimens** ~~criteria are met:~~

- ~~The requested medication will be used As a single agent subsequent therapy and the member has relapsed or refractory disease that was either heavily pretreated or there was a decrease in cardiac function.~~
- ~~The requested medication will be used In combination with brentuximab vedotin~~
- ~~or In combination with ICE (ifosfamide, carboplatin, etoposide) for relapsed or refractory disease.~~
- ~~The requested medication will be used as a single agent for disease refractory to at least three lines of prior therapy.~~
- ~~The requested medication will be used In combination with AVD (doxorubicin, vinblastine, and dacarbazine) for stage III-IV disease.~~

Head and Neck Cancers

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Authorization of 6 months may be granted for treatment of head and neck cancers in members **with** ~~who meet~~ either of the following ~~criteria~~:

- **Non-nasopharyngeal very advanced head and neck cancer that is** ~~For~~ unresectable, recurrent, persistent or metastatic, **in combination with cetuximab or as a single agent** ~~disease~~.
- ~~For~~ Nasopharyngeal cancer in combination with cisplatin and gemcitabine for unresectable, recurrent, persistent or metastatic disease.

Urothelial Carcinoma – Bladder Cancer

- Authorization of 6 months may be granted **when used** in combination with gemcitabine and cisplatin for up to 6 cycles followed by nivolumab maintenance therapy as first line treatment of 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:
 - As subsequent therapy for stage II, locally advanced, recurrent, persistent, or metastatic disease.
 - As adjuvant therapy in members who are at high risk of recurrence after undergoing resection.

Urothelial Carcinoma – Primary Carcinoma of the Urethra

- Authorization of 6 months may be granted in combination with gemcitabine and cisplatin for up to 6 cycles followed by nivolumab maintenance therapy as first line treatment of 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:
 - As subsequent therapy for recurrent, locally advanced, or metastatic disease.
 - As adjuvant therapy in members who are at high risk of recurrence after undergoing resection.

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

- Authorization of 6 months may be granted in combination with gemcitabine and cisplatin for up to 6 cycles followed by nivolumab maintenance therapy as first line treatment of metastatic upper genitourinary (GU) 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:
 - As subsequent therapy for locally advanced or metastatic disease.
 - As adjuvant therapy in members who are at high risk of recurrence after undergoing resection.

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 **with ultra-hypermutated phenotype (e.g., tumor mutational burden (TMB) > 50 mut/Mb)** when used as a single agent or in combination with ipilimumab (4 doses of ipilimumab, followed by Opdivo as a single agent).

Small Bowel Adenocarcinoma

Authorization of 6 months may be granted as a single agent or in combination with ipilimumab (4 doses of ipilimumab, followed by Opdivo as a single agent) for treatment of unresectable, medically inoperable, advanced or metastatic small bowel adenocarcinoma for microsatellite-instability high (MSI-H), mismatch repair deficient (dMMR), or polymerase epsilon/delta (POLE/POLD1) tumors **with ultra-hypermutated phenotype (e.g., tumor mutational burden (TMB) > 50 mut/Mb)**.

Ampullary Adenocarcinoma

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

Hepatocellular Carcinoma

Authorization of 6 months may be granted **for treatment of hepatocellular carcinoma for either of the following:**

- **First-line treatment of unresectable or extrahepatic/metastatic disease as a single agent or in combination with ipilimumab (4 doses of ipilimumab, followed by Opdivo as a single agent) for treatment of hepatocellular carcinoma.**
- **Subsequent treatment as a single agent or in combination with ipilimumab (4 doses of ipilimumab, followed by Opdivo as a single agent).**

Uveal Melanoma

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

Anal Carcinoma

Authorization of 6 months may be granted as a single agent for subsequent treatment of metastatic anal carcinoma.

Merkel Cell Carcinoma

Authorization of 6 months may be granted for treatment of Merkel cell carcinoma in any of the following settings:

- Metastatic disease.
- Neoadjuvant treatment of node positive disease and node negative locally advanced disease when used as a single agent.
- Unresectable, recurrent, or stage IV disease when used in combination with ipilimumab (4 doses of ipilimumab, followed by Opdivo as a single agent).

CNS Brain Metastases

Authorization of 6 months may be granted for treatment of CNS brain metastases when either of the following criteria are met:

- The requested medication will be used as a single agent or in combination with ipilimumab (4 doses of ipilimumab, followed by Opdivo as a single agent) in members with melanoma.
- The requested medication will be used as a single agent in members with PD-L1 positive non-small cell lung cancer.

Gestational Trophoblastic Neoplasia

Authorization of 6 months may be granted as a single agent or in combination with ipilimumab for treatment of gestational trophoblastic neoplasia for multiagent chemotherapy-resistant disease when either of the following criteria is met:

- Member has recurrent or progressive intermediate trophoblastic tumor (placental site trophoblastic tumor or epithelioid trophoblastic tumor).
- Member has high-risk disease.

Pleural or Peritoneal Mesothelioma

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Authorization of 6 months may be granted for the treatment of pleural or peritoneal mesothelioma, including pericardial mesothelioma and tunica vaginalis testis mesothelioma, in either of the following settings:

- The requested medication will be used as first line **or induction** therapy in combination with ipilimumab.
- The requested medication will be used as subsequent therapy as a single agent or in combination with ipilimumab.

Esophageal and Esophagogastric Junction Cancer

- Authorization of 6 months may be granted for treatment of esophageal or esophagogastric junction cancer in members who are not surgical candidates or have unresectable locally advanced, recurrent or metastatic disease **for either of the following: when the requested medication will be used in combination with ipilimumab or chemotherapy or will be used as subsequent therapy.**
 - **First-line therapy when PD-L1 ≥ 1 and the requested medication will be used in combination with ipilimumab or chemotherapy**
 - **Subsequent therapy**
- Authorization of 6 months may be granted for adjuvant treatment of completely resected esophageal or esophagogastric junction cancer with residual pathologic disease.
- Authorization of 6 months may be granted as a single agent or in combination with ipilimumab 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.~~
- Authorization of 6 months may be granted for induction therapy for relieving dysphagia in combination with ipilimumab or chemotherapy for members **with PD-L1 ≥ 1** planned for esophagectomy.

Extranodal NK/T-Cell Lymphoma

Authorization of 6 months may be granted for treatment of relapsed or refractory extranodal NK/T-cell lymphoma.

Endometrial Carcinoma

Authorization of 6 months may be granted as a single agent for subsequent treatment of recurrent ~~or metastatic~~ microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) endometrial carcinoma.

Vulvar Cancer

Authorization of 6 months may be granted for treatment of HPV-related advanced **or** recurrent/ metastatic vulvar cancer as subsequent therapy as a single agent.

Gastric Cancer

Authorization of 6 months may be granted for treatment of gastric cancer in any of the following settings:

- When the requested medication is being used in members who are not surgical candidates or have unresectable, recurrent, or metastatic disease **and PD-L1 ≥ 1** , when the requested medication will be used in combination with ipilimumab or chemotherapy.
- When the requested medication will be used as a single agent, ~~or~~ in combination with ipilimumab **or in combination with chemotherapy for treatment of** ~~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.~~
- ~~When the requested medication will be used in combination with ipilimumab or chemotherapy in members with early stage microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors and completed endoscopic resection.~~

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- ~~When the requested medication will be used in combination with chemotherapy in members with early stage HER-2 overexpression negative disease and completed endoscopic resection.~~

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.

Cervical Cancer

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

Pediatric Diffuse High-Grade Gliomas

Authorization of 6 months may be granted for hypermutant tumor pediatric diffuse high-grade glioma as adjuvant treatment or for recurrent or progressive disease.

Pediatric Primary Mediastinal Large B-Cell Lymphoma

Authorization of 6 months may be granted as a single agent or in combination with brentuximab vedotin for treatment of relapsed or refractory primary mediastinal large B-cell lymphoma.

Kaposi Sarcoma

Authorization of 6 months may be granted as a single agent or in combination with ipilimumab for subsequent treatment of relapsed/refractory ~~classic~~ Kaposi Sarcoma.

Bone Cancer

Authorization of 6 months may be granted in combination with ipilimumab for unresectable or metastatic disease when all of the following are met:

- Disease has tumor mutation burden-high (TMB-H) [≥ 10 mutations/megabase (mut/Mb)] tumors
- Disease has progressed following prior treatment and has no satisfactory alternative treatment options

Biliary Tract Cancers (Cholangiocarcinoma and Gallbladder Cancer)

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

Authorization of 6 months may be granted in combination with ipilimumab for neoadjuvant treatment of resectable locoregionally advanced gallbladder cancer that is tumor mutation burden-high (TMB-H) **when disease does not present as jaundice**.

Soft Tissue Sarcoma

Authorization of 6 months may be granted for treatment of soft tissue sarcoma in the following settings:

- 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.
- The requested medication will be used in combination with ipilimumab for the treatment of angiosarcoma.

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Anaplastic Thyroid Carcinoma

Authorization of 6 months may be granted as a single agent for treatment of stage IVC anaplastic thyroid carcinoma.

Histologic (Richter) transformation to diffuse large B-cell lymphoma

Authorization of 6 months may be granted for treatment of Histologic (Richter) transformation to diffuse large B-cell lymphoma as a single agent or in combination ibrutinib.

Vaginal Cancer

Authorization of 6 months may be granted as subsequent therapy for recurrent or metastatic vaginal cancer when the requested medication will be used as a single agent.

Squamous Cell Skin Carcinoma Cancer

Authorization of 6 months may be granted as a single agent for treatment of locally advanced, recurrent, unresectable, inoperable, incompletely resected, recurrent or metastatic squamous cell carcinoma that is not curable by when curative surgery or and curative radiation are not feasible.

CONTINUATION OF THERAPY

Adjuvant treatment of melanoma

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

Urothelial carcinoma

- Authorization of 6 months may be granted (up to 12 months total) for continued treatment in members requesting reauthorization for adjuvant treatment of urothelial carcinoma who have not experienced disease recurrence or an unacceptable toxicity.
- Authorization of 6 months may be granted (up to 24 months total) for continued treatment in members requesting reauthorization for urothelial carcinoma when the requested medication is used in combination with gemcitabine and cisplatin for up to 6 cycles followed by nivolumab maintenance therapy when the member has not experienced disease progression or an unacceptable toxicity.

Non-small cell lung cancer or pleural or peritoneal 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 (NSCLC) or pleural or peritoneal 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.
- Neoadjuvant treatment of resectable NSCLC will be approved for a total of 3 months of therapy (up to 3 cycles) when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

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- Authorization of 6 months may be granted for neoadjuvant treatment of resectable NSCLC (up to 4 cycles in combination with chemotherapy, followed by single agent adjuvant treatment up to 13 cycles) when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

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.

Gastric Cancer, Esophageal Cancer, and Esophagogastric Junction Carcinoma

Authorization of 6 months may be granted 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 for the following durations of therapy:

- Esophageal squamous cell carcinoma in combination with ipilimumab or chemotherapy for up to 24 months
- Unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma as a single agent until disease progression or unacceptable toxicity
- Adjuvant treatment of resected esophageal or esophagogastric junction cancer as a single agent for up to 12 months
- Gastric cancer, esophagogastric junction cancer, and esophageal adenocarcinoma in combination with chemotherapy for up to 24 months
- Gastric cancer in members who have completed endoscopic resection for up to 24 months

Biliary Tract Cancer (in combination with ipilimumab)

Authorization of 6 months may be granted (for 2 to 6 months total for neoadjuvant treatment, and for up to 24 months total for other clinical settings) for continued treatment in members requesting reauthorization for biliary tract cancer when the requested medication is being used in combination with ipilimumab and when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

Squamous Cell Skin Cancer

Authorization of 6 months may be granted (up to 24 months total) for continued treatment in members requesting reauthorization for squamous cell skin cancer when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

All Other Indications

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

MEDICATION QUANTITY LIMITS

Drug Name	Diagnosis	Maximum Dosing Regimen
Opdivo (Nivolumab)	Ampullary Adenocarcinoma	Route of Administration: Intravenous Initial: 3mg/kg every 3 weeks for 4 doses Maintenance: 240mg every 2 weeks or 480 mg every 4 weeks
Opdivo (Nivolumab)	Anal Carcinoma	Route of Administration: Intravenous



		240mg every 2 weeks 480mg every 4 weeks
Opdivo (Nivolumab)	Anaplastic Thyroid Carcinoma	Route of Administration: Intravenous 240mg every 2 weeks 480mg every 4 weeks
Opdivo (Nivolumab)	Biliary Tract Cancer: Gallbladder Cancer, Cholangiocarcinoma, Bone Cancer	Route of Administration: Intravenous 240mg every 2 weeks
Opdivo (Nivolumab)	(CNS) Cancer - Brain Metastases	Route of Administration: Intravenous 240mg every 2 weeks 480mg every 4 weeks Initial: 1mg/kg every 3 weeks for 4 doses Maintenance: 240mg every 2 weeks or 480 mg every 4 weeks
Opdivo (Nivolumab)	Cervical Cancer, Kaposi Sarcoma	Route of Administration: Intravenous 240mg every 2 weeks 480mg every 4 weeks
Opdivo (Nivolumab)	Classical Hodgkin Lymphoma	Route of Administration: Intravenous ≥18 Years 240mg every 2 weeks 480mg every 4 weeks 3mg/kg every 3 weeks for 4 to 8 doses
Opdivo (Nivolumab)	Colorectal Cancer, including Appendiceal Adenocarcinoma and Anal Adenocarcinoma	Route of Administration: Intravenous <u>≥12 Years</u> <40kg 3mg every 2 weeks Initial: 3mg/kg every 3 weeks for 4 doses Maintenance: 3mg/kg every 2 weeks ≥40kg 240mg every 2 weeks 480mg every 4 weeks Initial: 3mg/kg every 3 weeks for 4 doses Maintenance: 240mg every 2 weeks or 480 mg every 4 weeks
Opdivo (Nivolumab)	Endometrial Carcinoma	Route of Administration: Intravenous 240mg every 2 weeks 480mg every 4 weeks Initial: 3mg/kg every 2 weeks for 8 doses Maintenance: 480mg every 4 weeks
Opdivo (Nivolumab)	Esophageal Cancer, Gastric Cancer, Gastroesophageal Junction Cancer	Route of Administration: Intravenous 240mg every 2 weeks 360mg every 3 weeks
Opdivo (Nivolumab)	Esophageal Cancer, Gastroesophageal Junction Cancer	Route of Administration: Intravenous 480mg every 4 weeks



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Opdivo (Nivolumab)	Extranodal NK/T-Cell Lymphomas	Route of Administration: Intravenous 240mg every 2 weeks 480mg every 4 weeks
Opdivo (Nivolumab)	Gestational Trophoblastic Neoplasia	Route of Administration: Intravenous 240mg every 2 weeks 480mg every 4 weeks
Opdivo (Nivolumab)	Head and Neck Cancer, Squamous Cell Carcinoma	Route of Administration: Intravenous 240mg every 2 weeks 480mg every 4 weeks
Opdivo (Nivolumab)	Hepatocellular Carcinoma	Route of Administration: Intravenous 240mg every 2 weeks 480mg every 4 weeks Initial: 1mg/kg every 3 weeks for 4 doses Maintenance: 240mg every 2 weeks or 480 mg every 4 weeks
Opdivo (Nivolumab)	Histologic (Richter) Transformation to Diffuse Large B-cell Lymphoma	Route of Administration: Intravenous 240mg every 2 weeks 480mg every 4 weeks
Opdivo (Nivolumab)	Melanoma	Route of Administration: Intravenous <u>≥12 Years</u> <40kg 3mg/kg every 2 weeks 6mg/kg every 4 weeks Initial: 1mg/kg every 3 weeks for 4 doses Maintenance: 3mg/kg every 2 weeks or 6 mg/kg every 4 weeks ≥40kg Initial: 3mg/kg every 3 weeks for 4 doses Maintenance: 480mg every 4 weeks beginning 6 weeks after initial dose
Opdivo (Nivolumab)	Melanoma or Melanoma, Uveal	Route of Administration: Intravenous <u>≥12 Years</u> ≥40kg 240mg every 2 weeks 480mg every 4 weeks Initial: 1mg/kg every 3 weeks for 4 doses Maintenance: 240mg every 2 weeks or 480 mg every 4 weeks
Opdivo (Nivolumab)	Merkel Cell Carcinoma	Route of Administration: Intravenous 240mg every 2 weeks Initial: 3mg/kg every 3 weeks for 4 doses Maintenance: 3mg/kg every 2 weeks
Opdivo (Nivolumab)	Merkel Cell Carcinoma, Neoadjuvant	Route of Administration: Intravenous 240mg every 2 weeks for 2 doses



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Opdivo (Nivolumab)	Mesothelioma (Pleural, Peritoneal, Pericardial, or Tunica Vaginalis Testis)	Route of Administration: Intravenous 240mg every 2 weeks 360mg every 3 weeks 480mg every 4 weeks
Opdivo (Nivolumab)	Non-Small Cell Lung Cancer (NSCLC)	Route of Administration: Intravenous 360mg every 3 weeks
Opdivo (Nivolumab)	Non-Small Cell Lung Cancer, Neoadjuvant	Route of Administration: Intravenous 360mg every 3 weeks for 3 doses
Opdivo (Nivolumab)	Non-Small Cell Lung Cancer or Small Cell Lung Cancer	Route of Administration: Intravenous 240mg every 2 weeks 480mg every 4 weeks
Opdivo (Nivolumab)	Non-Small Cell Lung Cancer, Neoadjuvant and Adjuvant	Route of Administration: Intravenous Initial: 360mg every 3 weeks for 4 doses (neoadjuvant) Maintenance: 480mg every 4 weeks as adjuvant treatment after surgery
Opdivo (Nivolumab)	Pediatric Diffuse High-Grade Gliomas	Route of Administration: Intravenous <18 Year(s) 3mg/kg every 2 weeks
Opdivo (Nivolumab)	Pediatric Primary Mediastinal Large B-Cell Lymphoma	Route of Administration: Intravenous <18 Year(s) 3mg/kg every 2 weeks
Opdivo (Nivolumab)	Renal Cell Carcinoma	Route of Administration: Intravenous 240mg every 2 weeks 480mg every 4 weeks Initial: 3mg/kg every 3 weeks for 4 doses Maintenance: 240mg every 2 weeks or 480 mg every 4 weeks
Opdivo (Nivolumab)	Small Bowel Adenocarcinoma	Route of Administration: Intravenous 240mg every 2 weeks 480mg every 4 weeks Initial: 3mg/kg every 3 weeks for 4 doses Maintenance: 240mg every 2 weeks
Opdivo (Nivolumab)	Soft Tissue Sarcoma: Angiosarcoma, Extremity/Body Wall Sarcoma, Head/Neck Sarcoma, Retroperitoneal/Intra-Abdominal Sarcoma, Rhabdomyosarcoma	Route of Administration: Intravenous 240mg every 2 weeks 480mg every 4 weeks
Opdivo (Nivolumab)	Urothelial Carcinoma	Route of Administration: Intravenous 240mg every 2 weeks 480mg every 4 weeks Initial: 360mg every 3 weeks for 6 doses Maintenance: 480mg every 4 weeks
Opdivo (Nivolumab)	Vulvar Cancer	Route of Administration: Intravenous 240mg every 2 weeks 480mg every 4 weeks

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APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

BlueCross BlueShield of Tennessee's Medical Policy complies with Tennessee Code Annotated Section 56-7-2352 regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

ADDITIONAL INFORMATION

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).

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3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Anal Carcinoma. Version **2.2025**. https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf Accessed **March 19**, 2025.
4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Melanoma: Cutaneous. Version **2.2025**. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed **March 19**, 2025.
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EFFECTIVE DATE

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