CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Bevacizumab (Avastin®) and Biosimilars: Bevacizumab-adcd (Vegzelma®) Bevacizumab-awwb (Mvasi®) Bevacizumab-bvzr (Zirabev®) Bevacizumab-maly (Alymsys®)

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Please note the following:

Bevacizumab (Avastin®) and biosimilars; Bevacizumab-adcd (Vegzelma®); Bevacizumab-awwb (Mvasi®), Bevacizumab-bvzr (Zirabev®), Bevacizumab-maly (Alymsys®)

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

Note: For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Bevacizumab (Avastin) and biosimilars; Bevacizumab-adcd (Vegzelma); Bevacizumab-awwb (Mvasi), Bevacizumab-bvzr (Zirabev), Bevacizumab-maly (Alymsys): Discussion

Bevacizumab and its biosimilars are humanized monoclonal antibodies that target the vascular endothelial growth factor A (VEGF-A). These drugs are used to treat different cancers. They inhibit microvascular cell growth and angiogenesis. They are used to inhibit blood vessel formation needed by cancer cells to grow and get oxygen and nutrients from nearby blood vessels.[1]

Bevacizumab, bevacizumab-adcd, bevacizumab-awwb, bevacizumab-maly, and bevacizumab-bvzr are vascular endothelial growth factor inhibitors approved by the FDA for the treatment of colorectal cancer, non-small cell lung cancer, glioblastoma in adults, renal cell carcinoma, cervical cancer, Epithelial ovarian and Hepatocellular carcinoma**.**

Bevacizumab and its biosimilars have clinically significant adverse reactions which are gastrointestinal perforations and fistulae, surgery and wound healing complications, hemorrhage, arterial and venous thromboembolic events, hypertension, posterior reversible encephalopathy syndrome (PRES), renal injury, proteinuria, infusion-related reactions, ovarian failure, and congestive heart failure.[2,3,4,5,6]

The National Comprehensive Cancer Network (NCCN) allows bevacizumab and its biosimilars for use in ampullary cancer, central nervous system cancers, cervical cancer, colon cancer, hepatocellular cancer, kidney cancer, mesothelioma (both pleural and peritoneal), non-small cell lung cancer, ovarian cancer, pediatric central nervous system cancers, rectal cancer, small bowel cancer, soft tissue sarcoma, uterine cancer, and vulvar cancer.[7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22]

Bevacizumab and Biosimilars: Definitions

- **Angiogenesis** - The formation of new blood vessels.
- **Biosimilar Drug** - An FDA approved biological drug that is like another biological drug (called the reference drug), which is made from living organisms, but may be made in a different way from the reference drug and of slightly different substances. A biosimilar drug must be shown to be as safe, same dose, work as well, work in the same way, and for the same condition as the reference drug.
- **Deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H)** - When the microsatellite DNA segments in cancer cells show changes (mutations), this indicates that the tumor cells are deficient in the repair of the mismatch errors. These cancers have microsatellite instability (also called MSI-High, MSI-H, or mismatch repair deficiency, dMMR).
- **Food and Drug Administration (FDA)** - The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
- **National Comprehensive Cancer Network (NCCN)** - An alliance of more than 30 leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.
- **Proficient mismatch repair/microsatellite-stable (pMMR/MMS)** - When microsatellite DNA segments are unchanged (not mutated), the tumor cells are considered microsatellite stable (MSS) or have proficient mismatch repair. MSS cancers have normal levels of mismatch repair gene and protein expression and are able to correct DNA mismatch repair errors proficiently.
- **Vascular endothelial growth factor (VEGF)** - a signaling protein that promotes the growth of new blood vessels. VEGF forms part of the mechanism that restores the blood supply to cells and tissues when they are deprived of oxygenated blood due to compromised blood circulation.

Bevacizumab and biosimilars: Policy

Note: Coverage of bevacizumab or its biosimilars will be provided for an FDA-approved indication or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation OR when all criteria are met.

Bevacizumab and its biosimilars will be considered for coverage when the following criteria are met:

Ampullary Adenocarcinoma

First-Line Therapy

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. In patients with a good performance status (ECOG 0-1, with good biliary drainage and adequate nutritional intake) in combination with one of the following regimens:
   a) FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan)
   b) FOLFOX (fluorouracil, leucovorin, and oxaliplatin)
   c) FOLFIRI (fluorouracil, leucovorin, and irinotecan)
   d) CAPEOX (capecitabine and oxaliplatin); OR
4. In select patients (poor performance status [PS] and ECOG PS 2) in combination with one of the following regimens:
   a) FOLFOX (fluorouracil, leucovorin, and oxaliplatin)
   b) FOLFIRI (fluorouracil, leucovorin, and irinotecan)
   c) Fluorouracil and leucovorin
   d) Capecitabine
   e) CAPEOX (capecitabine and oxaliplatin).

Note: The above regimens for treatment indications 3 and 4, are used for intestinal type that is one of the following:
   a) Unresectable localized disease
   b) Stage IV resected disease
   c) Metastatic disease at initial presentation

Subsequent (Second-Line or Greater)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. In combination with FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen for disease progression in patients with a good performance status (ECOG of 0-1), with good biliary drainage and adequate nutritional intake and intestinal type if previously treated with oxaliplatin-based therapy; OR
4. Subsequent therapy, depending on the regimen used in first-line, for disease progression in select patients with a poor performance status (PS) and ECOG PS of 2 with intestinal type disease in combination with one of the following:
   a) Capecitabine
   b) Fluorouracil and leucovorin
   c) FOLFOX (fluorouracil, leucovorin, and oxaliplatin) regimen
   d) FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen
   e) CAPEOX (capecitabine and oxaliplatin) regimen.[7]

Adult Central Nervous System Cancers

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Used as short-course single agent therapy for the management of symptoms driven by radiation necrosis, poorly controlled vasogenic edema, or mass effect in one of the following CNS cancers:
   a) Circumscribed glioma
   b) IDH-mutant, 1p19q co-deleted, WHO grade 2 or 3 oligodendroglioma
   c) IDH-mutant, WHO grade 2, 3, or 4 astrocytoma
   d) Intracranial and spinal ependymoma (excluding subependymoma)
   e) H3-mutated high-grade glioma, glioblastoma or gliosarcoma
   f) Medulloblastoma
   g) Primary central nervous system lymphoma
   h) Meningiomas
   i) Limited brain metastases
   j) Extensive brain metastases
   k) Metastatic spine tumors; OR
4. Treatment as a single agent for progression or recurrent intracranial and spinal ependymoma in patients who are refractory to surgery or radiation therapy (RT), if the patient has received prior RT and any of the following:
   a) Gross total or subtotal resection with negative cerebrospinal fluid (CSF) cytology
   b) Subtotal resection and evidence of metastasis (brain, spine, or CSF)
   c) Unresectable disease; OR
5. Treatment for recurrent or progressive disease as a single agent or in combination with carmustine, lomustine, or temozolomide if bevacizumab monotherapy fails and it is desirable to continue the steroid-sparing effects of bevacizumab for one of the following pathologies:
   a) Glioblastoma
   b) Gliosarcoma
   c) H3-mutated high-grade glioma
   d) Oligodendroglioma (IDH-mutant, 1p19q codeleted) WHO Grade 3, if Karnofsky Performance Status (KPS) ≥ 60
   e) IDH-mutant Astrocytoma WHO Grade 3 or 4, if Karnofsky Performance Status (KPS) ≥ 60; OR
6. Treatment as a single agent or in combination with everolimus for surgically inaccessible recurrent or progressive disease when radiation is not possible or meningiomas.[8]

Cervical Cancer (excluding small cell neuroendocrine carcinoma of the cervix)

First-Line or Greater

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

3. First-line, second-line, or greater therapy (if not used previously as first-line) in combination with pembrolizumab, paclitaxel, and cisplatin or carboplatin for PD-L1 positive (combined positive score [CPS] ≥1) as determined by an FDA-approved test for one of the following:
   a) Local/regional recurrence
   b) Stage IVB or distant metastases; OR
4. First-line, second-line, or greater therapy (if not used previously as first-line) in combination with paclitaxel and cisplatin or carboplatin, or in combination with paclitaxel and topotecan for one of the following:
   a) Local/regional recurrence
   b) Stage IVB or distant metastases.

Second-Line or Greater

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Used as a single agent for one of the following:
   a) Local/regional recurrence
   b) Stage IVB or distant metastases

Small Cell Neuroendocrine Carcinoma of the Cervix

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. For persistent, recurrent, or metastatic disease for one of the following:
   a) In combination with topotecan and paclitaxel and continued for maintenance therapy, if not previously given as first-line
   b) Single agent therapy for second-line or greater.[9]

Colon Cancer

Adjuvant Therapy

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. In combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin), FOLFIRI (fluorouracil, leucovorin, and irinotecan), CAPEOX (capecitabine and oxaliplatin), or FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) regimen if intensive therapy is recommended for one of the following:
   a) Treatment following synchronized or staged resection and/or local therapy for synchronous liver and/or lung metastases that converted from unresectable to resectable disease after primary treatment (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H])

b) Treatment following resection and/or local therapy for resectable metachronous metastases in patients who have received previous chemotherapy (pMMR/MSS or ineligible for or progression on checkpoint inhibitor immunotherapy for dMMR/MSI-H)
c) Treatment following resection and/or local therapy for resectable metachronous metastases in patients who have received previous immunotherapy (dMMR/MSI-H)
d) Treatment for unresectable metachronous metastases that converted to resectable disease after initial treatment (pMMR/MSS or ineligible for or progression on checkpoint inhibitor immunotherapy for dMMR/MSI-H); OR

4. Therapy in combination with capecitabine or fluorouracil/ leucovorin regimen, if intensive therapy is not recommended for one of the following indications:
   a) Treatment following synchronized or staged resection and/or local therapy for synchronous liver and/or lung metastases that converted from unresectable to resectable disease after primary treatment (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H])
   b) Treatment following resection and/or local therapy for resectable metachronous metastases in patients who have received previous chemotherapy (pMMR/MSS or ineligible for or progression on checkpoint inhibitor immunotherapy for dMMR/MSI-H)
   c) Treatment following resection and/or local therapy for resectable metachronous metastases in patients who have received previous immunotherapy (dMMR/MSI-H)
   d) Treatment for unresectable metachronous metastases that converted to resectable disease after initial treatment (pMMR/MSS or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]); OR
5. In combination with irinotecan for unresectable metachronous metastases (proficient mismatch repair/microsatellite-stable [pMMR/MSS] only or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) that converted to resectable disease after initial treatment.

Primary First-Line Therapy

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. In combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin), FOLFIRI (fluorouracil, leucovorin, and irinotecan), CAPEOX (capecitabine and oxaliplatin), or FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]), if intensive therapy is recommended for one of the following:
   a) Locally unresectable or medically inoperable disease
   b) Synchronous abdominal/peritoneal metastases that are nonobstructing or following local therapy for patients with existing or imminent obstruction
   c) Synchronous unresectable metastases of other sites

d) Unresectable metachronous metastases in patients who have not received previous FOLFOX or CAPEOX within the past 12 months, who have received previous fluorouracil/leucovorin or capecitabine therapy, or who have not received any previous chemotherapy
e) Progressed on non-intensive therapy, except if received previous fluoropyrimidine, with improvement in functional status; OR

4. Therapy in combination with capecitabine or with fluorouracil and leucovorin regimen (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]), if intensive therapy not recommended, for one of the following indications:
   a) Locally unresectable or medically inoperable disease
   b) Synchronous abdominal/peritoneal metastases that are nonobstructing, or following local therapy for patients with existing or imminent obstruction
   c) Synchronous unresectable metastases of other sites
   d) Unresectable metachronous metastases in patients who have not received previous FOLFOX or CAPEOX within the past 12 months, who have received previous fluorouracil/leucovorin or capecitabine therapy, or who have not received any previous chemotherapy; OR
5. Unresectable synchronous liver and/or lung metastases (proficient mismatch repair/microsatellite-stable [pMMR/MSS] only or deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] and the patient is not a candidate for immunotherapy) in combination with one of the following regimens:
   a) FOLFOX (fluorouracil, leucovorin, and oxaliplatin)
   b) FOLFIRI (fluorouracil, leucovorin, and irinotecan)
   c) FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin)
   d) CAPEOX (capecitabine and oxaliplatin); OR
6. Unresectable metachronous metastases (proficient mismatch repair/microsatellite-stable [pMMR/MSS] only) and previous FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CAPEOX (capecitabine and oxaliplatin) within the past 12 months in combination with one of the following:
   a) Irinotecan
   b) FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen; OR
7. Advanced or metastatic disease (proficient mismatch repair/microsatellite-stable (pMMR/MSS) or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) in combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin) regimen, CAPEOX (capecitabine and oxaliplatin) regimen, FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen, or FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) regimen for one of the following:
   a) If intensive therapy is recommended
   b) If intensive therapy is recommended and progressed on non-intensive therapy, except if the patient received previous fluoropyrimidine, with improvement in functional status; OR

8. Advanced or metastatic disease (proficient mismatch repair/microsatellite-stable (pMMR/MSS) or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) in combination with one of the following regimens if intensive therapy is not recommended:
   a) Capecitabine
   b) Fluorouracil and leucovorin.

Second-Line or Greater

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. For progression of advanced or metastatic disease (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) in combination with one of the following regimens:
   a) Irinotecan or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen if previously treated with oxaliplatin-based therapy without irinotecan
   b) FOLFOX (fluorouracil, leucovorin, and oxaliplatin) regimen or CAPEOX (capecitabine and oxaliplatin) regimen if previously treated with irinotecan-based therapy without oxaliplatin
   c) Irinotecan or FOLFIRI if previously treated without irinotecan or oxaliplatin
   d) FOLFOX, CAPEOX, FOLFIRINOX (fluorouracil, leucovorin, irinotecan, oxaliplatin), or irinotecan and oxaliplatin if previously treated without irinotecan or oxaliplatin; OR
4. For the progression of advanced or metastatic disease (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) in combination with trifluridine and tipiracil in patients who have progressed through all available regimens and has previously received one of the following:
   a) Oxaliplatin-based therapy without irinotecan
   b) Irinotecan-based therapy without oxaliplatin
   c) Oxaliplatin and irinotecan
   d) Therapy without irinotecan or oxaliplatin
   e) Therapy without irinotecan or oxaliplatin followed by FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CAPEOX (capecitabine and oxaliplatin) with or without bevacizumab; OR
5. Progression of advanced or metastatic disease (proficient mismatch repair/microsatellite-stable (pMMR/MSS) or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) in combination for one of the following:
   a) Irinotecan or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen if previously treated with oxaliplatin-based therapy without irinotecan
   b) FOLFOX (fluorouracil, leucovorin, and oxaliplatin) regimen or CAPEOX (capecitabine and oxaliplatin) regimen if previously treated with irinotecan-based therapy without oxaliplatin

c) Irinotecan or FOLFIRI if previously treated without irinotecan or oxaliplatin
d) FOLFOX, CAPEOX, FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) or irinotecan and oxaliplatin if not previously treated with irinotecan or oxaliplatin.[10]

Hepatocellular Carcinoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. In combination with atezolizumab for the treatment of patients with unresectable or metastatic hepatocellular carcinoma who have not received prior systemic therapy; OR
4. First-line treatment in combination with atezolizumab (for Child-Pugh Class A or B) for patients who meet one of the following:
   a) Unresectable disease and who are not a transplant candidate
   b) Liver-confined disease, inoperable by performance status, comorbidity or with minimal or uncertain extrahepatic disease
   c) Metastatic disease or extensive liver tumor burden.[11]

Kidney Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Metastatic renal cell carcinoma in combination with interferon alfa.[2,3,4,5,6]

For **NCCN** required criteria coverage:

4. Therapy for relapse or stage IV disease for one of the following:
   a) Single agent subsequent therapy for clear cell histology
   b) Single agent systemic therapy for non-clear cell histology
   c) In combination with everolimus as systemic therapy for non-clear cell histology
   d) In combination with erlotinib for non-clear cell histology in selected patients with advanced papillary renal cell carcinoma (RCC) including hereditary leiomyomatosis and renal cell carcinoma-associated RCC.[12]

Mesothelioma - Peritoneal

First-Line Therapy

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

3. Used in combination with pemetrexed and cisplatin as therapy for unresectable disease for one of the following:
   a) Diffuse peritoneal mesothelioma (PeM) with unicavitary, epithelioid histology that is medically inoperable and/or complete cytoreduction not achievable (including high-risk features) and a performance status (PS) 0-2
   b) Diffuse PeM with biphasic/sarcomatoid histology or bicavitary disease and a PS 0-2
   c) Recurrence of diffuse PeM with unicavitary, epithelioid histology after prior cytoreductive surgery (CRS) + hyperthermic intraperitoneal chemotherapy (HIPEC), if no previous adjuvant systemic therapy given and a PS 0-2
   d) Recurrence of benign multicystic or well-differentiated papillary PeM after prior CRS ± HIPEC for a PS 0-2; OR
4. Used in patients who are not candidates for cisplatin in combination with pemetrexed and carboplatin therapy for unresectable disease in any of the following situations:
   a) Diffuse PeM with unicavitary, epithelioid histology that is medically inoperable and/or complete cytoreduction not achievable (including high-risk features) and PS 0-2
   b) Diffuse PeM with biphasic/sarcomatoid histology or bicavitary disease and a PS 0-2
   c) Recurrence of diffuse PeM with unicavitary, epithelioid histology after prior cytoreductive surgery (CRS) + hyperthermic intraperitoneal chemotherapy (HIPEC), if no previous adjuvant systemic therapy given and a PS 0-2
   d) Recurrence of benign multicystic or well-differentiated papillary PeM after prior CRS ± HIPEC for a PS 0-2.

Note:

1. Indication numbers 3 and 4 may also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma.
2. High-risk features include Ki-67 >9%, nodal metastasis, high tumor burden (Peritoneal Cancer Index [PCI] >17), completeness of cytoreduction (CC) score >1, biphasic disease, or bicavitary disease.

Second-Line or Greater

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Subsequent systemic therapy, if immunotherapy was administered as first-line treatment or to be considered as a rechallenge if the patient had a good response to front-line pemetrexed-based treatment and a PS 0-2 with one of the following:
   a) Pemetrexed and cisplatin
   b) Pemetrexed and carboplatin in patients who are not candidates for cisplatin; OR
4. In combination with atezolizumab if not previously treated with immune checkpoint inhibitors for a PS 0-2.

Note:

May also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma.[14]

Mesothelioma - Pleural

First-Line Therapy

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Used in combination with pemetrexed and cisplatin as therapy for any of the following situations:
   a) Unresectable clinical stage I-IIIA disease after surgical exploration (if induction chemotherapy was not given) and epithelioid histology
   b) Clinical stage I-IIIA disease and epithelioid histology who have not undergone surgical exploration (if induction chemotherapy was not given); OR
4. Clinical stage IIIB or IV disease, sarcomatoid or biphasic histology, or medically inoperable tumors in patients with a performance status (PS) 0-2; OR
5. Used in patients who are not candidates for cisplatin in combination with pemetrexed and carboplatin therapy for one of the following:
   a) Unresectable clinical stage I-IIIA disease after surgical exploration (if induction chemotherapy was not given) and epithelioid histology
   b) Clinical stage I-IIIA disease and epithelioid histology who have not undergone surgical exploration (if induction chemotherapy was not given)
   c) Clinical stage IIIB or IV disease, sarcomatoid or biphasic histology, or medically inoperable tumors in patients with a PS 0-2.

Second-Line or Greater

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Preferred subsequent systemic therapy, if immunotherapy was administered as first-line treatment or to be considered as a rechallenge if the patient had a good response to front-line pemetrexed-based treatment in combination with one of the following:
   a) Pemetrexed and cisplatin
   b) Pemetrexed and carboplatin in patients who are not candidates for cisplatin.

Note: May also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma.[14]

Non-Small Cell Lung Cancer (NSCLC)

First-Line Therapy

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. In combination with erlotinib for EGFR exon 19 deletion or exon 21 L858R nonsquamous cell histology, recurrent, advanced, or metastatic disease with no history of recent hemoptysis; OR

4. Recurrent, advanced, or metastatic disease for PD-L1 expression positive (≥1%) tumors that are negative for actionable molecular biomarkers and no contraindications to PD-1 or PD-L1 inhibitors and a performance status 0-2 in combination with atezolizumab, carboplatin, and paclitaxel for nonsquamous cell histology; OR
5. Treatment for recurrent, advanced, or metastatic disease in patients with a PS 0-1, tumors of nonsquamous cell histology, and no history of recent hemoptysis in combination with one of the following:
   a) Carboplatin and either paclitaxel or pemetrexed (if contraindications to PD-1 or PD-L1 inhibitors)
   b) Cisplatin and pemetrexed (if contraindications to PD-1 or PD-L1 inhibitors)

   Note: The above regimens are used for one of the following:
   1. Initial systemic therapy for PD-L1 expression positive (≥1%) and negative for actionable molecular biomarkers with contraindications to PD-1 or PD-L1 inhibitors
   2. Initial systemic therapy for PD-L1 <1% and negative for actionable molecular biomarkers
   3. EGFR exon 20 mutation-positive tumors
   4. KRAS G12C mutation-positive tumors
   5. ERBB2 (HER2) mutation-positive tumors; OR

6. Treatment for recurrent, advanced, or metastatic disease in patients with performance status 0-1, tumors of nonsquamous cell histology, and no history of recent hemoptysis in combination with atezolizumab, carboplatin and paclitaxel (if no contraindications to PD-1 or PD-L1 inhibitors) for one of the following:
   a) Initial systemic therapy for PD-L1 <1% and negative for actionable molecular biomarkers
   b) EGFR exon 20 mutation positive tumors
   c) KRAS G12C mutation positive tumors
   d) ERBB2 (HER2) mutation positive tumors.

First-Line or Greater or Second-Line or Greater Therapy

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Treatment for recurrent, advanced, or metastatic disease in those with a PS 0-1, tumors of nonsquamous cell histology, and no history of recent hemoptysis in combination with one of the following:
   a) Carboplatin and either paclitaxel or pemetrexed (if contraindications to PD-1 or PD-L1 inhibitors)
   b) Cisplatin and pemetrexed (if contraindications to PD-1 or PD-L1 inhibitors)

   Note: The above regimens are used as first-line or subsequent therapy for:
   1. BRAF V600E mutation positive tumors
   2. NTRK1/2/3 gene fusion positive tumors
   3. MET exon 14 skipping mutation positive tumors
   4. RET rearrangement positive tumors; OR

4. Treatment for recurrent, advanced, or metastatic disease in those with a PS 0-1, tumors of nonsquamous cell histology, and no history of recent hemoptysis in combination with atezolizumab, carboplatin, and paclitaxel (if no contraindications to PD-1 or PD-L1 inhibitors) as first-line or subsequent therapy for:
   a) BRAF V600E mutation positive tumors
   b) NTRK1/2/3 gene fusion positive tumors
   c) MET exon 14 skipping mutation positive tumors
   d) RET rearrangement positive tumors.

Second-line or Greater Therapy

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Treatment for recurrent, advanced, or metastatic disease in those with a PS 0-1, tumors of nonsquamous cell histology, and no history of recent hemoptysis in combination with one of the following:
   a) Carboplatin and either paclitaxel or pemetrexed (if contraindications to PD-1 or PD-L1 inhibitors)
   b) Cisplatin and pemetrexed (if contraindications to PD-1 or PD-L1 inhibitors)

   Note: The above regimens are used as subsequent therapy for one of the following:
      1. EGFR exon 19 deletion or exon 21 L858R tumors and prior erlotinib +/- (ramucirumab or bevacizumab), afatinib, gefitinib, osimertinib, or dacomitinib therapy
      2. EGFR S768I, L861Q, and/or G719X mutation positive tumors and prior afatinib, osimertinib, erlotinib, gefitinib, or dacomitinib therapy
      3. ALK rearrangement positive tumors and prior crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib therapy
      4. ROS1 rearrangement positive tumors and prior crizotinib, entrectinib, or ceritinib therapy
      5. PD-L1 expression positive (≥1%) tumors and negative for actionable molecular biomarkers after prior PD-1/PD-L1 inhibitor but no prior platinum-containing chemotherapy; OR
4. Treatment for recurrent, advanced, or metastatic disease in patients with a PS 0-1, tumors of nonsquamous cell histology, and no history of recent hemoptysis in combination with atezolizumab, carboplatin, and paclitaxel (if no contraindications to PD-1 or PD-L1 inhibitors) as subsequent therapy for one of the following:
   a) EGFR exon 19 deletion or exon 21 L858R tumors and prior erlotinib +/- (ramucirumab or bevacizumab), afatinib, gefitinib, osimertinib, or dacomitinib therapy
   b) EGFR S768I, L861Q, and/or G719X mutation positive tumors and prior afatinib, osimertinib, erlotinib, gefitinib, or dacomitinib therapy
   c) ALK rearrangement positive tumors and prior crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib therapy
   d) ROS1 rearrangement positive tumors and prior crizotinib, entrectinib, or ceritinib therapy.

Continuation Maintenance

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. In combination with erlotinib for EGFR exon 19 deletion or exon 21 L858R nonsquamous cell histology, recurrent, advanced, or metastatic disease with no history of recent hemoptysis as continuation of therapy following disease progression on combination of erlotinib with bevacizumab for asymptomatic disease, symptomatic brain lesions, or symptomatic systemic limited progression (if T790M negative); OR
4. Continuation maintenance therapy in combination with atezolizumab for recurrent, advanced, or metastatic disease for PD-L1 expression positive (≥1%) tumors that are negative for actionable molecular biomarkers and no contraindications to PD-1 or PD-L1 inhibitors in those with a PS 0-2 who achieve a response or stable disease following first-line therapy with atezolizumab/carboplatin/paclitaxel/bevacizumab for nonsquamous cell histology with no history of recent hemoptysis; OR
5. Continuation maintenance therapy for recurrent, advanced, or metastatic disease with PD-L1 expression <1% tumors that are negative for actionable molecular biomarkers in patients with a PS 0-2, tumors of nonsquamous cell histology, and no history of recent hemoptysis who achieve tumor response or stable disease following initial systemic therapy as one of the following:
   a) Single agent
   b) In combination with pemetrexed if previously used with a first-line pemetrexed/ platinum regimen
   c) In combination with atezolizumab if previously used first-line as part of an atezolizumab/carboplatin/paclitaxel/bevacizumab regimen and no contraindications to PD-1 or PD-L1 inhibitors.

Note:

1. If there is insufficient tissue to allow testing for all of EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, and ERBB2 (HER2), 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.
2. Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents, and some oncogenic drivers (i.e., EGFR exon 19 deletion or exon 21 L858R, ALK rearrangements) have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors.[15]

Ovarian Cancer (Includes fallopian tube cancer and primary peritoneal cancer)

Neoadjuvant Therapy

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Therapy for epithelial cancer; AND

4. Used in combination with carboplatin and either paclitaxel or docetaxel, or with oxaliplatin and docetaxel for patients who are poor surgical candidates or have low likelihood of optimal cytoreduction.

Adjuvant Therapy/Primary First-Line Therapy

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with one of the following:
   a) Carboplatin and paclitaxel, followed by bevacizumab as a single agent, for stage III or IV disease following initial surgical resection
   b) Paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who have not received more than 2 prior chemotherapy regimens
   c) Carboplatin and paclitaxel or carboplatin and gemcitabine, followed by bevacizumab as a single agent, for platinum-sensitive recurrent disease.[2,3,4,5,6]

For **NCCN** required criteria coverage:

4. Epithelial for one of the following:
   a) Used in combination with carboplatin and either paclitaxel or docetaxel, or with oxaliplatin and docetaxel for those who are poor surgical candidates or have a low likelihood of optimal cytoreduction for one of the following:
      i. Therapy following interval debulking surgery (IDS) in patients with response or stable disease to neoadjuvant therapy
      ii. Continued treatment for stable disease following neoadjuvant therapy; OR
   b) Primary adjuvant therapy for pathologic stage IB (grade 2 endometrioid or grade 3 endometrioid/high-grade serous carcinoma), stage IC (high grade serous or grade 2/3 endometrioid), or stage II-IV disease in combination with oxaliplatin and docetaxel
   c) Primary adjuvant therapy for pathologic stage II-IV disease in combination with paclitaxel or docetaxel and carboplatin; OR
5. Carcinosarcoma (malignant mixed Mullerian tumors) or clear cell carcinoma of the ovary in combination with one of the following:
   a) Oxaliplatin and docetaxel for pathologic stage IB-IV disease
   b) Carboplatin and paclitaxel or docetaxel for pathologic stage II-IV disease; OR
6. Mucinous carcinoma, grade I endometrioid carcinoma or low-grade serous carcinoma in combination with oxaliplatin and docetaxel for pathologic stage IC-IV; OR
7. Mucinous carcinoma for pathologic stage II-IV disease in combination with one of the following:
   a) Carboplatin and paclitaxel or docetaxel
   b) Fluorouracil, leucovorin, and oxaliplatin

c) Capecitabine and oxaliplatin; OR

8. Grade 1 endometrioid carcinoma or low-grade serous carcinoma in combination with one of the following:
   a) Oxaliplatin and docetaxel for pathologic stage IC-IV disease
   b) Carboplatin and paclitaxel or docetaxel for pathologic stage II-IV disease.

Note: Bevacizumab-containing regimens should be used with caution and withheld for 4-6 weeks prior to interval debulking surgery due to potential interference with postoperative healing.

First-Line or Greater

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Epithelial, carcinosarcoma (malignant mixed Mullerian tumors), clear cell carcinoma of the ovary, or grade 1 endometrioid carcinoma for one of the following:
   a) Rising CA-125 levels or clinical relapse in patients who have not received prior chemotherapy in combination with paclitaxel and carboplatin
   b) Single agent therapy for persistent disease or recurrence for one of the following:
      i. Immediate treatment for serially rising CA-125 in patients who previously received chemotherapy
      ii. Progression on primary, maintenance, or recurrence therapy (platinum-resistant disease)
      iii. Stable or persistent disease (if not on maintenance therapy) (platinum-resistant disease)
      iv. Complete remission and relapse <6 months after completing chemotherapy (platinum-resistant disease)
      v. Radiographic and/or clinical relapse in patients with previous complete remission and relapse ≥6 months after completing prior chemotherapy (platinum-sensitive disease); OR
   c) Used in combination with one of the following:
      i. Carboplatin and gemcitabine
      ii. Carboplatin and paclitaxel
      iii. Carboplatin and liposomal doxorubicin

      Note: The above regimens are used for persistent disease or recurrence for one of the following:
      1. As immediate treatment for serially rising CA-125 in patients that previously received chemotherapy (platinum-sensitive or platinum-resistant)
      2. For progression on primary, maintenance, or recurrence therapy (platinum-resistant)
      3. For stable or persistent disease (if not on maintenance therapy) (platinum-resistant)
      4. For complete remission and relapse <6 months after completing chemotherapy (platinum-resistant)

5. In patients with complete remission and relapse ≥6 months after completing prior chemotherapy (platinum-sensitive)

d) In combination with niraparib in platinum-sensitive persistent disease or recurrence for one of the following:
   i. As immediate treatment for serially rising CA-125 in patients that previously received chemotherapy
   ii. For radiographic and/or clinical relapse in patients with previous complete remission and relapse ≥6 months after completing prior chemotherapy

e) Platinum-resistant persistent disease or recurrence for one of the following:
   i. Immediate treatment for serially rising CA-125 in patients who previously received chemotherapy
   ii. Progression on primary, maintenance, or recurrence therapy
   iii. Stable or persistent disease (if not on maintenance therapy)
   iv. Complete remission and relapse <6 months after completing chemotherapy; AND
      1. Used in combination with one of the following:
         a) Oral cyclophosphamide
         b) Liposomal doxorubicin
         c) Weekly paclitaxel
         d) Topotecan
         e) Mirvetuximab soravtansine-gynx (in folate receptor-alpha expressing tumors)
         f) Ixabepilone (if previously treated with taxane)
         g) Gemcitabine; OR

4. Therapy for mucinous carcinoma of the ovary for one of the following:
   a) Treatment for rising CA-125 levels or clinical relapse in patients who have received no prior chemotherapy in combination with one of the following:
      i. Carboplatin and paclitaxel
      ii. Fluorouracil, leucovorin, and oxaliplatin
      iii. Capecitabine and oxaliplatin
   b) Single agent therapy for persistent disease or recurrence for one of the following:
      i. Immediate treatment for serially rising CA-125 in patients that previously received chemotherapy
      ii. Progression on primary, maintenance, or recurrence therapy (platinum-resistant disease)
      iii. Stable or persistent disease (if not on maintenance therapy) (platinum-resistant disease)
      iv. Complete remission and relapse <6 months after completing chemotherapy (platinum-resistant disease)
      v. Radiographic and/or clinical relapse in patients with previous complete remission and relapse ≥6 months after completing prior chemotherapy (platinum-sensitive disease)
   c) Used in combination with one of the following:
      i. Carboplatin and gemcitabine
      ii. Carboplatin and paclitaxel
      iii. Carboplatin and liposomal doxorubicin

Note: The above regimens are used for platinum-resistant persistent disease or recurrence for one of the following:

1. Immediate treatment for serially rising CA-125 in patients that previously received chemotherapy
2. Progression on primary, maintenance, or recurrence therapy
3. Stable or persistent disease (if not on maintenance therapy)
4. Complete remission and relapse <6 months after completing chemotherapy

d) Used in combination with one of the following:
   i. Carboplatin and gemcitabine
   ii. Carboplatin and paclitaxel
   iii. Carboplatin and liposomal doxorubicin
   iv. Fluorouracil, leucovorin, and oxaliplatin
   v. Capecitabine and oxaliplatin

Note: The above regimens are used for platinum-sensitive persistent disease or recurrence for one of the following:

1. As immediate treatment for serially rising CA-125 in patients that previously received chemotherapy
2. In patients with complete remission and relapse ≥6 months after completing prior chemotherapy

e) In combination with niraparib in platinum-sensitive persistent disease or recurrence for one of the following:
   i. As immediate treatment for serially rising CA-125 in patients that previously received chemotherapy
   ii. For radiographic and/or clinical relapse in patients with previous complete remission and relapse after ≥6 months after completing prior chemotherapy; OR

f) Therapy for platinum-resistant persistent disease or recurrence in combination with one of the following:
   i. Oral cyclophosphamide
   ii. Liposomal doxorubicin
   iii. Weekly paclitaxel
   iv. Topotecan
   v. Gemcitabine
   vi. Mirvetuximab soravtansine-gynx (in folate receptor-alpha expressing tumors)
   vii. Ixabepilone (if previously treated with taxane)

Note: The above regimens are used for one of the following:

1. Immediate treatment for serially rising CA-125 in patients that previously received chemotherapy
2. Progression on primary, maintenance, or recurrence therapy
3. Stable or persistent disease (if not on maintenance therapy)

4. Complete remission and relapse <6 months after completing chemotherapy; OR

5. Therapy for low-grade serous carcinoma and one of the following:
   a) Recurrence in patients who have received no prior chemotherapy in combination with paclitaxel and carboplatin
   b) Single agent therapy for platinum-sensitive or platinum-resistant recurrence
   c) In combination with gemcitabine for platinum-resistant recurrence
   d) Platinum-sensitive or platinum-resistant recurrence in combination with one of the following:
      i. Carboplatin and gemcitabine
      ii. Carboplatin and paclitaxel
      iii. Carboplatin and liposomal doxorubicin; OR
   e) In combination with niraparib in platinum-sensitive recurrence; OR
   f) Platinum-resistant recurrence in combination with one of the following:
      i. Oral cyclophosphamide
      ii. Liposomal doxorubicin
      iii. Weekly paclitaxel
      iv. Topotecan
      v. Mirvetuximab soravtansine-gynx (in folate receptor-alpha expressing tumors)
      vi. Ixabepilone (if previously treated with taxane); OR
6. Malignant sex cord-stromal tumors as a single agent for clinical relapse in patients with stage II-IV disease.

Maintenance Therapy

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Epithelial cancer for one of the following:
   a) Single agent if used previously as part of a combination therapy for patients with partial or complete response following recurrence therapy with chemotherapy plus bevacizumab for platinum-sensitive disease; OR
   b) Stage II-IV high-grade serous or grade 2/3 endometrioid carcinoma if complete response (CR) or partial response (PR) to primary therapy including bevacizumab as one of the following:
      i. Single agent in patients BRCA1/2 wild-type or unknown and HR proficient or status unknown
      ii. In combination with olaparib in patients BRCA1/2 wild-type or unknown and HR deficient
      iii. Single agent in patients BRCA1/2 wild-type or unknown and HR deficient
      iv. In combination with olaparib in patients with a germline or somatic BRCA1/2 mutation; OR
4. Carcinosarcoma (malignant mixed Müllerian tumors) or clear cell carcinoma for one of the following:

a) In combination with olaparib for stage II-IV carcinosarcoma with a germline or somatic BRCA1/2 mutation if complete response or partial response to primary therapy including bevacizumab
b) Single agent if used previously as part of a combination therapy for patients with partial or complete response following recurrence therapy with chemotherapy plus bevacizumab for platinum-sensitive disease; OR

5. Mucinous carcinoma of the ovary, grade 1 endometroid carcinoma, or low-grade serous carcinoma for maintenance therapy as a single agent if used previously as part of a combination therapy for patients with partial or complete response following recurrence therapy with chemotherapy plus bevacizumab for platinum-sensitive disease.[16]

Pediatric Central Nervous System Cancer

1. Less than 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Palliation of recurrent or progressive disease for diffuse high-grade glioma, except oligodendroglioma, IDH-mutant and 1p/19q co-deleted or astrocytoma IDH-mutant; OR
4. Recurrent or progressive disease for medulloblastoma all risk categories for one of the following:
   a) TEMR (temozolomide, irinotecan, bevacizumab)
   b) MEMMAT (thalidomide, celecoxib, fenofibrate, etoposide, cyclophosphamide, bevacizumab) regimen.[17]

Rectal Cancer

Adjuvant

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. In combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin), FOLFIRI (fluorouracil, leucovorin, and irinotecan), CAPEOX (capecitabine and oxaliplatin), or FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) regimen if intensive therapy recommended for one of the following indications:
   a) Following resection and/or local therapy for resectable metachronous metastases in patients who have received previous chemotherapy (proficient mismatch repair/microsatellite-stable [pMMR/MSS] only or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H])
   b) Following resection and/or local therapy for resectable metachronous metastases in patients who have received previous immunotherapy (dMMR/MSI-H only)
   c) Unresectable metachronous metastases that converted to resectable disease after initial treatment (pMMR/MSS only or ineligible for or progression on checkpoint inhibitor immunotherapy for dMMR/MSI-H); OR

5. In combination with capecitabine or fluorouracil/leucovorin regimen if intensive therapy not recommended for one of the following indications:
   a) Following resection and/or local therapy for resectable metachronous metastases in patients who have received previous chemotherapy (proficient mismatch repair/microsatellite-stable [pMMR/MSS] only or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H])
   b) Following resection and/or local therapy for resectable metachronous metastases in patients who have received previous immunotherapy (dMMR/MSI-H only)
   c) Unresectable metachronous metastases that converted to resectable disease after initial treatment (pMMR/MSS only or ineligible for or progression on checkpoint inhibitor immunotherapy for dMMR/MSI-H); OR
6. In combination with irinotecan for unresectable metachronous metastases (proficient mismatch repair/microsatellite-stable [pMMR/MSS] only) that converted to resectable disease after primary treatment.

First-Line - Primary Treatment

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. For T3, N Any; T1-2, N1-2; T4, N Any; or locally unresectable or medically inoperable disease if resection is contraindicated following total neoadjuvant therapy (proficient mismatch repair/microsatellite-stable [pMMR/MSS] only or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) or neoadjuvant/definitive immunotherapy (dMMR/MSI-H only) for one of the following:
   a) If intensive therapy is recommended, then may give in combination with one of the following:
      i. CAPEOX (capecitabine and oxaliplatin)
      ii. FOLFOX (fluorouracil, leucovorin, and oxaliplatin)
      iii. FOLFIRI (fluorouracil, leucovorin, and irinotecan)
   b) If intensive therapy is not recommended, then may give in combination with one of the following:
      i. Capecitabine
      ii. Fluorouracil/leucovorin regimen; OR
4. In combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin), FOLFIRI (fluorouracil, leucovorin, and irinotecan), CAPEOX (capecitabine and oxaliplatin), or FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) regimen if intensive therapy recommended (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) for one of the following:
   a) Synchronous abdominal/peritoneal metastases that are nonobstructing, or following local therapy for patients with existing or imminent obstruction
   b) Synchronous unresectable metastases of other sites

c) Unresectable isolated pelvic/anastomotic recurrence
d) Unresectable metachronous metastases in patients who have not received previous FOLFOX or CAPEOX within the past 12 months, who have received previous fluorouracil/leucovorin (5-FU/LV) or capecitabine therapy, or who have not received any previous chemotherapy
e) Progressed on non-intensive therapy, except if received previous fluoropyrimidine, with improvement in functional status; OR

5. In combination with capecitabine or fluorouracil/leucovorin regimen if intensive therapy is not recommended (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or the patient is ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]), for one of the following:
   a) Synchronous abdominal/peritoneal metastases that are nonobstructing, or following local therapy for patients with existing or imminent obstruction
   b) Synchronous unresectable metastases of other sites
   c) Unresectable isolated pelvic/anastomotic recurrence
   d) Initial treatment for unresectable metachronous metastases in patients who have not received previous FOLFOX or CAPEOX within the past 12 months, who have received previous fluorouracil/leucovorin or capecitabine therapy, or who have not received any previous chemotherapy; OR
6. For synchronous liver only and/or lung only metastases (proficient mismatch repair/microsatellite-stable [pMMR/MSS] only or deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] only and not a candidate for immunotherapy) that are unresectable or medically inoperable, in combination with one of the following:
   a) FOLFIRI (fluorouracil, leucovorin, and irinotecan)
   b) FOLFOX (fluorouracil, leucovorin, and oxaliplatin)
   c) CAPEOX (capecitabine and oxaliplatin)
   d) FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin); OR
7. Unresectable metachronous metastases (proficient mismatch repair/microsatellite-stable [pMMR/MSS] only) and previous FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CAPEOX (capecitabine and oxaliplatin) within the past 12 months in combination with one of the following:
   a) Irinotecan
   b) FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen.

Second-Line or Greater - Subsequent Therapy

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Subsequent therapy for progression of advanced or metastatic disease (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) in combination for one of the following:
   a) Irinotecan or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen if previously treated with oxaliplatin-based therapy without irinotecan

b) FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CAPEOX (capecitabine and oxaliplatin) regimen if previously treated with irinotecan-based therapy without oxaliplatin
c) Irinotecan or FOLFIRI if previously treated without irinotecan or oxaliplatin
d) FOLFOX, CAPEOX, irinotecan and oxaliplatin, or FOLFIRINOX (fluorouracil, leucovorin, irinotecan and oxaliplatin) if previously treated without irinotecan or oxaliplatin; OR

4. Subsequent therapy for progression of advanced or metastatic disease (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H]) in combination with trifluridine and tipiracil in patients who have progressed through all available regimens and has previously received one of the following:
   a) Oxaliplatin-based therapy without irinotecan
   b) Irinotecan-based therapy without oxaliplatin
   c) Therapy with oxaliplatin and irinotecan
   d) Therapy without irinotecan or oxaliplatin
   e) Therapy without irinotecan or oxaliplatin followed by FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CAPEOX (capecitabine and oxaliplatin) with or without bevacizumab.[18]

Small Bowel Adenocarcinoma

First-Line Therapy

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. In combination with one of the following:
   a) FOLFOX (fluorouracil, leucovorin, and oxaliplatin), CAPEOX (capecitabine and oxaliplatin), FOLFIRI (fluorouracil, leucovorin, and irinotecan) or FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) regimen for advanced or metastatic disease if intensive therapy recommended
   b) Capecitabine fluorouracil and leucovorin regimen, if intensive therapy not recommended, for advanced or metastatic disease
   c) FOLFIRI (fluorouracil, leucovorin, and irinotecan) for advanced or metastatic disease and patient has had prior oxaliplatin exposure in the adjuvant setting or contraindication to oxaliplatin.

Second-Line or Greater - Subsequent Therapy

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. In combination with one of the following:
   a) FOLFOX (fluorouracil, leucovorin, and oxaliplatin), CAPEOX (capecitabine and oxaliplatin), or FOLFIRI (fluorouracil, leucovorin, and irinotecan) for advanced or metastatic disease if intensive therapy recommended

b) FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) for advanced or metastatic disease if intensive therapy is recommended in patients who previously received initial therapy with nivolumab with or without ipilimumab, or pembrolizumab
c) Capecitabine or 5-FU/leucovorin (fluorouracil and leucovorin), if intensive therapy is not recommended, for advanced or metastatic disease in patients who previously received initial therapy with nivolumab with or without ipilimumab, or pembrolizumab
d) FOLFIRI (fluorouracil, leucovorin, and irinotecan) for advanced or metastatic disease and the patient has had prior oxaliplatin exposure in the adjuvant setting or contraindication to oxaliplatin in patients who previously received initial therapy with nivolumab with or without ipilimumab, pembrolizumab, or dostarlimab-gxly.[19]

Soft Tissue Sarcoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. First-Line or greater therapy for one of the following:
   a) Single agent for angiosarcoma
   b) In combination with temozolomide for the treatment of solitary fibrous tumor.[20]

Uterine Neoplasms

First-Line

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. In combination with carboplatin and paclitaxel for recurrent disease for one of the following:
   a) Isolated metastases
   b) Disseminated metastases with or without sequential palliative external beam radiation therapy (EBRT)
   c) With sequential EBRT and with or without brachytherapy for locoregional recurrence in patients with no prior RT to site of recurrence, or previous brachytherapy only
   d) After surgical exploration, with sequential EBRT for locoregional recurrence in patients with disease confined to the vagina or paravaginal soft tissue, or in pelvic, para-aortic, or common iliac lymph nodes
   e) After surgical exploration, with or without sequential EBRT for locoregional recurrence in patients with upper abdominal or peritoneal disease
   f) With or without sequential palliative EBRT or brachytherapy for locoregional recurrence in patients who have received prior EBRT to site of recurrence.

Second-Line - Subsequent Therapy

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

3. In combination with carboplatin and paclitaxel for recurrent disease or as a single agent for recurrent disease that has progressed on prior cytotoxic chemotherapy for one of the following:
   a) Isolated metastases
   b) Disseminated metastases with or without sequential palliative external beam radiation therapy (EBRT)
   c) Sequential EBRT and with or without brachytherapy for locoregional recurrence in patients with no prior RT to site of recurrence, or previous brachytherapy only
   d) After surgical exploration, with sequential EBRT for locoregional recurrence in patients with disease confined to the vagina or paravaginal soft tissue, or in pelvic, para-aortic, or common iliac lymph nodes
   e) After surgical exploration, with or without sequential EBRT for locoregional recurrence in patients with upper abdominal or peritoneal disease
   f) With or without sequential palliative EBRT or brachytherapy for locoregional recurrence in patients who have received prior EBRT to site of recurrence.[21]

Vulvar Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. First-line therapy for advanced or recurrent/metastatic disease (or second-line or subsequent therapy if not used previously) in combination with cisplatin and paclitaxel or carboplatin and paclitaxel as one of the following:
   a) Additional treatment following primary therapy with concurrent chemoradiation for locally advanced unresectable disease (larger T2, T3) or initially unresectable nodes regardless of T stage that is clinically positive for residual tumor at the primary site and/or nodes
   b) Additional treatment following primary therapy with concurrent chemoradiation for locally advanced disease (larger T2, T3) or initially unresectable nodes regardless of T stage with positive margins following resection
   c) Primary treatment for metastatic disease beyond the pelvis (Stage IVB)
   d) Isolated inguinofemoral/pelvic lymph node recurrence if prior external beam radiation therapy (EBRT)
   e) Clinical nodal or distant recurrence with multiple pelvic nodes, distant metastasis, or prior pelvic EBRT.[22]

Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

Bevacizumab and biosimilars: References

1. NIH National Library of Medicine Stat Pearls. https://www.ncbi.nlm.nih.gov/books/NBK482126/. Accessed September 9, 2024.
2. Bevacizumab (Avastin) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125085s340lbl.pdf. Accessed September 9, 2024.
3. Bevacizumab-awwb (Mvasi) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761028s011lbl.pdf. Accessed September 9, 2024.
4. Bevacizumab-bvzr (Zirabev) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761099Orig1s012lbl.pdf Accessed September 9, 2024.
5. Bevacizumab-abcd (Vegzelma) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761268Orig1s000Correctedlbl.pdf. Accessed September 9, 2024.
6. Bevacizumab-maly (Alymsys) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761231s000lbl.pdf. Accessed September 9, 2024.
7. National Comprehensive Cancer Network Guidelines. Ampullary Cancer. https://www.nccn.org/professionals/physician_gls/pdf/ampullary.pdf. Accessed September 9, 2024.
8. National Comprehensive Cancer Network Guidelines. Central Nervous System Cancers.https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed September 9, 2024.
9. National Comprehensive Cancer Network Guidelines. Cervical Cancer.https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. Accessed September 9, 2024.
10. National Comprehensive Cancer Network Guidelines. Colon Cancer. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed September 9, 2024
11. National Comprehensive Cancer Network Guidelines. Hepatocellular Carcinoma.https://www.nccn.org/professionals/physician_gls/pdf/hcc.pdf. Accessed September 9, 2024.
12. National Comprehensive Cancer Network Guidelines. Kidney Cancer. https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed September 9, 2024.
13. National Comprehensive Cancer Network Guidelines. Mesothelioma Peritoneal. https://www.nccn.org/professionals/physician_gls/pdf/meso_peritoneal.pdf. Accessed September 9, 2024.
14. National Comprehensive Cancer Network Guidelines. Mesothelioma Pleural https://www.nccn.org/professionals/physician_gls/pdf/meso_pleural.pdf. Accessed September 9, 2024.
15. National Comprehensive Cancer Network Guidelines. Non-Small Cell Lung Cancer.https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed September 9, 2024.

16. National Comprehensive Cancer Network Guidelines. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed September 9, 2024.
17. National Comprehensive Cancer Network Guidelines. Pediatric Central Nervous System Cancer. https://www.nccn.org/professionals/physician_gls/pdf/ped_cns.pdf. Accessed September 9, 2024.
18. National Comprehensive Cancer Network Guidelines. Rectal Cancer https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed September 9, 2024.
19. National Comprehensive Cancer Network Guidelines. Small Bowel Adenocarcinoma. https://www.nccn.org/professionals/physician_gls/pdf/small_bowel.pdf. Accessed September 9, 2024.
20. National Comprehensive Cancer Network Guidelines. Soft Tissue Sarcoma. https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Accessed September 9, 2024.
21. National Comprehensive Cancer Network Guidelines. Uterine Neoplasms. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed September 9, 2024.
22. National Comprehensive Cancer Network Guidelines. Vulvar Cancer. https://www.nccn.org/professionals/physician_gls/pdf/vulvar.pdf. Accessed September 9, 2024.

Bevacizumab and biosimilars: Coding (CPT®, ICD 10 and HCPCS) *

*Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

CODE	DESCRIPTION
C17.9	Malignant neoplasm of small intestine, unspecified
C18.9	Malignant neoplasm of colon, unspecified
C20	Malignant neoplasm of the rectum
C22.0	Liver cell carcinoma
C24.1	Malignant neoplasm of ampulla of vater

C34.90	Malignant neoplasm of unspecified par of unspecified bronchus or lung
C45.0	Mesothelioma of pleura
C45.1	Mesothelioma of peritoneum
C45.2	Mesothelioma of pericardium
C45.9	Mesothelioma, unspecified
C49.9	Malignant neoplasm of connective and soft tissue, unspecified
C51.8	Malignant neoplasm of overlapping sites of vulva
C56.9	Malignant neoplasm of unspecified ovary
C57.4	Malignant neoplasm of uterine adnexa, unspecified
C64.1	Malignant neoplasm of right kidney
C64.2	Malignant neoplasm of left kidney
C72.9	Malignant neoplasm of central nervous system, specified
J9035	Bevacizumab
Q5107	Bevacizumab-awwb
Q5118	Bevacizumab-bvzr
Q5126	Bevacizumab-maly
Q5129	Bevacizumab-adcd

Bevacizumab and Biosimilars: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	1/1/2024
2	Policy Review Dates:	9/6/2023, 9/9/2024
3	Policy Revision Dates:	9/9/2024
4	Department Owner:	Medical Affairs
5	NH Advisory Committee Approval Dates:	9/6/2023, 9/24/2024
6	Revision Changes:	9/9/2024 – Added indications for medulloblastoma for pediatric CNS cancer and adverse reactions in the discussion