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# Adding Avastin May Slow Disease Progression

BY LAURA BEIL

Angiogenesis inhibitors—drugs designed to choke off a tumor’s blood supply—have been met with both praise and skepticism. The one angiogenesis inhibitor approved for breast cancer, called Avastin (bevacizumab), has seen its share of controversy: In February 2008, the drug received government approval for treatment of metastatic breast cancer, despite the fact that an advisory panel for the Food and Drug Administration had voted to deny manufacturer Genentech’s application, saying that the drug did not have enough evidence to justify its use. (It is also approved to treat advanced lung and colorectal cancers, metastatic renal cell carcinoma, and glioblastoma.) In addition, the drug is highly expensive, with a price tag that can run about \$8,000 a month.

Hoping to more clearly define both the potential and the limits of the drug, researchers have continued testing Avastin in breast cancer, trying to determine whether the drug can help women live longer—its approval was based on evidence that it could delay tumor progression—or whether it could produce better results if taken differently during the course of disease. Three studies have found that adding Avastin to regular chemotherapy can slow down the growth of metastatic breast cancer, although so far research has not found that it helps women survive longer.

True to its history, new data from two pivotal studies described in San Antonio are both encouraging and disappointing. One study, the RIBBON-2 trial, involved 684 women with HER2-negative metastatic breast cancer who had already received one course of chemotherapy. The women received another session of chemotherapy (chosen by the investigators) either in combination with Avastin or in combination with a placebo. On Friday, researchers reported the results: adding Avastin to chemotherapy as a second-line treatment increased progression-free survival—the length of time that the disease did not worsen—by around two months (from 5.1 months to 7.2 months). However, this was an average, meaning some women taking Avastin experienced an even longer time to disease progression, said Adam Brufsky, MD, PhD, associate director of clinical investigation at the University of Pittsburgh Cancer Institute.

Another study updated in San Antonio, called the AVADO trial, tested whether adding Avastin to the chemotherapy drug Taxotere (docetaxel) worked better than Taxotere alone in 736 women with either recurrent or metastatic breast cancer. During the American Society of Clinical Oncology meeting in 2008, researchers released preliminary results: combining Avastin with Taxotere slightly

improved the length of time to progression, depending on the dose of drug administered. Among two doses studied, patients taking a higher amount had a better response.

On Friday, AVADO's European research team presented the final analysis. While the drug slowed the progression of the disease, it did not improve overall survival more than two years later. Researcher David Miles, MD, of Mount Vernon Hospital in the United Kingdom, nonetheless said the drug could still be beneficial for patients. Whether it is worth using a costly drug that might buy only a few weeks, he said, presents a dilemma for women and their doctors. "That is absolutely the crucial question," he said.

The results described Friday still leave many unanswered questions, Brufsky said. The RIBBON-2 study has not found an improvement in overall survival with the addition of Avastin, but 43 percent of the women in the study are still alive. He plans to present an updated analysis next year. Also, better results might be obtained if the drug is administered earlier in treatment, not waiting until conventional chemotherapy has failed. Also unclear is which chemotherapy works best when combined with Avastin. "Differences may come out with further analysis," he said.

In related research, investigators tried to address the question of whether Avastin is safe when used to shrink tumors before surgery (either mastectomy or lumpectomy). Data presented Friday by researchers from Harvard Medical School compared 51 women in one study who received chemotherapy plus Avastin six weeks before surgery to 28 women in another study who received only chemotherapy before surgery; researchers found no overall increased risk of surgical complications in the women taking Avastin. The study did raise concerns, however, about the impact of Avastin on wound healing when used with tissue expanders, devices that are used to grow new skin as part of breast reconstruction. Researchers cautioned that larger studies are needed before the full safety profile of Avastin's use before surgery is known.

*This article is a part of CURE's 2009 San Antonio Breast Cancer Symposium coverage. To read more articles from SABCS 2009, visit [sabcs2009.curetoday.com](http://sabcs2009.curetoday.com).*