

Bevacizumab (Avastin™) for Treatment of Solid Tumors

Key Points

- Bevacizumab (Avastin™) was the first U.S. Food and Drug Administration-approved biological therapy designed to inhibit the formation of new blood vessels to tumors.
- Bevacizumab is one of many angiogenesis inhibitors that have been developed based on a hypothesis of angiogenesis action published in 1971 by Judah Folkman, M.D., Harvard Medical School, Boston, Mass.
- Bevacizumab has been investigated for efficacy in treatment in a number of cancers. The National Cancer Institute, in collaboration with a network of investigators led by the Eastern Cooperative Oncology Group, recently sponsored three key randomized clinical trials of bevacizumab, the first of which was for metastatic colorectal cancer.

Bevacizumab (Avastin™) was the first U.S. Food and Drug Administration (FDA)- approved biological therapy designed to inhibit the formation of new blood vessels to tumors. It is manufactured by Genentech, South San Francisco, Calif. The National Cancer Institute (NCI), part of the National Institutes of Health, has been involved in the clinical development of bevacizumab in several tumor types under a cooperative research and development agreement (CRADA) with Genentech.

Tumor cells require a constant supply of blood to receive the oxygen and nutrients they need to survive. As a tumor grows, it signals the need for more blood by secreting growth factors that trigger the formation of new blood vessels, a process called angiogenesis. Of the



many growth factors implicated in the formation of new blood vessels, vascular endothelial growth factor (VEGF) has been identified as one of the most potent proteins supporting tumor growth. In addition to affecting tumor growth, VEGF promotes formation of new capillaries surrounding the tumor, providing increased nutrients for growth and a convenient route for tumor cells to spread throughout the body.

Bevacizumab was developed to inhibit VEGF. It was designed to cause the destruction of the blood vessel networks that feed cancer cells, as the lack of a constant source of blood may slow tumor growth. Bevacizumab is an antibody—a type of targeting device produced by the immune system that can locate and bind to a specific protein. In the case of bevacizumab, it is a monoclonal (cells derived from a single common ancestor) antibody that binds to and inhibits VEGF.

History of Development

Bevacizumab is one of many angiogenesis inhibitors that have been developed based on a hypothesis of angiogenesis action published in 1971 by Judah Folkman, M.D., Harvard Medical School, Boston, Mass. By 1983, scientists had demonstrated that tumors secrete VEGF and by 1989, VEGF had been cloned for investigational purposes. The first clinical trials to examine the efficacy of anti-angiogenic agents for cancer patients began in the 1990s.

In February 2004, the FDA approved the use of bevacizumab based on a Phase III clinical trial sponsored by Genentech that showed benefit in first-line treatment of metastatic colorectal cancer when the drug was added to standard chemotherapy (Hurwitz H, Fehrenbach L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *New England Journal of Medicine* 2004; 350:2335-42). The results of this trial

demonstrated that, when compared to the standard chemotherapy being prescribed for untreated metastatic colon cancer at the time, bevacizumab in combination with standard chemotherapy:

- Increased median overall survival by 30 percent (20.3 months vs. 15.6 months).
- Increased median progression-free survival, or the time that a patient's cancer was not growing, by 71 percent (10.6 months vs. 6.2 months).
- Increased response rate (45 percent vs. 35 percent) and duration of response to bevacizumab (10.4 months vs. 7.1 months).

Recent Trial Results

Bevacizumab has been investigated for efficacy in treatment in a number of cancers. The NCI, in collaboration with a network of investigators led by the Eastern Cooperative Oncology Group (ECOG), recently sponsored three key randomized clinical trials of bevacizumab, the first of which was a trial of metastatic colorectal cancer:

Preliminary results from a large, randomized clinical trial for patients with advanced colorectal cancer who had previously received treatment were released in November 2004 (<http://www.nci.nih.gov/newscenter/pressreleases/BevacizumabOxaliplatin>). This trial is different from the Genentech trial in February 2004 in several respects, particularly because it offered a different choice of chemotherapy. Researchers in this trial (known as E3200) found that the patients who received bevacizumab in combination with FOLFOX4 (a regimen of oxaliplatin, 5-fluorouracil and leucovorin) had a median overall survival of 12.5 months compared to patients treated with FOLFOX4 alone, who had a median overall survival of 10.7 months. This difference is statistically significant and corresponds to a 17 percent improvement in median overall survival. There was a 26 percent reduction in the risk of death for patients in this study who received bevacizumab plus FOLFOX4 compared to those who received FOLFOX4 alone.

A breast cancer clinical trial, which released initial results in April 2005 (<http://www.nci.nih.gov/newscenter/pressreleases/AvastinBreast>), demonstrated that bevacizumab, in combination with standard chemotherapy, delayed the progression of disease by an average of approximately 5 months. From December 2001 to May 2004, this randomized study enrolled 722 women who had recurrent or metastatic breast cancer, or cancer that had spread to other organs, that had not been previously treated with chemotherapy. The women were treated with bevacizumab in combination with paclitaxel, or paclitaxel alone. Those women receiving combination therapy showed a delay in development of their breast cancer that was statistically significant. This was the first study to show the benefit of anti-angiogenic therapy for breast cancer and was a major advance in the treatment of patients with metastatic disease.

A lung cancer study, which released its preliminary results in March 2005 (<http://www.nci.nih.gov/newscenter/pressreleases/AvastinLung>), showed that those patients receiving a combination therapy of bevacizumab and chemotherapy were living longer than patients receiving only standard chemotherapy. The interim results of this study were made public because the primary endpoint of improving overall survival had been achieved. Patients receiving a regimen of chemotherapy (paclitaxel and carboplatin) and bevacizumab had a median overall survival of 12.5 months compared to the control group, receiving only paclitaxel and carboplatin, who survived an average of 10.2 months. The improved survival of 2.3 months was statistically significant. The results of this randomized study were noteworthy because they revealed the potential for improved survival rates with the addition of an anti-angiogenic therapy. It should be noted, however, that these results apply only to patients in the study (those with advanced non-squamous, non-small cell lung cancer who had not previously received systemic

chemotherapy) and that the most significant adverse event observed in this study was life-threatening or fatal bleeding, primarily from the lungs.

NCI, in collaboration with Genentech, is currently evaluating the potential use of bevacizumab in a number of different cancers. NCI is sponsoring more than 30 trials using this drug, including Phase III clinical trials in advanced or metastatic renal cell carcinoma, pancreatic cancer, and ovarian cancer. NCI also is conducting a Phase III trial evaluating the use of the drug for colorectal cancer patients who have undergone potentially curative surgery. For current information about ongoing clinical trials using bevacizumab, please go to <http://www.cancer.gov/clinicaltrials/search>.

It is important to note that there are general toxicities associated with bevacizumab therapy, including bleeding, arterial clots (which could lead to stroke and heart attack), bowel perforation, wound healing difficulties, and hypertension.

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Related NCI materials and Web pages:

- National Cancer Institute Fact Sheet 7.2, *Biological Therapies for Cancer: Questions and Answers* (<http://www.cancer.gov/cancertopics/factsheet/Therapy/biological>)
- National Cancer Institute Fact Sheet 7.42, *Angiogenesis Inhibitors Therapy* (<http://www.cancer.gov/cancertopics/factsheet/Therapy/angiogenesis-inhibitors>)
- *Bevacizumab (Avastin™) for Metastatic Colorectal Cancer* (<http://www.cancer.gov/newscenter/pressreleases/bevacizumab>)
- *Bevacizumab (Avastin™) for Treatment of Solid Tumors: Questions and Answers* (<http://www.cancer.gov/cancertopics/factsheet/AvastinFactSheet>)

How can we help?

We offer comprehensive research-based information for patients and their families, health professionals, cancer researchers, advocates, and the public.

- **Call** NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237)
- **Visit** us at <http://www.cancer.gov> or <http://www.cancer.gov/espanol>
- **Chat** using LiveHelp, NCI's instant messaging service, at <http://www.cancer.gov/livehelp>
- **E-mail** us at cancergovstaff@mail.nih.gov
- **Order** publications at <http://www.cancer.gov/publications> or by calling 1-800-4-CANCER
- **Get help** with quitting smoking at 1-877-44U-QUIT (1-877-448-7848)

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