

## Evidence Based Guideline

# Bevacizumab in Advanced Adenocarcinoma of the Pancreas

<b>File Name:</b>	bevacizumab_in_advanced_adenocarcinoma_of_the_pancreas
<b>Origination:</b>	3/2/2010
<b>Last CAP Review:</b>	11/2010
<b>Next CAP Review:</b>	11/2011
<b>Last Review:</b>	1/2012

### Description of Procedure or Service

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Bevacizumab (Avastin®, Genentech BioOncology) is a humanized monoclonal antibody directed against vascular endothelial growth factor-A (VEGF-A). Vascular endothelial growth factors (VEGFs) and their receptors (VEGF-Rs) contribute to tumor growth and metastasis by promoting angiogenesis. This policy examines the available evidence for the off-label use of bevacizumab in patients with advanced adenocarcinoma of the pancreas.

In the U.S., pancreatic adenocarcinoma is the tenth most common cancer in men and the fourth leading cause of cancer deaths in men and women. Only 7% of cases are detected at an early stage, and more than 90% of patients develop metastases. The 1-year survival rate is 24%; the 5-year survival rate is 5% overall, and 20% for those diagnosed early with only local disease. For patients with advanced, unresectable disease, the standard of care is gemcitabine (Gemzar®). Gemcitabine is approved by the U.S. Food and Drug Administration (FDA) as single-agent first-line treatment for patients with locally advanced (stage II or stage III when surgery is not an option) or metastatic (stage IV) adenocarcinoma of the pancreas, including patients previously treated with 5-fluorouracil. Gemcitabine is sometimes given as part of combination therapy with another agent, such as erlotinib (Tarceva®), which is approved by the FDA for first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine.

Vascular endothelial growth factors (VEGFs) and their receptors (VEGF-Rs) contribute to tumor growth and metastasis by promoting angiogenesis, the growth of new vasculature.)

Without angiogenesis, nutrients, oxygen and other essential molecules reach malignant cells only by passive diffusion from pre-existing blood vessels, which would limit most tumors to diameters of several millimeters. Certain normal physiologic processes (e.g., embryonic development, menstruation, wound healing) require angiogenesis, and some non-cancer pathologic processes are linked to angiogenesis (e.g., macular degeneration, atherosclerosis, psoriasis).

In February 2004, bevacizumab (Avastin®, Genentech BioOncology) was approved by the FDA through the Biologic License Application (BLA) process for use in combination with intravenous 5-fluorouracil-based chemotherapy, for first-line treatment of patients with metastatic carcinoma of the colon or rectum.

Timeline of FDA supplemental indication approvals are as follows:

- June 2006: Indication was expanded to first- or second-line use in the treatment of metastatic carcinoma of the colon or rectum.
- October 2006: Added use in combination with carboplatin and paclitaxel as first-line treatment of patients with unresectable, locally advanced, recurrent, or metastatic non squamous, non-small cell lung cancer.
- February 2008: Added use in combination with paclitaxel for patients who have not received

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chemotherapy for metastatic HER2-negative breast cancer based on improvement in progression free survival observed in clinical trials. There are no data demonstrating an improvement in disease related symptoms or increased survival with bevacizumab. Bevacizumab is not indicated for patients with breast cancer that has progressed following anthracycline and taxane chemotherapy.

- May 2009: Added use for the treatment of glioblastoma with progressive disease following prior therapy as a single agent. This was based on an improvement in objective response rate. There are no data demonstrating an improvement in disease-related symptoms or increased survival with bevacizumab.
- July 2009: Added use for the treatment of metastatic renal cell carcinoma in combination with interferon alfa.
- November 2011: FDA approval withdrawn for breast cancer.

The FDA-approved label for bevacizumab includes a black-box warning about gastrointestinal perforations, surgery and wound healing complications, and hemorrhage. Other potential adverse events listed on the label include non-gastrointestinal fistula, arterial thromboembolic events (including cerebral infarction, transient ischemic attacks, myocardial infarction, and angina), hypertension, reversible posterior leukoencephalopathy syndrome, neutropenia and infection, proteinuria, and congestive heart failure. Bevacizumab should not be given for at least 28 days following major surgery, and the surgical incision should be fully healed. In July 2008, Genentech sent a letter to healthcare providers indicating that the use of bevacizumab in combination with sunitinib maleate (Sutent®, Pfizer Oncology) was not recommended, because of the potential for microangiopathic hemolytic anemia seen in a Phase I dose-escalation study using both medications.

This guideline only discusses the use of bevacizumab in advanced adenocarcinoma of the pancreas.

**\*\*\*Note: This Evidence Based Guideline is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

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Not applicable

## Medical Evidence regarding Bevacizumab in Advanced Adenocarcinoma of the Pancreas indicates it is not recommended in the following situations:

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Treatment of advanced adenocarcinoma of the pancreas with bevacizumab is not an FDA-approved indication. The available evidence does not clearly demonstrate that addition of bevacizumab to chemotherapy regimens for advanced adenocarcinoma of the pancreas improves the net health outcome of those patients. Therefore, bevacizumab for patients with advanced adenocarcinoma of the pancreas is not recommended.

## Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

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## **Billing/Coding/Physician Documentation Information**

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This guideline may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: J9035*

## **Scientific Background and Reference Sources**

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BCBSA Medical Policy Reference Manual – 5.01.18, 10/6/2009

Senior Medical Director - 2/2010

Specialty Matched Consultant Advisory Panel – 11/2010

BCBSA Medical Policy Reference Manual – 5.01.18, 11/10/2012

## **Policy Implementation/Update Information**

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3/2/10 New Evidence Based Guideline implemented. “Bevacizumab for patients with advanced adenocarcinoma of the pancreas is not recommended.” Senior Medical Director review 2/1/2010. (btw)

6/22/10 Policy Guideline Number(s) removed (amw)

12/21/10 Specialty Matched Consultant Advisory Panel review 11/29/2010. No changes to the intent of the guideline. (btw)

2/7/12 Added 6<sup>th</sup> bullet to Description section to indicate; “November 2011: FDA approval withdrawn for breast cancer.” Specialty Matched Consultant Advisory Panel review 11/30/2011. Reference added. (btw)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.