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Avastin® Plus Paclitaxel For Metastatic HER2-Negative Breast Cancer

Avastin® (bevacizumab) is the first medicine approved by the U.S. Food and Drug Administration (FDA) designed to inhibit angiogenesis, a process that connects tumors to the blood supply.¹

In February 2008, Avastin plus paclitaxel (chemotherapy) was granted accelerated approval by the FDA for treatment of women who had not received previous chemotherapy for metastatic HER2-negative breast cancer.² Three out of four women (75 percent) who have breast cancer have a form known as HER2-negative breast cancer.

The effectiveness of Avastin plus paclitaxel in metastatic HER2-negative breast cancer is based on an improvement in progression-free survival (PFS), the amount of time that a person lives without the disease worsening. Avastin is not approved for women with breast cancer that has progressed following anthracycline and taxane chemotherapy administered for metastatic disease. Currently, no data are available that demonstrate an improvement in disease-related symptoms or increased survival with Avastin in breast cancer.²

How Avastin Is Thought To Work

- Avastin is a biologic antibody designed to specifically bind to a protein called vascular endothelial growth factor (VEGF) that plays an important role throughout the lifecycle of the tumor to develop and maintain blood vessels, a process known as angiogenesis¹
- The tumor blood supply is thought to be critical to a tumor's ability to grow and spread in the body (metastasize)¹

Evaluating Avastin Plus Paclitaxel In Metastatic Breast Cancer

- In the pivotal Phase III study (E2100), patients who received Avastin plus paclitaxel chemotherapy lived longer without the disease worsening (PFS), compared to paclitaxel alone³
 - Patients receiving Avastin lived nearly twice as long without their disease worsening (11.3 months [95% CI=10.5, 13.3] vs. 5.8 months [95% CI=5.4, 8.2], p-value<0.0001)²
 - Patients who received Avastin plus paclitaxel showed no significant improvement in overall survival, compared to paclitaxel alone (26.5 months [95% CI= 23.7, 29.2] vs. 24.8 months [95% CI= 21.4, 27.4] p-value=0.14)²
 - Tumors shrank in nearly 50 percent of patients receiving Avastin³

- Partial response (PR) was 48.9% for Avastin plus paclitaxel compared to 22.2% for paclitaxel alone²
 - PR included only patients with measurable disease²
 - The difference in PR is 26.7% (95% CI: 18.4%, 35.0%)²
 - No complete responses were observed in either treatment arm²
- No data are available demonstrating improvement in disease-related symptoms or survival with Avastin in metastatic breast cancer²
- Grade 1-2 adverse events were not collected
- Grade 3-5 (non-blood-related) and Grade 4-5 (blood-related) adverse events were increased by 20.5 percent in patients who received Avastin plus paclitaxel, compared to paclitaxel alone²
- The most common Grade 3-5 (non-blood-related) and Grade 4-5 (blood-related) adverse events occurred at a rate of at least 5 percent more often in patients who received Avastin plus paclitaxel, compared to paclitaxel alone:²
 - Sensory neuropathy (numbness and tingling in the fingers and toes) (24.2% vs. 17.5%)³
 - Hypertension (high blood pressure) (16.0% vs. 1.4%)²
 - Fatigue (tiredness) (10.7% vs. 5.2%)²
- Fatal adverse reactions occurred in 6 of 363 (1.7%) patients who received Avastin plus paclitaxel²

Avastin Safety

Avastin safety information: People receiving Avastin may experience side effects. In clinical trials, some people treated with Avastin experienced serious and sometimes fatal side effects, including:

Gastrointestinal (GI) perforation: Treatment with Avastin can result in the development of a potentially serious side effect called GI perforation, which is the development of a hole in the stomach, small intestine, or large intestine. In clinical trials, this event occurred in more people who received Avastin than in the comparison group (0.3% to 2.4%). In some cases, GI perforation resulted in fatality. Avastin therapy should be permanently stopped if GI perforation occurs.²

Surgery and wound healing problems: Treatment with Avastin can lead to slow or incomplete wound healing (for example, when a surgical incision has trouble healing or staying closed). In some cases, this event resulted in fatality. Surgery and wound healing problems occurred more often in people who received Avastin than in the comparison group. Avastin therapy should not be started for at least 28 days after surgery and until the surgical wound is fully healed. The length of time between stopping Avastin and having voluntary surgery without the risk of having surgery and wound healing problems has not been determined. Treatment with Avastin should be stopped at least 28 days before voluntary surgery and in people with surgery and wound healing problems that require medical treatment.²

Severe bleeding: Treatment with Avastin can result in serious bleeding, including coughing up blood, bleeding in the stomach, vomiting of blood, bleeding in the brain, nosebleeds, and vaginal bleeding. These events occurred up to 5 times more often in people who received Avastin. Across cancer types, 1.2% to 4.6% of people who received Avastin experienced severe to fatal bleeding. People who have recently coughed up blood (greater than or equal to a half teaspoon of red blood) or have serious bleeding should not receive Avastin. Treatment with Avastin should be permanently stopped if serious bleeding occurs (ie, requiring medical attention).²

In clinical trials for different cancer types, there were additional serious, and sometimes fatal, side effects that occurred in more people who received Avastin than in those in the comparison group. The formation of an abnormal passage from parts of the body to another part (non-GI fistula formation) was seen in 0.3% or less of people. Severe to life-threatening stroke or heart problems were seen in 2.4% of people. Too much protein in the urine, which led to kidney problems, was seen in less than 1% of people. Additional serious side effects that occurred in more people who received Avastin than in those in the comparison group included severe to life-threatening high blood pressure, which was seen in 5% to 18% of people, and nervous system and vision disturbances (reversible posterior leukoencephalopathy syndrome), which was seen in less than 0.1% of people. Infusion reactions with the first dose of Avastin were uncommon and occurred in less than 3% of people, and severe reactions occurred in 0.2% of people.²

Common side effects that occurred in more than 10% of people who received Avastin for different cancer types, and at least twice the rate of the comparison group, were nosebleeds, headache, high blood pressure, inflammation of the nose, too much protein in the urine, taste change, dry skin, rectal bleeding, tear production disorder, back pain, and inflammation of the skin (exfoliative dermatitis). Across all trials, treatment with Avastin was permanently stopped in 8.4% to 21% of people because of side effects.²

In the metastatic breast cancer trial, there was a 20.5% increase in severe to life-threatening and fatal side effects for Avastin plus paclitaxel (chemotherapy) vs paclitaxel (chemotherapy) alone. Because mild side effects of Avastin plus paclitaxel (chemotherapy) were not studied, they are not known. The most common severe to life-threatening and fatal side effects that increased by 5% or more in people who received Avastin plus paclitaxel (chemotherapy) vs paclitaxel (chemotherapy) alone included numbness and tingling in fingers and toes (24% vs 18%), high blood pressure (16% vs 1%), and tiredness (11% vs 5%). Congestive heart failure was seen in more people who received Avastin plus paclitaxel (chemotherapy) vs paclitaxel (chemotherapy) alone (2.2% vs 0.3%). Among people receiving anthracyclines, congestive heart failure was more common in people who received Avastin plus paclitaxel (chemotherapy) vs paclitaxel (chemotherapy) alone (3.8% vs 0.6%). Deaths due to side effects were seen in 1.7% (6 of 363) of people who received Avastin plus paclitaxel (chemotherapy). Causes of death were the development of a hole in the stomach, small intestine, or large intestine (2), heart attack (2), and diarrhea/abdominal pain/weakness/low blood pressure (2).²

Avastin may impair fertility. If you are pregnant or thinking of becoming pregnant, talk with your doctor about the potential risk of loss of the pregnancy or the potential risk of Avastin to the fetus during and following Avastin therapy, and the need to continue an effective birth control method for at least 6 months following the last dose of Avastin.²

Please visit www.gene.com for the Avastin full prescribing information, including **Boxed WARNINGS** and additional important safety information.

References

1. Ranieri G, Patruno R, Ruggieri E, Montemurro S, et al. Vascular Endothelial Growth Factor (VEGF) As a Target of Bevacizumab in Cancer: From the Biology to the Clinic. *Curr Med Chem.* 2006;13:1845-1857.
2. Genentech. "Avastin. Full Prescribing Information."
3. Miller K, Wang M, Gralow J, et al. Paclitaxel Plus Bevacizumab Versus Paclitaxel Alone For Metastatic Breast Cancer. *N Engl J Med* 2007;357:2666-2676.

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