BlueCross BlueShield of Kansas City

An Independent Licensee of the Blue Cross and Blue Shield Association

# Avastin® (bevacizumab)

**Policy Number:** 5.02.502
**Origination:** 04/2006
**Last Review:** 04/2014
**Next Review:** 04/2015

## Policy

BCBSKC will provide coverage for bevacizumab when it is determined to be medically necessary because the criteria shown below are met.

## When Policy Topic is covered

Bevacizumab is considered medically necessary for the following indications:

- Metastatic cancer of the colon or rectum,
- Metastatic renal cell carcinoma,
- Non-squamous, non-small cell lung cancer,
- Gliomas (salvage therapy),
- Intravitreal injection for the treatment of ocular conditions (e.g. macular degeneration, retinal vein occlusion, diabetic retinopathy).

## When Policy Topic is not covered

Bevacizumab is considered experimental and investigational for the treatment of other indications.

## Considerations

This Blue Cross and Blue Shield of Kansas City policy was developed using available resources such as, but not limited to: Hayes Medical Technology Directory, Food and Drug Administrative (FDA) approvals, Facts and Comparisons, National specialty guidelines, Local medical policies of other health plans, Medicare (CMS), Local providers.

## Description of Procedure or Service

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.

## Rationale

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

***Clinical Efficacy***

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. [1]

* 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. [2] 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. [3]

COLORECTAL CANCER

Several studies in patients with metastatic colorectal cancer have reported an improved overall survival with bevacizumab when used with standard chemotherapy; however, the overall quality of this evidence is poor. Three phase III trials studied the addition of bevacizumab to fluorouracil-based chemotherapy in patients with metastatic colorectal cancer. [4-6] ]

* 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 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 [4] and 2.1 months in another [5]. A third trial showed an improvement in PFS (primary endpoint), but not in overall survival. [6]

NCCN treatment guidelines recommend the addition of bevacizumab to fluorouracil-based chemotherapy as a first- or second-line therapy in patients with metastatic or unresectable advanced colorectal cancer (CRC) when KRAS mutations are present. For CRC with the KRAS wild-type gene, bevacizumab, cetuximab or panitumumab are among the potential add-on treatment options. [7]

GLIOBLASTOMA

Bevacizumab has not been shown to improve overall survival in patients with recurrent glioblastoma. The evidence for the efficacy of bevacizumab in recurrent glioblastoma is based on tumor response and is of poor quality. [8]

* 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 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 treatment of recurrent glioblastoma multiforme, a high-grade virtually incurable astrocytoma (brain tumor), based on the NCCN Central Nervous System Tumors guideline. [9]

NON-SMALL CELL LUNG CANCER

Studies have reported an improvement in overall survival [10] and progression-free survival (PFS) [11] 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. [10,11]

* The reported overall survival difference with the addition of bevacizumab to platinum-based chemotherapy was approximately 2 months.

The NCCN treatment guideline lists bevacizumab added to platinum-based chemotherapy among the options for the treatment of unresectable stage IIIb or IV non-squamous non-small cell lung cancer. [12] 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. [12]

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 III trials studying bevacizumab in the treatment of advanced renal cell carcinoma is poor. [13,14]

* 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. 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. [15]

INVESTIGATIONAL USES

Bevacizumab has been studied in a variety of other cancers, including but not limited to cervical cancer, ovarian and primary peritoneal cancer, pancreatic cancer, and soft tissue sarcomas.

* *Cervical cancer*: A small, (n = 46) single-arm (uncontrolled), poor quality trial studied bevacizumab in women with recurrent cervical cancer. [16] Larger, well controlled studies are necessary to establish a clinical benefit in this population. Because the quality of the evidence for bevacizumab in recurrent cervical cancer is poor and there are several alternative treatments listed as options in the NCCN Cervical Cancer treatment guideline, its use in this condition is considered investigational. [17,18]

* *Ovarian and primary peritoneal cancer*: There are several small, published, single-arm (uncontrolled) poor quality trials that studied bevacizumab in ovarian or primary peritoneal cancer. [19-22] A larger, controlled, phase III trial that studied bevacizumab plus chemotherapy (carboplatin and paclitaxel) in women with stage III or IV ovarian cancer was recently presented at the American Society of Clinical Oncologists (ASCO) 2010 annual meeting [19]; however, the study has not yet been published in a peer-reviewed medical journal. The quality of the evidence from this new trial will be evaluated pending publication of the study. Because the available evidence for bevacizumab in ovarian cancer is of poor quality and there are several alternative options listed in the NCCN guideline [23], use of bevacizumab in ovarian cancer is considered investigational.

* *Pancreatic Cancer*: A phase III trial studied the addition of bevacizumab to gemcitabine plus erlotinib in patients with metastatic pancreatic cancer using overall survival as the endpoint. [24] 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 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. [17]

* *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. [25]

***Safety***

Bevacizumab package labeling carries box warnings for gastrointestinal perforations, surgery and wound healing complications, and potential for hemorrhage. [26] 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. [26] The incidence of neutropenia and febrile neutropenia are increased in patients that receive bevacizumab plus chemotherapy versus chemotherapy alone. [26]

References

1. Miller, K, Wang, M, Gralow, J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med*. 2007 Dec 27;357(26):2666-76. PMID: 18160686
2. Miller, KD, Chap, LI, Holmes, FA, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. *J Clin Oncol*. 2005 Feb 1;23(4):792-9. PMID: 15681523
3. NCCN Clinical Practice Guidelines in Oncology™. Breast Cancer v.2.2011. [cited June 2, 2011]; Available from: http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf
4. Hurwitz, H, Fehrenbacher, L, Novotny, W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004 Jun 3;350(23):2335-42. PMID: 15175435
5. Giantonio, BJ, Catalano, PJ, Meropol, NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol*. 2007 Apr 20;25(12):1539-44. PMID: 17442997
6. Saltz, LB, Clarke, S, Diaz-Rubio, E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol*. 2008 Apr 20;26(12):2013-9. PMID: 18421054
7. NCCN Clinical Practice Guidelines in Oncology™. Colon Cancer v.3.2011. [cited June 2, 2011]; Available from: http://www.nccn.org/professionals/physician_gls/PDF/colon.pdf

8. Friedman, HS, Prados, MD, Wen, PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol*. 2009 Oct 1;27(28):4733-40. PMID: 19720927
9. NCCN Clinical Practice Guidelines in Oncology™. Central Nervous System Cancers v.2.2011. [cited June 2, 2011]; Available from: http://www.nccn.org/professionals/physician_gls/PDF/cns.pdf
10. Sandler, A, Gray, R, Perry, MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006 Dec 14;355(24):2542-50. PMID: 17167137
11. Reck, M, von Pawel, J, Zatloukal, P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. *J Clin Oncol*. 2009 Mar 10;27(8):1227-34. PMID: 19188680
12. NCCN Clinical Practice Guidelines in Oncology™. Non-Small Cell Lung Cancer v.3.2011. [cited 06/02/2011]; Available from: http://www.nccn.org/professionals/physician_gls/PDF/nscl.pdf.© 2011 RegenceRx. All rights reserved. dru215.1 Page 11 of 12
13. Rini, BI, Halabi, S, Rosenberg, JE, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. *J Clin Oncol*. 2008 Nov 20;26(33):5422-8. PMID: 18936475
14. Escudier, B, Pluzanska, A, Koralewski, P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet*. 2007 Dec 22;370(9605):2103-11. PMID: 18156031
15. NCCN Clinical Practice Guidelines in Oncology™. Kidney Cancer v.2.2011. [cited June 2, 2011]; Available from: http://www.nccn.org/professionals/physician_gls/PDF/kidney.pdf
16. Monk, BJ, Sill, MW, Burger, RA, Gray, HJ, Buekers, TE, Roman, LD. Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a gynecologic oncology group study. *J Clin Oncol*. 2009 Mar 1;27(7):1069-74. PMID: 19139430
17. NCCN Drugs and Biologics Compendium (NCCN Compendium™). [cited June 2, 2011]; Available from: http://www.nccn.org/clinical.asp
18. NCCN Clinical Practice Guidelines in Oncology™. Cervical Cancer v.1.2011. [cited 06/02/2011]; Available from: http://www.nccn.org/professionals/physician_gls/PDF/cervical.pdf
19. Burger, RA, Sill, MW, Monk, BJ, Greer, BE, Sorosky, JI. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2007 Nov 20;25(33):5165-71. PMID: 18024863
20. Cannistra, SA, Matulonis, UA, Penson, RT, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. *J Clin Oncol*. 2007 Nov 20;25(33):5180-6. PMID: 18024865
21. Garcia, AA, Hirte, H, Fleming, G, et al. Phase II clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer: a trial of the California, Chicago, and Princess Margaret Hospital phase II consortia. *J Clin Oncol*. 2008 Jan 1;26(1):76-82. PMID: 18165643
22. Penson, RT, Dizon, DS, Cannistra, SA, et al. Phase II study of carboplatin, paclitaxel, and bevacizumab with maintenance bevacizumab as first-line chemotherapy for advanced mullerian tumors. *J Clin Oncol*. Jan 1;28(1):154-9. PMID: 19917843
23. NCCN Clinical Practice Guidelines in Oncology™. Ovarian Cancer (including Fallopian Tube cancer and Primary Peritoneal cancer) v.2.2011. [cited June 2, 2011]; Available from: http://www.nccn.org/professionals/physician_gls/PDF/ovarian.pdf
24. Van Cutsem, E, Vervenne, WL, Bennouna, J, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. *J Clin Oncol*. 2009 May 1;27(13):2231-7. PMID: 19307500
25. NCCN Clinical Practice Guidelines in Oncology™. Soft Tissue Sarcoma v.1.2011. [cited June 2, 2011]; Available from: http://www.nccn.org/professionals/physician_gls/PDF/sarcoma.pdf© 2011 RegenceRx. All rights reserved. dru215.1 Page 12 of 12
26. Avastin® [package insert]. South San Francisco, CA: Genentech, Inc.; February 2011.
27. Martin, DF, Maguire, MG, Ying, GS, Grunwald, JE, Fine, SL, Jaffe, GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. May 19;364(20):1897-908. PMID: 21526923
28. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically.

## Billing Coding/Physician Documentation Information

J9035 Injection, bevacizumab, 10 mg

## Additional Policy Key Words

5.02.502

## Related Topics

N/A

## Policy Implementation/Update Information

| | |
|---|---|
| 04/2006 | New policy titled Avastin® (bevacizumab) |
| 11/2006 | Policy updated to include age related macular degeneration as a covered indication. |
| 04/2007 | Reviewed – no changes made |
| 04/2008 | Policy updated to include the following indications: Metastatic epithelial ovarian cancer, Gliomas (salvage therapy) |
| 04/2009 | Reviewed – no changes made |
| 04/2010 | Reviewed – no changes made |
| 04/2011 | Reviewed – no changes made |
| 04/2012 | Updated policy to state medically necessary as an intravitreal injection for ocular conditions, removed breast and ovarian cancers as medically necessary. |
| 04/2014 | Reviewed – no changes made |