Medical Drug Clinical Criteria

Subject:	Bevacizumab for Non-ophthalmologic Indications		
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Overview

This document addresses the use of bevacizumab agents (Avastin and its biosimilars Alymsys, Avzivi, Jobevne, Mvasi, Vegzelma, and Zirabev) in the treatment of oncologic conditions and other non-ophthalmologic indications. This document does not address the ophthalmologic uses of intraocular bevacizumab. Bevacizumab is a monoclonal antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF).

Ampullary Adenocarcinoma

Bevacizumab is recommended by NCCN as first-line therapy and/or progression in combination with 5-fluorouracil-based (including capecitabine) regimen for intestinal metastatic disease.

Central Nervous System Cancer

While bevacizumab is FDA approved to treat recurrent glioblastoma, NCCN recommends bevacizumab in a number of central nervous system cancers which have failed to respond to radiation therapy. NCCN specifically recommends bevacizumab in high grade (World Health Organization [WHO] Grade III/IV) gliomas which would include: anaplastic astrocytoma, glioma, oligoastrocytoma, and oligodendroglioma; glioblastomas; and glioblastoma multiforme. NCCN also recommends bevacizumab as a single agent for meningiomas in certain circumstances. NCCN additionally recommends bevacizumab for management of symptoms driven by radiation therapy necrosis of the central nervous system.

Colorectal Cancer

Bevacizumab is FDA approved to treat metastatic colorectal cancer in combination with 5-fluorouracil-based chemotherapy, irinotecan, or oxaliplatin. The FDA label points out that bevacizumab should not be used in the adjuvant treatment of colon cancer based on two studies in stage II or III colon cancer which did not show efficacy of this agent in the adjuvant setting (de Gramont 2012, Allegra 2013). Bevacizumab in combination with chemotherapy may be used in the first-line setting or as subsequent therapy. Within the non-first line setting, NCCN guidelines and the FDA approved indication suggest continuing bevacizumab following progression on a bevacizumab-containing regimen. NCCN additionally recommends adding bevacizumab following progression on an initial regimen that did *not* contain bevacizumab. The CAIRO3 study (Simkens 2015) studied induction therapy (capecitabine, oxaliplatin, and bevacizumab) followed by either maintenance with bevacizumab + capecitabine or observation, followed by re-induction after first progression. The group receiving maintenance therapy showed prolonged second progression free survival, supporting the efficacy of bevacizumab after progression on bevacizumab in this disease state. NCCN guidelines also recommend the combination of bevacizumab with trifluridine and tipiracil (Lonsurf) in individuals who have progressed through standard therapies; including those who have previously received bevacizumab therapy.

Within the guidelines, NCCN recommends that appendiceal adenocarcinoma be treated with chemotherapy according to colon cancer guidelines. Similarly, it is recommended that anal adenocarcinoma, a rare histologic form of anal cancer, may be treated according to guidelines for rectal cancer. Guidelines for squamous cell anal cancer, the most common type of anal cancer, do not currently include bevacizumab among recommended treatments.

Mesothelioma

NCCN recommends bevacizumab in the treatment of unresectable malignant pleural mesothelioma. It is recommended as first line in combination with pemetrexed and either cisplatin or carboplatin followed by single agent bevacizumab until disease progression. Studies cited in these recommendations included patients with Eastern Cooperative Oncology Group (ECOG) Performance Status 0-2 with no evidence of bleeding or thrombosis (Zalcman 2016, Ceresoli 2013).

Cervical, Vaginal, Vulvar, and Endometrial Carcinoma

Bevacizumab is FDA approved to treat persistent, recurrent, or metastatic cervical cancer in combination with paclitaxel and topotecan or paclitaxel and cisplatin. This was approved based on a study that excluded patients that were candidates for curative therapy by means of pelvic exenteration (Tewari 2014). NCCN additionally recommends bevacizumab in combination with paclitaxel and either cisplatin, carboplatin, or topotecan for the treatment of advanced, recurrent, or metastatic disease. Keytruda (pembrolizumab) is FDA approved, in combination with chemotherapy and bevacizumab, for the treatment of persistent, recurrent, or metastatic cervical cancer. NCCN also recommends bevacizumab in advanced, recurrent, or metastatic vulvar cancer in combination with paclitaxel and either carboplatin (2B) or cisplatin (2A). Within the uterine neoplasms NCCN guidelines, it is recommended that bevacizumab be used for endometrial carcinoma in combination with paclitaxel and carboplatin for advanced or recurrent disease. The evidence behind this recommendation (Rose 2017) also studied bevacizumab maintenance after original combination with paclitaxel + carboplatin and found a favorable overall response rate. Bevacizumab is also recommended as single agent therapy for disease that has progressed on prior cytotoxic chemotherapy, but recommendation was based on a phase 2 trial of 52 participants.

Hepatocellular Carcinoma

Bevacizumab is FDA approved in combination with atezolizumab for the treatment of unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy. NCCN considers this combination a preferred first line treatment for individuals who have Child-Pugh Class A or B liver function based on the clinical trial population. NCCN also allows the use as subsequent-line systemic therapy.

Mesothelioma Peritoneal (PeM)/Pleural (MPM)

In Peritoneal mesothelioma NCCN Panel has recommended for first-line and subsequent (second-line and beyond) systemic therapy regimens in those who are not eligible for surgery, pemetrexed plus cisplatin plus bevacizumab as a preferred option. In addition, the
NCCN Panel clarified that atezolizumab plus bevacizumab should only be considered as subsequent therapy if patients have not previously been treated with ICIs.

In Pleural mesothelioma, the NCCN panel also recommends bevacizumab in combination with chemotherapy as first-line therapy in unresectable disease and as a single agent for maintenance therapy post combination use until disease progression.

Non-Small Cell Lung Cancer (NSCLC):

Bevacizumab is FDA approved for the treatment of unresectable, locally advanced, recurrent, or metastatic non-squamous NSCLC in combination with carboplatin and paclitaxel. For initial therapy, NCCN also recommends bevacizumab in combination with carboplatin+paclitaxel, carboplatin+pemetrexed, or cisplatin+pemetrexed (i.e. platinum based therapy and a taxane or pemetrexed) OR in combination with atezolizumab, carboplatin, and paclitaxel for recurrent, advanced, or metastatic disease in those with no history of hemoptysis. It should be noted that NCCN recommends these treatments as first-line in patients without treatment-driving mutations. In the presence of these mutations, patients should be treated with targeted therapy first (i.e. tyrosine kinase inhibitors).

NCCN also recommends bevacizumab as maintenance therapy as a single agent, or in combination with atezolizumab or pemetrexed. However, the trial that assessed the efficacy in combination with pemetrexed (Barlesi 2013, 2014) found that although participants had longer progression free survival (PFS), the 1-year and 2-year overall survival differences did not meet statistical significance. In addition, the health-related quality of life (HRQOL) was not improved in the bevacizumab + pemetrexed arm (Rittmeyer 2013). Consequently, there is a lack of evidence in the peer-reviewed literature to support the efficacy of this combination over bevacizumab alone.

NCCN also recommends bevacizumab as treatment for recurrent, advanced, or metastatic non-squamous NSCLC when an individual has EGFR positive mutations when used in combination with erlotinib as first-line therapy or continuation therapy.

Ovarian Cancer

Bevacizumab is FDA approved to treat epithelial ovarian, fallopian tube, or primary peritoneal cancer, in combination with certain chemotherapy regimens, followed by bevacizumab monotherapy until disease progression. Bevacizumab is also approved as adjuvant therapy after surgical resection in combination with chemotherapy. NCCN also recommends bevacizumab as a single agent for recurrent disease that is either platinum-sensitive or platinum-resistant. NCCN only recommends bevacizumab as part of combination chemotherapy when used in the adjuvant setting. In contrast to NCCN recommendations for maintenance therapy for colon cancer, it is specifically not recommended as maintenance therapy for ovarian cancer in patients who did not receive a primary treatment regimen containing bevacizumab. Bevacizumab is FDA approved as a single agent for maintenance therapy. NCCN additionally recommends the combination with olaparib as maintenance therapy for those with BRCA 1/2 mutation (category 1) or for BRCA wild-type or unknown (category 2A). The trial investigating this use (Ray-coquard 2019) showed progression free survival (PFS) advantage in those with *and* without BRCA mutations, with a more pronounced advantage in BRCA+ tumors. In patients with homologous recombination deficiency (HRD)- positive tumors, PFS was extended in the combination (bevacizumab + olaparib) group compared to bevacizumab alone. HRD includes but is not limited to tumors with BRCA mutations. Those with HRD-positive, BRCA-negative disease also showed a PFS advantage leading to FDA approval in the expanded HRD-positive population.

NCCN also recommends the use of bevacizumab in the neoadjuvant setting for ovarian cancer. However, it is noted that neoadjuvant chemotherapy remains controversial and should only be considered in those with advanced, unresectable disease who have been assessed by a gynecologic oncologist. In addition, the only literature cited involving bevacizumab is an unpublished, phase II abstract.
NCCN recommends combination use of bevacizumab and niraparib in recurrent platinum-sensitive disease, but this use is under investigation (Mirza 2019). NCCN notes that single agent bevacizumab or single agent niraparib are preferred in this setting.

Renal Cell Carcinoma

Bevacizumab is FDA approved to treat metastatic renal cell carcinoma in combination with interferon alfa. NCCN also recommends bevacizumab as a single agent of in combination with everolimus in non-clear cell histology as well as in combination with erlotinib for non-clear cell histology in selected patients with advanced papillary renal cell carcinoma including hereditary leiomyomatosis and renal cell cancer (HLRCC).

Soft Tissue Sarcoma

NCCN recommends that bevacizumab be used as a single agent treatment of angiosarcoma, a vascular tumor which is a type of soft tissue sarcoma. NCCN also recommends that bevacizumab be used in combination with temozolomide for the treatment of solitary fibrous tumor, another type of soft tissue sarcoma.

Small Bowel Adenocarcinoma

NCCN recommends that bevacizumab be used in combination with 5-fluorouracil-based (including capecitabine) regimen as initial therapy for advanced or metastatic small bowel adenocarcinoma. This use also includes ampullary adenocarcinoma.

Biosimilar Agents

Biosimilar products must be highly similar to the reference product and there must be no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product. Biosimilars must utilize the same mechanism of action (MOA), route of administration, dosage form and strength as the reference product; and the indications proposed must have been previously approved for the reference product. The potential exists for a biosimilar product to be approved for one or more indications for which the reference product is licensed based on extrapolation of data intended to demonstrate biosimilarity in one indication. Sufficient scientific justification for extrapolating data is necessary for FDA approval. Factors and issues that should be considered for extrapolation include the MOA for each indication, the pharmacokinetics, bio-distribution, and immunogenicity of the product in different patient populations, and differences in expected toxicities in each indication and patient population.

Alymsys (bevacizumab-maly), Avzivi (bevacizumab-tnjn), Jobevne (bevacizumab-nwgd), Mvasi (bevacizumab-awwb), Vegzelma (bevacizumab-adcd) and Zirabev (bevacizumab-bvzr) are FDA approved biosimilar agents to Avastin. They share the same FDA approved uses as Avastin, with some exception, see the table below. Since all

Avastin biosimilars, Alymsys, Avzivi, Mvasi, Vegzelma, and Zirabev have demonstrated biosimilarity to Avastin for FDA indications, it is reasonable that biosimilarity can be extrapolated to other FDA indications, and off-label indications, as well. NCCN guidelines support the use of biosimilar agents for all FDA approved and off label uses of bevacizumab.

Definitions and Measures

5FU-based: A treatment regimen that includes fluorouracil (5-FU) or capecitabine.

Adenocarcinoma: Cancer originating in cells that line specific internal organs and that have gland-like (secretory) properties.

Adjuvant therapy: Treatment given after the primary treatment to increase the chances of a cure; may include chemotherapy, radiation, hormone or biological therapy.

Anal cancer: Cancer originating in the tissues of the anus; the anus is the opening of the rectum (last part of the large intestine) to the outside of the body.

Colon cancer: Cancer originating in the tissues of the colon (the longest part of the large intestine). Most colon cancers are adenocarcinomas that begin in cells that make and release mucus and other fluids.

Colorectal cancer: Cancer originating in the colon (the longest part of the large intestine) or the rectum (the last several inches of the large intestine before the anus).

ECOG or Eastern Cooperative Oncology Group Performance Status: A scale and criteria used by doctors and researchers to assess how an individual's disease is progressing, assess how the disease affects the daily living abilities of the individual, and determine appropriate treatment and prognosis. This scale may also be referred to as the WHO (World Health Organization) or Zubrod score which is based on the following scale:

- 0 = Fully active, able to carry on all pre-disease performance without restriction
- 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
- 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- 5 = Dead

Hormonal therapy: Treatment that adds, blocks, or removes hormones. Agents that slow or stop the growth of certain cancers, synthetic hormones or other drugs may be given to block the body's natural hormones.

Line of Therapy:

- First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
- Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
- Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second-line therapy) are not effective or there is disease progression.

Locally advanced cancer: Cancer that has spread only to nearby tissues or lymph nodes.

Maintenance therapy: Designed to maintain a condition to prevent a relapse.

Melanoma: A type of cancer that begins in the melanocytes. Melanoma is also referred to as malignant melanoma and cutaneous melanoma.

Metastasis: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.

Neoadjuvant therapy: Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy.

Non-small cell lung cancer: A group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of non-small cell lung cancer are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma.

One line of therapy: Single line of therapy.

Primary treatment: The first treatment given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation. Also called first-line therapy, induction therapy, and primary therapy.

Rectal cancer: Cancer originating in tissues of the rectum (the last several inches of the large intestine closest to the anus).

Refractory Disease: Illness or disease that does not respond to treatment.

Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.

Taxane: A type of mitotic inhibitor and antimicrotubule drug used to treat cancer that blocks cell growth by stopping mitosis (cell division).

Unresectable: Unable to be removed with surgery.

Vascular endothelial growth factor (VEGF): A substance made by cells that stimulates new blood vessel formation.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Avastin (bevacizumab); Alymsys (bevacizumab-maly), Avzivi (bevacizumab-tnjn), Jobevne (bevacizumab-nwgd), Mvasi (bevacizumab-awwb); Vegzelma (bevacizumab-adcd), Zirabev (bevacizumab-bvzr)

Requests for Avastin (bevacizumab), Alymsys (bevacizumab-maly), Avzivi (bevacizumab-tnjn), Jobevne (bevacizumab-nwgd), Mvasi (bevacizumab-awwb), Vegzelma (bevacizumab-adcd), or Zirabev (bevacizumab-bvzr) may be approved if the following criteria are met:

I. Individual has a diagnosis of Ampullary adenocarcinoma and the following are met (NCCN 2A):
   A. Bevacizumab is used in combination with a 5-fluorouracil-based (including capecitabine) regimen; **AND**
   B. Individual is using for a metastatic intestinal disease;

OR

II. Individual has a diagnosis of Central Nervous System- Primary Tumor and the following are met (Label, NCCN 2A):
   A. Individual has failed radiation therapy; **AND**
   B. Bevacizumab is used in a single line of therapy or as a single agent; **AND**
   C. The tumor to be treated includes but is not limited to:
      1. Adult medulloblastoma in combination with temozolomide and irinotecan; **OR**
      2. Adult intracranial and spinal ependymoma (excluding subependymoma) as a single agent only; **OR**
      3. IDH-mutant astrocytoma; **OR**
      4. Anaplastic glioma; **OR**
      5. Glioblastoma; **OR**
      6. Glioblastoma multiforme; **OR**
      7. High-grade glioma, recurrent; **OR**
      8. Meningiomas as a single agent only; **OR**
      9. Oligodendroglioma IDH-mutant, 1Q19 codeleted;

OR

III. Individual is using bevacizumab to treat symptomatic post-radiation necrosis of the central nervous system (NCCN 2A);

OR

IV. Individual is using bevacizumab as a single agent treatment for neurofibromatosis type 2 vestibular schwannomas with hearing loss (NCCN 2A);

OR

V. Individual has a diagnosis of pediatric central nervous system cancers and the following are met:
   A. Bevacizumab is part of a treatment for recurrent or progressive disease when:
      1. Used in combination for treatment of palliation in diffuse high-grade gliomas; **OR**
      2. Used as part of TEMR (temzolomide, irinotecan, bevacizumab) regimen; **OR**
      3. Used as part of MEMMAT (thalidomide, celecoxib, fenofibrate, etoposide, cyclophosphamide, bevacizumab regimen);

OR

VI. Individual has a diagnosis of advanced or metastatic colorectal, appendiceal, or anal adenocarcinoma and the following are met (Label, NCCN 2A):
   A. Individual has not progressed on more than two lines of a bevacizumab-containing chemotherapy regimen (Simkens 2015); **AND**
   B. Individual has either pMMR/MSS, dMMR/MSI-H, or POLE/POLD1 mutation with ultra-hypermutated phenotype [e.g. TMB >50 mut/Mb]; **AND**
   C. Individual is ineligible or has progressed on checkpoint inhibitor immunotherapy; **AND**
      1. Bevacizumab is used in combination with 5-fluorouracil-based (including capecitabine) chemotherapy, irinotecan, or oxaliplatin; OR
      2. Bevacizumab is used in combination with trifluridine and tipiracil (Lonsurf) in patients who have progressed through standard therapies;

OR

VII. Individual has a diagnosis of advanced or metastatic small bowel adenocarcinoma, including ampullary adenocarcinoma, and the following are met (NCCN 2A):
   A. Bevacizumab is used in combination with 5-fluorouracil-based (including capecitabine) regimen; **AND**
   B. Bevacizumab is used as initial therapy or subsequent therapy for disease progression; **AND**
   C. Bevacizumab is used in a single line of therapy; **AND**
   D. Individual is pMMR/MSS (proficient mismatch repair/microsatellite-stable);

OR

VIII. Individual has a diagnosis of Vulvar Cancer and the following are met (NCCN 2A):
   A. Individual has advanced, recurrent, or metastatic disease; **AND**
   B. Used in one of the following ways:
      1. Bevacizumab is used in combination with paclitaxel *and* cisplatin; **AND**
      2. Bevacizumab is used in a single line of therapy;
      OR
      3. Bevacizumab is used in combination with pembrolizumab, paclitaxel, a platinum agent for PD-L1 positive disease; **AND**
      4. Bevacizumab and pembrolizumab may be continued as maintenance therapy;

OR

IX. Individual has a diagnosis of Cervical Cancer, including vaginal cancer and the following are met (Label, NCCN 1, 2A):
   A. Individual has persistent, recurrent, or metastatic disease; **AND**
   B. Bevacizumab is used in a single line of therapy; **AND**
   C. Bevacizumab is used in combination with paclitaxel *and* either topotecan, cisplatin, or carboplatin for disease that is not amenable to curative treatment with surgery or radiotherapy (Tewari 2014); **OR**
   D. Bevacizumab is used in combination with pembrolizumab, paclitaxel, and a platinum agent for PD-L1 positive disease; **OR**
   E. Bevacizumab is used as a single agent for second-line or subsequent therapy;

OR

X. Individual has a diagnosis of locally advanced, recurrent, or metastatic cervical cancer (NCCN 1); **AND**
   A. Individual is using bevacizumab in combination with atezolizumab, platinum-containing agent, and paclitaxel; **OR**
   B. Individual is using Bevacizumab in combination with atezolizumab for maintenance therapy;

OR

XI. Individual has a diagnosis of locally advanced, recurrent, or metastatic small cell neuroendocrine carcinoma of the cervix (NECC) (NCCN 2A); **AND**
   A. Individual is using in combination with paclitaxel and topotecan; **OR**

B. As second-line or subsequent therapy as a single agent;

OR

XII. Individual has a diagnosis of Endometrial Carcinoma and the following are met (NCCN 2A):
- A. Individual has advanced or recurrent disease;

AND

- B. Bevacizumab is used in combination with carboplatin and paclitaxel;

OR

- C. Following combination therapy with carboplatin and paclitaxel, bevacizumab is used as single-agent maintenance therapy until disease progression or prohibitive toxicity.

OR

XIII. Individual has a diagnosis of Malignant Pleural or Peritoneal Mesothelioma (including pericardial mesothelioma and tunica vaginalis testis) and the following are met (NCCN 1, 2A):
- A. Bevacizumab is used as first-line therapy for Malignant Pleural Mesothelioma unresectable disease or Peritoneal Mesothelioma when (DP A IIa):
  1. Used in combination chemotherapy with pemetrexed *and* either cisplatin or carboplatin; **AND**
  2. Individual has an Eastern Cooperative Oncology Group performance status of 0-2 and no history of bleeding or thrombosis (Zalcman 2016, Ceresoli 2013); **AND**
  3. Individual is not eligible for surgery;

OR

- B. Bevacizumab is used as maintenance therapy for Malignant Pleural Mesothelioma unresectable disease or Peritoneal Mesothelioma, as a single agent, when:
  1. Bevacizumab was previously administered as an agent in a first-line combination chemotherapy regimen; **AND**
  2. Bevacizumab is used until disease progression*;
     ***Note:** Once disease progression has occurred, bevacizumab is not to be re-instituted

OR

- C. Bevacizumab is used as subsequent systemic therapy for Malignant Pleural or Peritoneal Mesothelioma, if immunotherapy was administered as first-line treatment in combination with pemetrexed and cisplatin or carboplatin (in those not eligible for cisplatin); **OR**
- D. Bevacizumab is used as subsequent systemic therapy for Malignant Peritoneal Mesothelioma in combination with atezolizumab if individual has not previously been treated with immune checkpoint inhibitors;

OR

XIV. Individual has a diagnosis of recurrent, advanced, or metastatic non-squamous Non-Small Cell Lung Cancer (NSCLC) and the following criteria are met (NCCN 2A):
- A. Individual has a current ECOG performance status of 0-2, no history of hemoptysis; **AND**
- B. Individual has EGFR positive mutations; **AND**
- C. Individual is using in combination with erlotinib; **AND**
- D. Individual is using for one of the following:
  1. As first-line therapy; **OR**
  2. As continuation of therapy following disease progression of erlotinib with bevacizumab for asymptomatic disease, symptomatic brain lesions, or symptomatic systemic limited progression (if T790M negative);

OR

XV. Individual has a diagnosis of advanced, recurrent, or metastatic non-squamous Non-Small Cell Lung Cancer (NSCLC) and the following are met (Label, NCCN 1, 2A):
- A. Individual has a current Eastern Cooperative Oncology Group performance status of 0-2, no history of hemoptysis; **AND**
- B. Individual is using in combination with platinum-based therapy and either a taxane or pemetrexed; **AND**
- C. Individual is using for one of the following:
  1. As first-line therapy (Label); **OR**
  2. As subsequent therapy if disease has progressed during or following treatment with a targeted agent for the expressed oncogene (including but not limited to, kinase inhibitors that target EGFR, KRAS, ALK, ROS1, BRAF, NTRK, RET, NRG1, ERBB2 (HER2) or MET mutations) (NCCN 2A);

OR

XVI. Individual has a diagnosis of advanced, recurrent, or metastatic non-squamous Non-Small Cell Lung Cancer (NSCLC) and the following are met (NCCN 1):
- A. Individual has a current Eastern Cooperative Oncology Group performance status of 0-2, no history of hemoptysis; **AND**

B. Individual does not have any contraindications for treatment with PD-1/PD-L1 inhibitors which include but not limited to active or previously documented autoimmune disease and /or current use of immunosuppressive agents; **AND**
C. Individual is using in combination with platinum-based therapy, a taxane, and atezolizumab; **AND**
D. Individual is using for one of the following:
    1. As first line therapy for PD-L1 expression positive (≥ 1%) tumors and if individual does not have presence of actionable molecular markers* (may be KRAS G12C mutation positive); **OR**
    2. As subsequent therapy if disease has progressed during or following treatment with a targeted agent for the expressed oncogene (including but not limited to, kinase inhibitors that target EGFR, KRAS, ALK, ROS1, BRAF, NTRK, RET, NRG1, ERBB2 (HER2) or MET mutations) (NCCN 2A);

OR

XVII. Individual has a diagnosis of non-squamous Non-Small Cell Lung Cancer (NSCLC) and the following are met (NCCN 1):
A. Individual is using as maintenance therapy for advanced, recurrent, or metastatic disease; **AND**
B. Bevacizumab was previously administered as an agent in a first-line combination chemotherapy regimen; **AND**
C. Individual is using as a single agent (DP B IIa), in combination with pemetrexed, or in combination with atezolizumab; **AND**
D. May be used until disease progression;

OR

XVIII. Individual has a diagnosis of Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer for stages II-IV disease and the following are met:
A. Bevacizumab is used for advanced or metastatic disease following initial surgical resection (as adjuvant therapy) when (NCCN 1):
    1. Used in combination with other chemotherapy (except oxaliplatin and docetaxel in Grade 1 endometrioid and low-grade serous borderline epithelial ovarian cancer); **AND**
    2. Used as maintenance therapy as a single agent;

OR

B. Bevacizumab is used for recurrent, metastatic disease that is relapsed or refractory when:
    1. Used as a single agent or in combination with other chemotherapy (NCCN 2A, Label); **AND**
    2. Used as maintenance therapy as a single agent;

    OR
    3. Used in combination with mirvetuximab soravtansine-gynx for FRα-expressing tumor for recurrent or platinum-resistant persistent disease (NCCN 2A); **OR**
    4. Used in combination with other chemotherapy for platinum-resistant persistent disease (except in combination with ixabepilone) (NCCN 2A);

OR

XIX. Individual has a diagnosis of Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer for stage II-IV disease and the following are met:
A. Bevacizumab is used as maintenance therapy for advanced, recurrent, or metastatic disease (NCCN 2A); **AND**
B. Was previously administered as an agent in a combination chemotherapy regimen; **AND**
C. May be used until disease progression; **AND**
D. Used as a single agent;
OR
E. Bevacizumab is used in combination with olaparib when the following applies (NCCN 1, 2A, Lynparza label):
    1. Individual has achieved complete clinical remission (CR) or partial remission (PR) to primary therapy; **AND**
    2. Individual has a homologous recombination deficiency (HRD) positive status defined by either;
        a. Deleterious germline and/or somatic BRCA 1/2 mutation with test results confirmed**; OR**
        b. Genomic instability;

OR

XX. Individual has a diagnosis of Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer and the following are met (NCCN 1, 2A):

A. Individual is ising in combination with carboplatin and either paclitaxel or docetaxel OR with oxaliplatin and docetaxel and individual is a poor surgical candidate or has a low likelihood of optimal cytoreduction; **AND**
B. Individual is using in one of the following ways:
    1. Bevacizumab as neoadjuvant therapy (except oxaliplatin and docetaxel in Grade I endometroid carcinoma); **OR**
    2. Bevacizumab as adjuvant therapy if individual has stable disease following neoadjuvant therapy;

OR

XXI. Individual has a diagnosis of Hepatocellular Carcinoma and the following are met (Label, NCCN 1):
A. Individual has advanced, unresectable, or metastatic disease; **AND**
B. Using in one of the following ways in combination with atezolizumab:
    1. As first-line treatment; **OR**
    2. As subsequent-line systemic therapy (NCCN 2A); **AND**
C. Individual has Child-Pugh Class A or B liver function (NCCN 1, 2A); **AND**
D. Individual has an ECOG performance status of 0-2; **AND**
E. Bevacizumab may be used until disease progression;

OR

XXII. Individual has a diagnosis of Renal Cell Carcinoma (RCC) and the following are met:
A. Individual has metastatic RCC and bevacizumab is used in combination with interferon alpha (Label); **OR**
B. Individual has relapsed or medically unresectable stage IV disease when:
    1. Bevacizumab is used as a single agent in those with non-clear cell histology (NCCN 2A); **OR**
    2. Bevacizumab is used in combination with erlotinib or everolimus in those with non-clear cell histology (including papillary RCC and hereditary leiomyomatosis and RCC [HLRCC]) (NCCN 2A);

OR

XXIII. Individual has a diagnosis of Soft Tissue Sarcoma and the following are met (NCCN 2A):
A. Bevacizumab is used as a single agent for treatment of angiosarcoma; **OR**
B. Bevacizumab is used in combination with temozolomide for the treatment of solitary fibrous tumor.

Requests for Avastin (bevacizumab), Alymsys (bevacizumab-maly), Avzivi (bevacizumab-tnjn), Jobevne (bevacizumab-nwgd), Mvasi (bevacizumab-awwb), or Zirabev (bevacizumab-bvzr) may not be approved for the following:

I. All other non-ophthalmologic indications not included above; **OR**
II. Individuals is using as adjuvant therapy following surgery for stage II or III adenocarcinoma of the colon; **OR**
III. Individual is using bevacizumab in combination with the same irinotecan-based regimen that was previously used in combination with ziv-aflibercept; **OR**
IV. Individual is using for treatment of a single condition with concomitant use of other targeted biologic agents (including, cetuximab, panitumumab, trastuzumab, lapatinib, and ziv-aflibercept); **OR**
V. Individual is using for the treatment of any of the following:
    A. Prostate cancer; **OR**
    B. Carcinoid tumors; **OR**
    C. Metastatic melanoma; **OR**
    D. Metastatic adenocarcinoma of the pancreas; **OR**
    E. Metastatic breast cancer, second line therapy or greater, for example when progression noted following anthracycline and taxane chemotherapy; **OR**
    F. Neurofibromatosis type 2; **OR**
    G. AIDS-related Kaposi sarcoma; OR
    H. Pseudoprogression of glioblastoma.

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

Step Therapy

Summary of FDA-approved and off-label non-ophthalmic indications for bevacizumab agents

	Avastin (bevacizumab)	Alymsys (bevacizumab-maly)	Avzivi (bevacizumab-tnjn)	Jobevne (bevacizumab-nwgd)	Mvasi (bevacizumab-awwb)	Vegzelma (bevacizumab-adcd)	Zirabev (bevacizumab-bvzr)
Central Nervous System Cancer	Y	Y	Y	Y	Y	Y	Y
Cervical Cancer	X	X	X	Y	X	X	X
Colorectal Cancer	X	X	X	X	X	X	X
Endometrial Cancer	Y	Y	Y	Y	Y	Y	Y
Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	X	X	X	Y	Y	X	X
Hepatobiliary Carcinoma	X	Y	Y	Y	Y	Y	Y
Malignant Mesothelioma	Y	Y	Y	Y	Y	Y	Y
Non-small Cell Lung Cancer	X	X	X	X	X	X	X
Recurrent Glioblastoma	X	X	X	X	X	X	X
Renal Cell Carcinoma	X	X	X	X	X	X	X
Small Bowel Adenocarcinoma	Y	Y	Y	Y	Y	Y	
Soft Tissue Sarcoma	Y	Y	Y	Y	Y	Y	Y
Vaginal Cancer	Y	Y	Y	Y	Y	Y	Y
Vulvar Cancer	Y	Y	Y	Y	Y	Y	Y

X = FDA approved use; Y= Off-label indication

Note: When a bevacizumab agent is deemed approvable based on the clinical criteria above, the benefit plan may have additional criteria requiring the use of a preferred[1] agent or agents.

Bevacizumab Reference and Biosimilar Agents for Non-ophthalmologic Indications Step Therapy

A list of the preferred bevacizumab or biosimilar agents for non-ophthalmologic indications is available here.

Requests for a non-preferred bevacizumab or biosimilar agent for non-ophthalmologic indications may be approved when the following criteria are met:

I. Individual has had a trial and intolerance to one preferred agent:

OR

II. Individual is currently stabilized on the requested non-preferred bevacizumab agent.

[1]Preferred, as used herein, refers to agents that were deemed to be clinically comparable to other agents in the same class or disease category but are preferred based upon clinical evidence and cost effectiveness.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

C9399	Unclassified drugs or biologicals [when specified as Avzivi (bevacizumab-tnjn) or Jobevne (bevacizumab-nwgd)]
J9035	Injection, bevacizumab, 10 mg [Avastin]
J9999	Not otherwise classified, antineoplastic drugs [when specified as Avzivi (bevacizumab-tnjn) or Jobevne (bevacizumab-nwgd)]
Q5107	Injection, bevacizumab-awwb, biosimilar, (Mvasi), 10 mg
Q5118	Injection, bevacizumab-bvzr, biosimilar, (Zirabev), 10 mg
Q5126	Injection, bevacizumab-maly, biosimilar, (Alymsys), 10 mg
Q5129	Injection, bevacizumab-adcd (Vegzelma), biosimilar, 10 mg

ICD-10 Diagnosis

C17.0-C17.9	Malignant neoplasm of small intestine
C18.0-C20	Malignant neoplasm of colon, rectosigmoid junction, rectum
C21.2-C21.8	Malignant neoplasm of cloacogenic zone, overlapping sites of rectum, anus
C22.0	Liver cell carcinoma
C22.3	Angiosarcoma of liver
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C24.1	Malignant neoplasm of ampulla of Vater
C33	Malignant neoplasm of trachea
C34.00-C34.92	Malignant neoplasm of bronchus and lung
C45.0-C45.9	Mesothelioma
C48.0-C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C49.0-C49.9	Malignant neoplasm of other connective and soft tissue [angiosarcoma, hemangiopericytoma]
C51.0-C51.9	Malignant neoplasm of vulva
C52	Malignant neoplasm of vagina
C53.0-C53.9	Malignant neoplasm of cervix uteri
C54.0-C55	Malignant neoplasm of corpus uteri, uterus part unspecified
C56.1-C56.9	Malignant neoplasm of ovary
C57.00-C57.9	Malignant neoplasm of other and unspecified female genital organs
C64.1-C64.9	Malignant neoplasm of kidney, except renal pelvis
C65.1-C65.9	Malignant neoplasm of renal pelvis
C71.0-C71.9	Malignant neoplasm of brain
C72.0-C72.1	Malignant neoplasm of spinal cord and cauda equina
C78.00-C78.02	Secondary malignant neoplasm of lung

I67.89	Other cerebrovascular disease [radiation necrosis]
Q85.02	Neurofibromatosis, type 2
Q85.03	Schwannomatosis
T66.XXXS	Radiation sickness, unspecified, sequela
Z51.11	Encounter for antineoplastic chemotherapy
Z85.038	Personal history of other malignant neoplasm of large intestine
Z85.048	Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus
Z85.068	Personal history of other malignant neoplasm of small intestine
Z85.09	Personal history of malignant neoplasm of other digestive organs
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
Z85.43	Personal history of malignant neoplasm of ovary
Z85.528	Personal history of malignant neoplasm of kidney
Z85.841	Personal history of malignant neoplasm of brain

Document History

Revised: 05/16/2025
Document History:

- 10/01/2025 – Step therapy table updates.
- 07/23/2025 – Step therapy table updates.
- 05/16/2025 – Annual Review: New FDA approval for another biosimilar Jobevne (bevacizumab-nwgd). Jobevne was added to the criteria and the step therapy. From NCCN: update uses in CNS cancer, add treatment in NF type 2 vestibular schwannomas with hearing loss, and add bevacizumab uses in pediatric CNS cancers; add specific mutations for bevacizumab targeted therapy in colorectal, appendiceal, anal cancers, and small bowel cancers; update uses in vulvar cancer, cervical cancer (including SCNECC); add mutations regarding NSCLC targeted therapy; clarify bevacizumab's use in ovarian cancer subtypes; and include combination use of atezolizumab in hepatocellular cancer. Coding Reviewed: Removed HCPCS NOC J3490 and J3590. Added HCPCS NOC C9399 and J9999 for Avzivi and Jobevne. Added ICD-10-CM C72.0-C72.1, Q85.02, Q85.03. Removed ICD-10-CM C22.1, C22.2, C22.4, C22.7, C78.4-C78.5, C79.00-C79.02, C79.60-C79.62, C79.81, Z51.12, Z85.3.
- 05/17/204 – Annual Review: For Vulvar cancer update use only with paclitaxel and cisplatin from 2A NCCN recommendation. Add use in vaginal cancer to cervical cancer criteria when used in combination with chemotherapy or pembrolizumab and chemotherapy. Remove "unresectable" disease type and add criteria for use as subsequent systemic therapy in combination with atezolizumab for Malignant Pleural or Peritoneal mesothelioma if prior treatments did not include checkpoint inhibitors. Add criteria for use in non-squamous NSCLC when used in combination with erlotinib in those with EGFR mutations. Add criteria for use in non-squamous NSCLC when an individual expresses PD-L1 as first-line therapy. For maintenance therapy in non-squamous NSCLC, add criteria for use in combination with pemetrexed. For ovarian cancer criteria, clarify use in only stage II-IV disease. Add criteria for use in combination with mirvetuximab sorvantansine-gyxn in FR-α expressing tumors. Clarify criteria when used in adjuvant and neoadjuvant therapy. For hepatocellular cancer add criteria for use in Child-Pugh Class A or B. Update summary table for FDA-approved and off-label uses. Coding Reviewed: Added ICD-10-CM C52, Z85.09.
- 03/01/2024 – Step therapy table updates.
- 12/11/2023 – Select Review: Add new biosimilar Avzivi (bevacizumab-tnjn) to the Avastin criteria and Bevacizumab Reference and Biosimilar Agents for Non-ophthalmologic Indications Step Therapy. Coding Reviewed: Added HCPCS J3490, J3590 for Avzivi.
- 11/01/2023 – Step therapy table updates.
- 08/18/2023 – Select Review: Add NCCN 1 criteria for use as neoadjuvant therapy in ovarian cancer in combination with paclitaxel and carboplatin in those who are poor surgical candidates or have low likelihood of optimal cytoreduction. Coding Reviewed: No changes.
- 08/15/2023 – Step therapy table updates.
- 05/19/2023 – Annual Review: Add NCCN 2A criteria for use as subsequent therapy in ampullary cancer and use as a single agent in subsequent therapy for cervical cancer. Add mutation updates to criteria. Wording and formatting updates. Coding Reviewed: Added ICD-10-CM C24.1.

- 05/15/2023 – Step therapy table updates.
- 05/01/2023 – Step therapy table updates.
- 04/24/2023 – Step therapy table updates.
- 03/27/2023 – Step therapy table updates.
- 01/25/2023 – Step therapy table updates.
- 11/18/2022 – Select Review: Add new biosimilar agent Vegzelma (bevacizumab-adcd) to the PA and ST criteria. Coding Reviewed: Added Vegzelma to HCPCS J3590, J9999. Added HPCPS C9142 for Alymsys, Removed HCPCS C9399. Removed HCPCS C9142, J9999 for Alymsys. Effective 1/1/2023 Added HCPCS Q5129 for Vegzelma. Removed HCPCS J3590, J9999.
- 10/24/2022 – Step therapy table updates.
- 09/12/2022 – Select Review: Added Alymsys (bevacizumab-maly) to the may not be approved criteria. Step therapy table updates. Coding Reviewed: Added HCPCS J9999. Removed HCPCS J3490.
- 08/19/2022 – Select Review: Add criteria for use in ampullary adenocarcinoma within small bowel criteria. Maintain criteria for use in metastatic RCC in combination with interferon alfa , FDA label based indication. Add criteria for maintenance use with niraparib (Zejula) in ovarian cancer in those with BRCA 1/2 mutation.
- 07/25/2022 – Step Therapy table updates.
- 05/20/2022 – Annual Review: Remove criteria for use in breast cancer and use in relapsed or stage IV RCC in combination with interferon alfa-2b as first line therapy for clear cell histology, both removed from NCCN. Update criteria for colon cancer to include advanced disease. Update Bevacizumab with new agent Alymsys. Update use in mesothelioma for malignant pleural and peritoneal disease. Add usage as subsequent systemic use in mesothelioma from NCCN. Coding Reviewed: Added HCPCS J9999, J3490, J3590, C9399. Removed C50.011-C50.929.
- 03/28/2022 – Step therapy tables updates.
- 11/19/2021 – Select Review: Update criteria for cervical cancer to allow use in combination with pembrolizumab. Coding reviewed: No changes.
- 05/21/2021 – Annual Review: Reformat and update criteria in non-small cell lung cancer to align with NCCN; update soft tissue sarcoma per NCCN; update indication table; add combination use with Lonsurf in colorectal cancer per NCCN; specify pseudoprogression of glioblastoma as not approvable; wording and formatting updates. Coding Reviewed: No changes.
- 02/25/2021 – Step Therapy table updates.
- 12/21/2020 – Add step therapy for Medicaid line of business.
- 06/08/2020 – Select Review: Update combination use with olaparib per olaparib FDA label; update references for new FDA indication in hepatocellular carcinoma; update indication table; wording and formatting updates for clarity. Coding reviewed: No changes
- 05/15/2020 – Annual Review: Update lung cancer criteria to align with other agents and NCCN; specify use in small bowel adenocarcinoma as initial therapy; add criteria for hepatocellular carcinoma; add combination use with olaparib for ovarian cancer; remove subsequent treatment of clear cell kidney cancer; wording and formatting updates. Coding Review: Added ICD-10-dx C22.0-C22.9
- 08/16/2019 – Select Review: Apply current criteria to new biosimilar agent Zirabev. Add new step therapy for bevacizumab reference and biosimilar agents in non-ophthalmologic indications. Coding Reviewed: Added HCPCS code Q5118 for Zirabev
- 05/17/2019 – Annual Review: First review of bevacizumab clinical criteria. Wording and formatting updates for clarity and consistency. Clarify cervical cancer use in combination with platinum therapy. Clarify and streamline NSCLC criteria. Clarify meaning of “first-line” in NSCLC criteria. Add references for off label criteria. Coding Reviewed: No changes.

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    c. Cervical Cancer. 4.2025. Revised March 24, 2025.
    d. Colon Cancer. V1.2025. Revised February 7, 2025.
    e. Hepatocellular Carcinoma. V1.2025. Revised March 20, 2025.
    f. Malignant Peritoneal Mesothelioma. V2. 2025. January 14, 2025.
    g. Malignant Pleural Mesothelioma. V2.2025. January 14, 2025.
    h. Ovarian Cancer. 1.2025. Revised March 5, 2025.
    i. Pediatric Central Nervous System Cancers. V2.2025. Revised January 17, 2025.
    j. Kidney Cancer. V3.2025. Revised January 9, 2025.
    k. Non-Small Cell Lung Cancer. V3.2025. Revised January 14, 2025.
    l. Small Bowel Adenocarcinoma. V3.2025. Revised March 31, 2025.
    m. Soft tissue sarcoma. V5.2024. Revised March 10, 2025.
    n. Rectal Cancer. V2. 2025. Revised March 31, 2025.
    o. Uterine Neoplasms. 3.2025. March 7, 2025.
    p. Vaginal Cancer. V1.2025. Revised March 26, 2024.
    q. Vulvar Cancer. V1.2025. Revised February 10, 2025.
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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

CC-0107 Bevacizumab for Non-ophthalmologic Indications Step Therapy
Commercial Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
06/01/2024	Avastin Mvasi	Alymsys Avzivi Vegzelma Zirabev
11/01/2025	Avastin Mvasi	Alymsys Avzivi Jobevne Vegzelma Zirabev

Medicaid Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
12/01/2022: LA 01/01/2023: IN	Mvasi	Avastin Zirabev
02/01/2023: OH 04/01/2023: DC 05/01/2023: GA, KY, MD, NJ, NV, NY, WNY, SC, TN, VA, WI 07/01/2023: CA, IA 08/01/2023: AR	Mvasi	Avastin Alymsys Zirabev
11/01/2023: DC, OH	Mvasi	Avastin Alymsys Vegzelma Zirabev

Medicare Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
~~06/01/2023~~	~~Avastin~~ ~~Mvasi~~	~~Alymsys~~ ~~Vegzelma~~ ~~Zirabev~~
06/01/2024	Avastin Mvasi	Alymsys Avzivi Vegzelma Zirabev
~~11/01/2025~~	~~Avastin~~ ~~Mvasi~~	~~Alymsys~~ ~~Avzivi~~ ~~Jobevne~~ ~~Vegzelma~~ ~~Zirabev~~

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