IMPORTANT REMINDER
This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description
Bevacizumab (Avastin) is a monoclonal antibody that binds to and inhibits the activity of vascular endothelial growth factor (VEGF). This prevents formation of new blood vessels, which halts cell growth. Bevacizumab is used in the treatment of various cancers. It is given as an intravenous infusion.
Policy/Criteria

I. **USE IN THE EYE:**
Bevacizumab may be considered medically necessary when used as an intravitreal (inside the eye) injection for the treatment of ocular conditions (e.g. macular degeneration, retinal vein occlusion, diabetic retinopathy).

II. **USE IN CANCERS:**
Most contracts require prior authorization approval of bevacizumab prior to coverage. Bevacizumab may be considered medically necessary when the following criteria below are met:

A. A diagnosis of **metastatic or recurrent cervical cancer**, when given in combination with a platinum (such as cisplatin or carboplatin) plus a taxane (such as paclitaxel).

OR

B. A diagnosis of **metastatic colorectal cancer** (adenocarcinoma), when given in combination with fluorouracil (5FU)- or capecitabine-based chemotherapy.

OR

C. A diagnosis of **anaplastic (grade 3) astrocytoma, glioblastoma (grade 4 astrocytoma), or ependymoma** that has progressed after at least one prior therapy (e.g. radiation, temozolomide).

OR

D. A diagnosis of **unresectable, locally advanced, recurrent, or metastatic non-squamous non-small cell lung cancer (NSCLC)**, when criteria 1 and 2 below are met (See Appendix A for NSCLC subtypes):
   1. Patient has had no prior chemotherapy.
   AND
   2. Bevacizumab is administered in combination with carboplatin and paclitaxel.

OR

E. A diagnosis of **persistent or recurrent platinum-resistant epithelial ovarian cancer** (including fallopian tube cancer and primary peritoneal cancer), when:
   1. Documented platinum-resistant disease (criteria a. or b. below):
      a. Disease progression on platinum-based therapy.
      OR
      b. Relapsed disease within six months of completing platinum-based chemotherapy regimen.
   AND
   2. Bevacizumab is administered in combination with paclitaxel, liposomal doxorubicin, or topotecan.

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F. A diagnosis of metastatic renal cell carcinoma, when criteria 1 and 2 below are met:
   1. Tumor with clear cell histology.
   AND
   2. Treatment with a tyrosine kinase inhibitor [pazopanib (Votrient™), sorafenib (Nexavar®), or sunitinib (Sutent®)] has been ineffective, contraindicated or not tolerated.

III. Administration and Authorization Period
   A. OmedaRx does not consider bevacizumab to be a self-administered medication.
   B. Authorization may be reviewed at least every 6 months to confirm that current medical necessity criteria are met and that the medication is effective.

IV. Bevacizumab is considered not medically necessary when:
   A. Used concomitantly with pemetrexed (Alimta®) for NSCLC.
   B. Used concomitantly with pemetrexed (Alimta) for mesothelioma.
   C. Used concomitantly with erlotinib (Tarceva®) for NSCLC.
   D. Used for the treatment of metastatic HER2-negative breast cancer.

V. Bevacizumab is considered investigational when used concomitantly with any other targeted therapy, including, but not limited to, afatinib (Gilotrif®), axitinib (Inlyta®), cetuximab (Erbitux®), ceritinib (Zykadia®), crizotinib (Xalkori®), gefitinib (Iressa®), nivolumab (Opdivo®), panitumumab (Vectibix®), pazopanib (Votrient™), sorafenib (Nexavar®), ramucirumab (Cyramza®), or sunitinib (Sutent®).

VI. Bevacizumab is considered investigational when used for all other conditions, including but not limited to:
   A. Bevacizumab maintenance therapy initiated after completion of induction therapy (without bevacizumab)
   B. Biliary cancer/cholangiocarcinoma
   C. Triple negative breast cancer
   D. HER2-positive breast cancer
   E. Early (non-metastatic) HER2-negative breast cancer
   F. Gastric or gastroesophageal cancer
   G. Melanoma
   H. Pancreatic cancer.
   I. Radiation-induced necrosis.
   J. Soft tissue sarcoma
   K. Uterine sarcoma/endometrial carcinoma

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Position Statement

Summary

- Bevacizumab is a monoclonal antibody that has been used in the treatment of many different kinds of cancers and ocular conditions.

- The intravitreal use of bevacizumab to treat ocular conditions, like age-related macular degeneration, has emerged as the most cost-effective targeted treatment.

- In the treatment of cancer, bevacizumab has been shown to improve survival in certain patients with cervical cancer, colorectal cancer and non-small cell lung cancer. In other types of cancer, its cost versus benefit is not as clear.

- In the treatment of metastatic renal cell carcinoma, there is no evidence to suggest that bevacizumab is more effective than tyrosine kinase inhibitors; however, it is more costly.

- For primary treatment of ovarian cancer, cytotoxic chemotherapy is associated with improved overall survival. Bevacizumab is not proven to improve overall survival in patients with ovarian cancer in the primary or recurrent treatment settings; however, its addition to standard chemotherapy may result in added toxicity.

- For patients with ovarian cancer that is refractory to standard platinum-based treatment, bevacizumab is another treatment option when used with specific chemotherapy (paclitaxel, topotecan, or liposomal doxorubicin).

- The use of bevacizumab with platinum-based chemotherapy in platinum-sensitive ovarian cancer has not been shown to improve clinically relevant outcomes such as survival or quality of life versus platinum-based chemotherapy without bevacizumab. However, this combination is more costly. Platinum-based chemotherapy is the standard of care treatment, with proven overall survival benefit, and is a NCCN Category 1 recommended treatment. Because there are less costly options with proven health benefit, the use of bevacizumab for platinum-sensitive ovarian cancer is considered not medically necessary.

- Use of bevacizumab in combination with pemetrexed (Alimta)-based chemotherapy for NSCLC has not been shown to improve clinically relevant outcomes such as survival or quality of life over pemetrexed regimens without bevacizumab. However, this combination is more costly. For mesothelioma, the small change in survival with the addition of bevacizumab to pemetrexed must be balanced with significant additional adverse events. Therefore, the use of bevacizumab in combination with pemetrexed for NSCLC or mesothelioma is considered not medically necessary.

- The concomitant use of bevacizumab with other targeted therapies, including erlotinib, has not been shown to improve clinically relevant outcomes in any condition.

- There is insufficient evidence to support the use of bevacizumab in a variety of other cancers and conditions, such as melanoma, pancreatic cancer, soft tissue sarcoma, uterine sarcoma, endometrial carcinoma, and radiation-induced necrosis.

- Safety concerns with intravenous administration of bevacizumab include gastrointestinal perforation, surgery and wound healing complications, and hemorrhage.
Clinical Efficacy

CERVICAL CANCER

- One phase 3 study reported a survival advantage when bevacizumab was added to standard chemotherapy (cisplatin-paclitaxel or topotecan-paclitaxel) as compared with standard chemotherapy alone. [1]
  * The survival advantage with the addition of bevacizumab to chemotherapy (combined regimens) was 3.7 months. However, based on subset evaluation, the benefit of the addition of bevacizumab was not seen with the topotecan-paclitaxel arm of the trial compared to chemotherapy alone. Use of bevacizumab should be in combination with a platinum and taxane.
  * Flaws affecting the quality of this study included high rates of therapy discontinuation, and crossover to other cancer therapies, both of which may confound the survival endpoint.

- NCCN cervical cancer treatment guidelines recommend the addition of bevacizumab to cisplatin-paclitaxel as one of several options (Category 1) for the first-line treatment of recurrent or metastatic cervical cancer. [2]
  * Cisplatin is considered the most active agent for cervical cancer and should be used whenever possible.

- All second-line options, including bevacizumab monotherapy, are lower level (Category 2B) recommended therapies, based on response or PFS endpoints. Because of the limited evidence to support its use, the use of bevacizumab monotherapy is considered investigational. Other second-line recommended monotherapies include, but are not limited to, docetaxel, 5-fluorouracil, gemcitabine, irinotecan, and topotecan.

COLORECTAL CANCER (CRC)

- Several studies in patients with metastatic colorectal cancer have reported an improved overall survival with bevacizumab when used with standard fluorouracil-based chemotherapy; however, the overall quality of this evidence is poor.

- Three phase 3 trials studied the addition of bevacizumab to fluorouracil-based chemotherapy in patients with metastatic colorectal cancer. [3-5]
  * Flaws affecting the quality of these studies included lack of information on prior cancer treatments, high rates of therapy discontinuation, and crossover to other cancer therapies, all of which may confound the overall survival (OS) endpoint.
  * Bevacizumab was added to a fluorouracil-based chemotherapy regimen in patients with metastatic colorectal cancer, as either initial or second-line therapy.
  * The overall survival advantage with the addition of bevacizumab to fluorouracil-based chemotherapy was 4.7 months in one study [3] and 2.1 months in another [4]. A third trial showed an improvement in PFS (primary endpoint), but not in OS. [5]

- A large phase 3 trial that studied the addition bevacizumab to a standard chemotherapy regimen in the adjuvant treatment of colon cancer (patients with high risk stage II disease or stage III disease following surgery). Bevacizumab failed to improve disease-free survival over standard chemotherapy alone in this setting and appears to negatively impact OS. [6]
NCCN treatment guidelines recommend the addition of bevacizumab to pyrimidine-based chemotherapy (fluorouracil or capecitabine) as a first- or second-line therapy in patients with metastatic or unresectable advanced colorectal cancer (CRC) when KRAS mutations are present. In addition, the guidelines specify that bevacizumab should not be used in the adjuvant setting for stage II or III colon cancer outside of the clinical trial setting. For CRC with the KRAS wild-type gene, bevacizumab, cetuximab or panitumumab are among the potential add-on treatment options. Because capecitabine is metabolized in vivo to fluorouracil (5FU), this policy considers the use of fluorouracil- (usually FOLFIRI or FOLFOX) and capecitabine-based chemotherapy (usually CapeOX) interchangeable for the purpose of coverage decisions.

**GLIOBLASTOMA**

Bevacizumab has not been shown to improve overall survival in patients with recurrent glioblastoma, an aggressive (Grade 4) astrocytoma. However, bevacizumab is FDA-approved for the treatment of recurrent glioblastoma, a disease with relatively few treatment options. The evidence for the efficacy of bevacizumab in recurrent glioblastoma is based on tumor response and is of poor quality. Flaws contributing to the poor quality of this evidence include the lack of comparator (placebo or active) and use of tumor response as an endpoint. Tumor response has not been shown to correlate with improved survival or quality of life in this population. Bevacizumab (10 mg/kg every other week) or bevacizumab plus irinotecan were given to patients with glioblastoma in first or second relapse. All patients had prior treatment with temozolomide and radiation therapy. The study was not designed to compare the two treatment groups. Study endpoints included 6-month progression-free survival (PFS) and tumor response. Tumor response was between 28% and 38%, and 6-month PFS was between 43% and 50%.

Although the evidence is of poor quality, there are limited options for recurrence/salvage therapy for glioblastoma multiforme, a high-grade virtually incurable astrocytoma (brain tumor), based on the NCCN Central Nervous System Tumors guideline (category 2A recommendation). NCCN also supports the use of bevacizumab for the treatment of recurrent anaplastic (Grade 3) astrocytoma (a.k.a. anaplastic glioma or anaplastic glioblastoma), as well as recurrent ependymoma (intracranial, anaplastic, or spinal), both category 2A recommendations. The use in low-grade gliomas, such as oligodendroglioma and low-grade infiltrative astrocytoma, leptomeningeal metastases, or metastatic spinal cord tumors is not supported by evidence or NCCN guidelines.

Two recent trials evaluated the use of bevacizumab as a therapy in newly diagnosed patients with glioblastoma, in combination with radiation with or without temozolomide. Neither trial found in improvement in overall survival with the addition of bevacizumab versus standard first-line treatment options. In addition, adverse events were increased with bevacizumab and the quality of life was not improved. Therefore, the use of bevacizumab in the first-line treatment of patients with newly diagnosed glioblastoma is considered not medically necessary.
NON-SMALL CELL LUNG CANCER (NSCLC)

- Studies have reported an improvement in overall survival \(^{[13]}\) and progression-free survival (PFS) \(^{[14]}\) when bevacizumab was added to standard chemotherapy for the treatment of advanced non-small cell lung cancer. The quality of this evidence is poor.

  * Flaws contributing to the poor quality of the evidence included cross-over to alternate cancer therapies which confounds the overall survival endpoint, failure to analyze all randomized patient for the primary endpoint (lack of intent-to-treat analysis), and low trial completion rate with a significant differential loss between treatment arms.

  * Progression-free survival (PFS) has not been correlated with improved overall survival in advanced non-small cell lung cancer.

  * Both trials studied bevacizumab (15 mg/kg every three weeks) as add-on therapy to first-line platinum-based chemotherapy in patients with advanced (stage IIIb or stage IV) non-squamous non-small cell lung cancer. \(^{[13,14]}\)

  * The reported overall survival difference with the addition of bevacizumab to platinum-based chemotherapy was approximately 2 months in one trial (with carboplatin and paclitaxel) \(^{[13]}\), but not the other regimens (with cisplatin plus gemcitabine or docetaxel). \(^{[14,15]}\) Therefore, the use of bevacizumab with platin-doublet therapy other than carboplatin and paclitaxel is considered not medically necessary.

- The NCCN treatment guideline lists bevacizumab added to chemotherapy among the options for the treatment of unresectable stage IIIb or IV non-squamous non-small cell lung cancer. Hemoptysis is listed as a contraindication to bevacizumab therapy. Additionally, the guideline lists continuation maintenance with bevacizumab as a possible option if there is a tumor response or stable disease following first-line treatment with a bevacizumab-containing regimen. \(^{[16]}\)

- Maintenance therapy with bevacizumab should be continued until there is disease progression. Use of bevacizumab after progression is not supported by the evidence or the NCCN guidelines. \(^{[16]}\) The evidence is limited to Phase 2 data. More trials are needed to establish the benefit of bevacizumab after disease progression. \(^{[62]}\)

- There is insufficient evidence to support the use of bevacizumab as maintenance therapy unless it was used as part of the induction therapy (in combination with paclitaxel and carboplatin) and as monotherapy maintenance. Therefore, the use of bevacizumab maintenance therapy initiated after completion of induction therapy (without bevacizumab) is considered investigational, as is the use of combination maintenance therapy. \(^{[63]}\)

- There is insufficient evidence to support the use of bevacizumab in earlier stage cancers (stage I, II, or IIIa). The evidence is limited to Phase 2 trials. Phase 3 trials are ongoing.
Use of pemetrexed (Alimta) in combination with bevacizumab (Avastin):
- There is significant interest in using bevacizumab in combination with pemetrexed (Alimta) for NSCLC. However, there is currently no published evidence that the addition of bevacizumab (Avastin) to pemetrexed-based chemotherapy improves survival or quality of life over the same pemetrexed-based chemotherapy without bevacizumab or other any other chemotherapy regimen used for NSCLC. However, costs are increased. Because the use of this combination is not superior to less costly treatment options, the use of bevacizumab in combination with pemetrexed is considered not medically necessary.
  * There are no published, well-controlled studies demonstrating superiority of bevacizumab in combination with pemetrexed versus other chemotherapy regimens, including pemetrexed-based regimens without bevacizumab. The claims of superiority are based on preliminary (Phase 2 trial) evidence.
  * The POINTBREAK study compared overall survival with pemetrexed plus carboplatin plus bevacizumab followed by maintenance therapy with pemetrexed plus bevacizumab versus paclitaxel plus carboplatin plus bevacizumab followed by maintenance therapy with bevacizumab. No difference in median overall survival (OS) was shown between the two treatment arms. [17]
  * Additionally, there is no evidence that bevacizumab plus pemetrexed-based chemotherapy is better than bevacizumab plus any other chemotherapy doublet used for NSCLC.
  * There is currently no evidence that the addition of bevacizumab (Avastin) to pemetrexed maintenance therapy improves survival or quality of life over pemetrexed monotherapy. The AVAPERL study compared maintenance therapy with cisplatin plus bevacizumab versus bevacizumab alone after first-line induction therapy in patients with nonsquamous NSCLC. Final overall survival analysis (OS) failed to demonstrate a statistically significant difference in median overall survival between the two treatment arms. [18,19]

Use of bevacizumab in combination with other targeted therapies:
- The addition of erlotinib to bevacizumab has not been shown to improve clinically relevant outcomes when used in the first-line treatment of advanced NSCLC.
  * A large randomized, double-blind, placebo-controlled trial (ATLAS) studied bevacizumab both with and without erlotinib in 1,145 patients with advanced NSCLC. [20]
  * There was no improvement in median overall survival observed in the dual therapy arm versus the bevacizumab-alone treatment arm. The effect on quality of life measures was not reported; however, there was a greater incidence of adverse events and serious adverse events reported in the dual treatment arm.

RENAL CELL CARCINOMA
- Bevacizumab has not been shown to improve overall survival in the treatment of advanced renal cell carcinoma (RCC).
- Efficacy of bevacizumab in advanced RCC is based on progression-free survival (PFS). There is no correlation between overall survival and PFS for this condition.
The quality of evidence from two phase 3 trials studying bevacizumab in the treatment of advanced renal cell carcinoma is poor. \[21,22\]

Flaws contributing to the poor quality of the evidence included a high rate of study discontinuation, lack of blinding, and a large differential loss between study groups.

* Both trials studied bevacizumab (10 mg/kg every two weeks) as add-on therapy to interferon alfa in previously untreated patients with advanced renal cell carcinoma. The primary endpoint in both studies was overall survival (OS), with progression-free survival (PFS) as a secondary endpoint.

* Neither of the trials was able to show a difference in overall survival. An improvement in PFS was reported with bevacizumab in both trials.

There are many options for the treatment of advanced RCC with the majority being better tolerated than the combination of bevacizumab and interferon alfa.

There is insufficient evidence to support the use of bevacizumab in combination with axitinib. The evidence is limited to Phase 2 data. More trials are needed.

The NCCN kidney cancer treatment guideline lists bevacizumab plus interferon alfa as one of several possible class 1 recommendations for the treatment of relapsed or unresectable stage IV renal cell carcinoma with clear cell histology. A lower level recommendation is given for use after progression of a first-line therapy. \[23\]

**OVARIAN CANCER** (including Fallopian Tube Cancer and Primary Peritoneal Cancer)

Bevacizumab improves progression-free survival (PFS) in the first- and second-line treatment of epithelial ovarian cancer (including fallopian tube and primary peritoneal cancers); however, to date, none of the studies has demonstrated an improvement in median overall survival.

**As primary therapy:**

Although there is interest in adding bevacizumab to the standard of care taxane-carboplatin in the primary treatment of ovarian cancer, there is no evidence to suggest the addition of bevacizumab increases overall survival or improves quality of life. Because there are less-costly treatment options available with proven survival benefit, the use of bevacizumab in the primary treatment of ovarian cancer is considered not medically necessary.

Two large, phase 3 trials (ICON7 and GOG-0218) that studied bevacizumab as an add-on to standard chemotherapy in the first-line management of ovarian cancer demonstrated a two to four month improvement in median PFS over standard chemotherapy alone. \[24,25\]

* In ICON7, an early overall survival advantage was reported with bevacizumab in a subgroup of women who are at high risk for progression of disease; however, there was no difference in overall survival with the addition of bevacizumab. \[26\]

* A follow-up analysis of quality of life (QoL) in the ICON7 trial found that bevacizumab is associated with a small but clinically significant decrease in QoL as compared with standard ovarian cancer treatment. \[27\]
The NCCN guideline gives bevacizumab plus cytotoxic chemotherapy a low recommendation (category 3) in the primary/adjuvant setting for epithelial ovarian cancer (including fallopian tube and primary peritoneal cancers). There was major disagreement among the panel members regarding the inclusion of Avastin as an upfront treatment option, given the lack of statistically significant increase in overall survival and/or improvement in quality of life. Platinum-based doublets (paclitaxel or docetaxel with carboplatin) are given the highest recommendation (category 1).[28]

**As a second-line therapy (recurrent/refractory):**

- There is uncertainty regarding the benefit of bevacizumab in the treatment of recurrent or refractory ovarian cancer (and primary peritoneal cancer). The available evidence has failed to demonstrate an improvement in overall survival with the addition of bevacizumab to cytotoxic chemotherapy versus cytotoxic chemotherapy alone. However, treatment options may be limited to patients with multi-drug refractory disease.

- Platinum-based therapy remains the standard of care, highest-rated recommended treatment option for patients with platinum-sensitive disease. [28]

- **For platinum-resistant disease:**
  
  * An open-label, unpublished, phase 3 trial (AURELIA) studied the addition of bevacizumab to standard chemotherapy (weekly paclitaxel, liposomal doxorubicin, or topotecan, chosen by investigator) in patients with platinum-resistant recurrent ovarian or primary peritoneal cancer. [31]
  
  * Platinum-resistant disease was defined as progression of disease while receiving platinum-based therapy or relapsed disease within six months of completing platinum-based chemotherapy regimen.
  
  * A 3.3 month improvement in PFS was reported in the bevacizumab arm relative to standard chemotherapy alone. However, the improvement in median overall survival was non-significant with the addition of bevacizumab to standard chemotherapy. [31]

- **For platinum-sensitive disease:**
  
  * A phase 3 trial (OCEANS) in recurrent (second-line treatment after front-line platinum-based therapy) ovarian, primary peritoneal, or fallopian tube carcinoma reported a 4-month improvement in PFS (investigator assessment) when bevacizumab was added to carboplatin plus gemcitabine versus carboplatin and gemcitabine alone. [29]
  
  * However, the addition of bevacizumab to standard chemotherapy did not improve median overall survival. [30]
  
  * Platinum-based therapy remains the standard of care treatment option for these patients and has the highest-level (Category 1) recommendation from NCCN. The use of bevacizumab in platinum-sensitive ovarian cancer has a lower-level Category 2B recommendation. [28]

  * Given the lack of overall survival benefit and availability of multiple other standard of care treatment options, including platinum-based therapies, the use of bevacizumab for platinum-sensitive ovarian cancer is considered not medically necessary.
- For recurrent epithelial ovarian cancer (including fallopian tube and primary peritoneal cancers), the National Comprehensive Cancer Network (NCCN) gives: [28]

*For platinum-sensitive disease*
- Carboplatin plus paclitaxel or liposomal doxorubicin the highest recommendation (category 1)
- Bevacizumab plus carboplatin/gemcitabine is a lower level (category 2B) recommendation
- Most all other options, including bevacizumab, single agent non-platinum therapies (e.g. docetaxel, gemcitabine), and combinations, are given a lower (category 2A) recommendation.

*For platinum-resistant disease*
- All treatment options are category 2A recommendations, including numerous single agent non-platinum therapies (e.g. docetaxel, oral etoposide, gemcitabine, paclitaxel, topotecan), and combinations of bevacizumab plus paclitaxel, liposomal doxorubicin, or topotecan.

- “Less common ovarian histopathologies (LCOH),” such as malignant germ cell tumors and sex-cord stromal tumors are not epithelial ovarian cancers. There are no published trials of bevacizumab for malignant germ cell tumors and sex-cord stromal tumors. Therefore, the use of bevacizumab for these less common ovarian histopathologies is considered investigational.

**BREAST CANCER**
- Bevacizumab has not been shown to improve overall survival in patients with metastatic HER2-negative breast cancer.

- Improvement in progression-free survival (PFS) has been reported with bevacizumab in patients with metastatic HER2-negative breast cancer; however, the quality of this evidence is poor and inconsistent.

- A single study reported an improved progression-free survival with bevacizumab in patients with HER2-negative metastatic breast cancer when given with paclitaxel; however, the study failed to show an improvement in overall survival, the primary endpoint. [32]
  - This study was appraised as not reliable for reasons that included lack of blinding combined with an endpoint (progression-free survival) that contained subjective measures, and erosion of randomization (lack of an intent-to-treat analysis).

  * Paclitaxel alone versus paclitaxel plus bevacizumab was studied in women with metastatic HER2-negative breast cancer who had no prior chemotherapy.

  * The endpoint of interest (primary endpoint) was overall survival. The study reported that the addition of bevacizumab to paclitaxel does not improve overall survival. An improvement in progression-free survival was noted in the bevacizumab group.

- A second unreliable study studied the addition of bevacizumab to capecitabine. In this study, there was no difference in progression-free survival when bevacizumab was added to capecitabine. [33]
- The addition of bevacizumab to a standard first-line regimen of trastuzumab plus docetaxel failed to provide any additional benefit over trastuzumab plus docetaxel alone in patients with metastatic HER2-positive breast cancer. \cite{34}

- The National Comprehensive Cancer Network (NCCN) breast cancer guideline lists the combination of bevacizumab plus paclitaxel among possible treatment options for women with metastatic HER2-negative breast cancer based on improved PFS over single-agent paclitaxel. Other options include but are not limited to anthracyclines (doxorubicin, epirubicin), anti-metabolites (gemcitabine, capecitabine), and vinorelbine. \cite{35}

- There is insufficient evidence to support the use of bevacizumab for the treatment of triple negative and HER2-positive breast cancer. The evidence is limited to Phase 2 data. \cite{36,37}

- There is insufficient evidence to support the use of bevacizumab for the treatment of early (non-metastatic) HER-2 positive. Results for disease response (PFS) are inconsistent and the effect on overall survival is unknown. \cite{38}

**MESOTHELIOMA**

- The evidence to support the safety or efficacy of bevacizumab in combination with cisplatin/pemetrexed for treatment of unresectable malignant pleural mesothelioma (MPM) limited to one phase 3 trial. \cite{60}

  * The addition of bevacizumab to cisplatin/pemetrexed in patients with unresectable MPM improved overall survival versus cisplatin/pemetrexed alone (18.8 months versus 16.1 month); however, there was greater toxicity associated with bevacizumab, including grade 3 hypertension (23% vs. 0%) and grade 3-4 arterial thrombotic events (2.7% vs. 0%).

  * Although the addition of bevacizumab to cisplatin/pemetrexed is listed in the NCCN guideline as a category 2A recommended therapy, cisplatin/pemetrexed remains the gold standard (category 1). \cite{42}

  * Because there is no conclusive superior benefit versus the standard of care, the use of bevacizumab in combination with pemetrexed is considered not medically necessary.

- One additional trial found no significant benefit (PFS or OS) from the addition of bevacizumab to gold standard cisplatin based therapy (cisplatin/gemcitabine) in patients with advanced mesothelioma. \cite{61}

**OmedaRx performs independent analyses of oncology medications. The OmedaRx analysis and coverage policy may differ from NCCN guidelines.**

**USE IN OTHER CANCERS AND CONDITIONS**

- Bevacizumab has been studied in a variety of other cancers, including but not limited to biliary cancer/intrahepatic cholangiocarcinoma, gastric cancer, advanced melanoma, pancreatic cancer, prostate cancer, uterine sarcoma, endometrial carcinoma, and soft tissue sarcomas, as well as radiation-induced necrosis. There is insufficient evidence to support the use of bevacizumab in any of these conditions; therefore, the use of bevacizumab is considered investigational.
* **Biliary cancer:** There is inconclusive evidence to support the safety or efficacy of bevacizumab for treatment of intrahepatic cholangiocarcinoma. The evidence is limited to two Phase 2 trials. [39,40]

* **Gastric or gastroesophageal cancer:** One phase 3 trial studied the addition of bevacizumab to capecitabine plus cisplatin in patients with locally advanced or metastatic gastric cancer. No improvement in overall survival was demonstrated. Progression free survival was similar. [41]

* **Melanoma:** There is no conclusive evidence to support the safety or efficacy of bevacizumab for treatment of advanced melanoma. Currently available evidence is limited to retrospective case series and Phase 2 trials. One Phase 3 trial is ongoing; however, the pre-planned interim analysis found no significant difference in overall survival. [43]

* **Pancreatic Cancer:** A phase 3 trial studied the addition of bevacizumab to gemcitabine plus erlotinib in patients with metastatic pancreatic cancer using overall survival as the endpoint. [44] The evidence from this study was of poor quality for reasons that included lack of information on blinding and a high rate of withdrawals. No overall survival advantage was reported with bevacizumab in this condition. Use of bevacizumab is not listed as a potential therapy for pancreatic cancer on the NCCN compendium. [45]

* **Soft tissue sarcomas:** Although bevacizumab is listed in the NCCN guideline as one of several potential options for the treatment of soft tissue sarcomas, there is no reliable, published evidence supporting its use in this condition. [46]

* **Prostate cancer:** A large phase 3 trial studied the addition of bevacizumab to docetaxel plus prednisone in men with metastatic castration-resistant prostate cancer. No improvement in overall survival was demonstrated; however, there was greater toxicity associated with bevacizumab. [47]

* **Uterine sarcoma (carcinosarcoma) and endometrial carcinoma:** The evidence for the use of bevacizumab for recurrent or metastatic endometrial carcinoma is limited to non-comparative Phase 2 trials. [48-50] Phase 3 study results are not yet available. There are several alternative options listed in the NCCN guideline (including ifosfamide ± paclitaxel, Category 1). Therefore, the use of bevacizumab in uterine sarcoma (carcinosarcoma) and endometrial carcinoma cancer is considered investigational. [51]

* **Uterine sarcoma** One phase 3 trial studied the addition of bevacizumab to gemcitabine plus docetaxel for the first-line treatment of women with metastatic leiomyosarcoma. No improvement in progression free survival, overall survival, or overall response rate was demonstrated. [52]

* **Radiation-induced necrosis:** Although initial results may be promising, there is no conclusive evidence supporting the use of bevacizumab for the treatment of radiation-induced necrosis. The evidence is limited to small case series. [53-55] A systematic review of the available evidence concluded improvement of neurological symptoms, but potentially serious complications, including worsening of hemiplegia, seizures, and venous thromboemboli (PE and DVT).
Additional evidence is needed to support the safety and efficacy of bevacizumab for this indication. [56]

**Safety** [57]
- Bevacizumab package labeling carries box warnings for gastrointestinal perforations, surgery and wound healing complications, and potential for hemorrhage.
- The most commonly reported adverse effects with bevacizumab include: epistaxis, headache, hypertension, proteinuria, alterations of taste, dry skin, rectal hemorrhage, abnormal tearing, back pain, and exfoliative dermatitis.
- The incidence of neutropenia and febrile neutropenia are increased in patients that receive bevacizumab plus chemotherapy versus chemotherapy alone.

**Dosing and Administration** [57]
- Bevacizumab is given via an intravenous infusion over a minimum of 30 minutes (over 90 minutes for first infusion, and over 60 minutes for second infusion, as tolerated), every two to three weeks.
- Bevacizumab has been administered via intravitreal injection in doses of 1.25 mg (in 0.05 ml of solution) for the treatment of neovascular age-related macular degeneration. [58,59]

### Appendix A: Lung cancer histological subtypes (and approximate incidence, %)

**Lung cancer (162.0, 162.2-162.5, 162.8, 162.9)**

<table>
<thead>
<tr>
<th>A. Non-small cell lung cancer (NSCLC) (85-90%)</th>
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<tbody>
<tr>
<td>1) Squamous cell (epidermoid) carcinoma (25-30%)</td>
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<tr>
<td>2) Non-squamous cell (55%)</td>
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<td>- Adenocarcinoma (40%)</td>
</tr>
<tr>
<td>- Large cell (undifferentiated) carcinoma (10-15%)</td>
</tr>
<tr>
<td>- Other</td>
</tr>
</tbody>
</table>

| B. Small cell lung cancer (SCLC) (10-15%) |

| C. Unspecified lung cancer (< 5%) |

### Cross References

<table>
<thead>
<tr>
<th>Cross References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alimta®, pemetrexed, Medication Policy Manual, Policy No. 213</td>
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<tr>
<td>Inlyta®, axitinib, Medication Policy Manual, Policy No. 273</td>
</tr>
<tr>
<td>Nexavar®, sorafenib, Medication Policy Manual, Policy No. 134</td>
</tr>
<tr>
<td>Sutent®, sunitinib, Medication Policy Manual, Policy No. 128</td>
</tr>
<tr>
<td>Tarceva®, erlotinib, Medication Policy Manual, Policy No. 118</td>
</tr>
<tr>
<td>Votrient®, pazopanib, Medication Policy Manual, Policy No. 199</td>
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</table>

<table>
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<tr>
<th>Codes</th>
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<tbody>
<tr>
<td>HCPCS</td>
<td>J9035</td>
<td>Injection, bevacizumab, 10 mg</td>
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</table>

### References


Revision History

<table>
<thead>
<tr>
<th>Revision Date</th>
<th>Revision Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/17/2017</td>
<td>No changes with this annual update.</td>
</tr>
<tr>
<td>6/10/2016</td>
<td>- Clarify coverage criteria for recurrent/refractory ovarian cancer, to allow coverage for platinum-resistant disease, when used in combination with paclitaxel, liposomal doxorubicin, or topotecan.</td>
</tr>
</tbody>
</table>
| 2/12/2016     | - Add mesothelioma to “Not medically necessary” indications.  
- Updated list of investigational uses, including biliary cancer/cholangiocarcinoma, early (non-metastatic) HER2-negative breast cancer, gastric cancer, uterine sarcoma/endometrial carcinoma. |