AVASTIN® (bevacizumab)

Avastin is a tumor-starving (anti-angiogenic) medicine. Avastin is designed to block a protein called vascular endothelial growth factor, or VEGF. Normal cells make VEGF, but some cancer cells make too much VEGF. Blocking VEGF may prevent the growth of new blood vessels.¹

Unlike chemotherapy that attacks fast-growing cells, like cancer cells, Avastin is designed to prevent the growth of new blood vessels. This includes normal blood vessels and blood vessels that feed tumors.¹

**POSSIBLE SERIOUS SIDE EFFECTS**

Everyone reacts differently to Avastin therapy. So it’s important to know what the side effects are. Although some people may have a life-threatening side effect, most do not. Your doctor will stop treatment if any serious side effects occur. Be sure to contact your health care team if you have symptoms related to these side effects.

Most serious side effects (not common, but sometimes fatal):

- **GI perforation.** A hole that develops in your stomach or intestine. Symptoms include pain in the abdomen, nausea, vomiting, constipation, or fever
- **Wounds that don’t heal.** A cut made during surgery can be slow to heal or may not fully heal. Avastin should not be used for at least 28 days before or after surgery and until surgical wounds are fully healed
- **Serious bleeding.** This includes vomiting or coughing up blood; bleeding in the stomach, brain, or spinal cord; nosebleeds; and vaginal bleeding. If you recently coughed up blood or had serious bleeding, be sure to tell your doctor

Please see the following pages and Avastin full Prescribing Information including Most Serious Side Effects for Important Safety Information.
Other Possible Serious Side Effects

- Abnormal passage in the body. This type of passage — known as a fistula — is an irregular connection from one part of the body to another and can sometimes be fatal
- Severe high blood pressure. Blood pressure that severely spikes or shows signs of affecting the brain. Blood pressure should be monitored every 2 to 3 weeks while on Avastin and after stopping treatment
- Kidney problems. These may be caused by too much protein in the urine and can sometimes be fatal
- Infusion reactions. These were uncommon with the first dose (less than 3% of patients). Severe reactions occurred in 0.2% of patients. Infusion reactions include high blood pressure or severe high blood pressure that may lead to stroke, trouble breathing, decreased oxygen in red blood cells, a serious allergic reaction, chest pain, headache, tremors, and excessive sweating. Your doctor or nurse will monitor you for signs of infusion reactions
- Severe stroke or heart problems. These may include blood clots, mini-stroke, heart attack, and chest pain. These can sometimes be fatal
- Nervous system and vision problems. Signs include headache, seizure, high blood pressure, sluggishness, confusion, and blindness

Please see the following pages and Avastin full Prescribing Information including Most Serious Side Effects for Important Safety Information.

Avastin Efficacy Profiles

<table>
<thead>
<tr>
<th>mCRC&lt;sup&gt;2,3&lt;/sup&gt;</th>
<th>2004</th>
<th>mCRC&lt;sup&gt;2,3&lt;/sup&gt;</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIRST-LINE TREATMENT</strong></td>
<td></td>
<td><strong>SECOND-LINE TREATMENT AFTER FIRST-LINE CHEMOTHERAPY</strong></td>
<td></td>
</tr>
<tr>
<td>Avastin reduced the risk of death by 34 percent</td>
<td></td>
<td>Avastin reduced the risk of death by 25 percent</td>
<td></td>
</tr>
<tr>
<td>(HR=0.66, 95% CI: 0.54-0.81; p&lt;0.001).</td>
<td></td>
<td>(HR=0.75, 95% CI: 0.63-0.89; p&lt;0.001).</td>
<td></td>
</tr>
<tr>
<td><strong>AVF2107 Study</strong></td>
<td><em><em>Avastin</em> + IFL</em>*</td>
<td><strong>IFL</strong></td>
<td></td>
</tr>
<tr>
<td>Median Overall Survival (mOS) (primary endpoint)</td>
<td>N=402</td>
<td>N=411</td>
<td></td>
</tr>
<tr>
<td>20.3 months</td>
<td>15.6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Progression-Free Survival (mPFS) (secondary endpoint)</td>
<td>10.6 months</td>
<td>6.2 months</td>
<td></td>
</tr>
<tr>
<td>HR=0.54, 95% CI: 0.45-0.66; p&lt;0.001.</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*5 mg/kg IV every 2 weeks

**AVF2107 STUDY**
The approval of Avastin for first-line treatment of mCRC was based on the results of the AVF2107 study, a Phase III, randomized, double-blind study that evaluated Avastin plus IV 5-FU-based chemotherapy (IFL) compared to IFL alone in 813 people with newly diagnosed mCRC.

<table>
<thead>
<tr>
<th>NSCLC&lt;sup&gt;2&lt;/sup&gt;</th>
<th>2006</th>
<th><strong>FIRST-LINE TREATMENT</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Avastin reduced the risk of death by 20 percent</td>
<td></td>
<td>Avastin reduced the risk of death by 40 percent</td>
<td></td>
</tr>
<tr>
<td>(HR=0.80, 95% CI: 0.69-0.94; p&lt;0.013).</td>
<td></td>
<td>(HR=0.60, 95% CI: 0.49-0.72; p&lt;0.0001).</td>
<td></td>
</tr>
<tr>
<td><strong>E4599 Study</strong></td>
<td><em><em>Avastin</em> + Chemotherapy</em>*</td>
<td><strong>Chemotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>mOS (primary endpoint)</td>
<td>N=434</td>
<td>N=444</td>
<td></td>
</tr>
<tr>
<td>12.3 months</td>
<td>10.3 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*15 mg/kg IV every 3 weeks

**E4599 STUDY**
The approval of Avastin for first-line treatment of non-squamous NSCLC was based on the results of the pivotal randomized, open label, active-controlled Phase III E4599 study. This study investigated Avastin plus chemotherapy (paclitaxel and carboplatin) compared to chemotherapy alone in 878 people with newly diagnosed, unresectable, locally advanced, recurrent, or metastatic, non-squamous NSCLC.

<table>
<thead>
<tr>
<th>mRCC&lt;sup&gt;2&lt;/sup&gt;</th>
<th>2009</th>
<th><strong>FIRST-LINE TREATMENT</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Avastin reduced the risk of disease worsening by 40 percent</td>
<td></td>
<td>Avastin reduced the risk of disease worsening by 50 percent</td>
<td></td>
</tr>
<tr>
<td>(HR=0.60, 95% CI: 0.49-0.72; p&lt;0.0001).</td>
<td></td>
<td>(HR=0.60, 95% CI: 0.49-0.72; p&lt;0.0001).</td>
<td></td>
</tr>
<tr>
<td><strong>AVOREN Study</strong></td>
<td><em><em>Avastin</em>+Interferon alpha 2a</em>*</td>
<td><strong>Interferon alpha 2a</strong></td>
<td></td>
</tr>
<tr>
<td>mPFS (primary endpoint)</td>
<td>N=327</td>
<td>N=322</td>
<td></td>
</tr>
<tr>
<td>10.2 months</td>
<td>5.4 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Response Rate (ORR) (secondary endpoint)</td>
<td></td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12%</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.0001

*10 mg/kg IV every 2 weeks

**AVOREN STUDY**
The approval of Avastin for first-line treatment of mRCC was based on the results of the pivotal randomized, double-blind Phase III AVOREN study. This study investigated Avastin plus interferon alfa 2a versus interferon alfa 2a alone in 649 people with newly diagnosed mRCC. The study did not demonstrate a significant difference in overall survival.
Avastin Efficacy Profiles

**ML18147 STUDY**

The approval of Avastin for second-line treatment of mCRC following progression with an Avastin-based regimen was based on the results of the ML18147 study, a Phase III, randomized, prospective open-label study that evaluated the use of Avastin plus a fluoropyrimidine-based chemotherapy, compared to chemotherapy alone, as a second-line medicine after the disease worsened in 820 patients. In the first line, all patients received Avastin plus a different fluoropyrimidine-based chemotherapy (irinotecan or oxaliplatin-based). The study did not demonstrate a significant difference in overall response rates.

**GOG-0240 STUDY**

The approval of Avastin plus chemotherapy for treatment of patients with persistent, recurrent, or metastatic cervical cancer was based on the results of the GOG-0240 study. This study investigated Avastin plus chemotherapy (paclitaxel and cisplatin or paclitaxel and topotecan) compared to chemotherapy alone in 452 women with persistent, recurrent, or metastatic cervical cancer (Stage IVb).

**Side Effects Seen Most Often**

*In clinical studies across different types of cancers, some patients experienced the following side effects:*

- HIGH BLOOD PRESSURE
- TOO MUCH PROTEIN IN THE URINE
- NOSEBLEEDS
- RECTAL BLEEDING
- BACK PAIN
- HEADACHE
- TASTE CHANGE
- DRY SKIN
- INFLAMMATION OF THE SKIN
- INFLAMMATION OF THE NOSE
- WATERY EYES

For full prescribing information including Boxed WARNINGS and other important safety information for Avastin, please visit www.avastin.com.
Avastin Efficacy Profiles

RECURRENT, PLATINUM-SENSITIVE TREATMENT (OCEANS)

<table>
<thead>
<tr>
<th>Study</th>
<th>Avastin + Chemotherapy</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>242</td>
<td>242</td>
</tr>
<tr>
<td>mPFS (primary endpoint)</td>
<td>12.4 months</td>
<td>8.4 months</td>
</tr>
<tr>
<td>ORR (secondary endpoint)</td>
<td>78%</td>
<td>57%</td>
</tr>
</tbody>
</table>

Avastin reduced the risk of disease worsening by 54 percent (HR=0.46, 95% CI: 0.37-0.58; p<0.0001).

RECURRENT, PLATINUM-SENSITIVE TREATMENT (GOG 213)

<table>
<thead>
<tr>
<th>Study</th>
<th>Avastin + Chemotherapy</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>337</td>
<td>336</td>
</tr>
<tr>
<td>OS (primary endpoint)</td>
<td>42.6 months</td>
<td>37.3 months</td>
</tr>
<tr>
<td>mPFS (secondary endpoint)</td>
<td>13.8 months</td>
<td>10.4 months</td>
</tr>
<tr>
<td>ORR (secondary endpoint)</td>
<td>78%</td>
<td>56%</td>
</tr>
</tbody>
</table>

Avastin reduced the risk of death by 16 to 18 percent (eCRF HR=0.82, 95% CI: 0.68-0.996; IVRS HR=0.84, 95% CI: 0.69-1.01).

The approval of Avastin for the treatment of platinum-sensitive recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer either in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine chemotherapy, followed by Avastin alone, was based on the results of the OCEANS and GOG-0213 studies.

OCEANS STUDIES

The OCEANS study investigated Avastin plus chemotherapy (carboplatin and gemcitabine) compared to placebo plus chemotherapy in 484 women with disease that had recurred after six months from the most recent platinum-based therapy. Overall survival was not significantly improved with the addition of Avastin to chemotherapy.

GOG-0213 STUDY

The GOG-0213 study investigated Avastin plus chemotherapy (carboplatin and paclitaxel) followed by continued use of Avastin alone compared to chemotherapy alone in 673 women with disease that had recurred after six months from the most recent platinum-based therapy.

Avastin Is Not For Everyone

Talk to your doctor if you are:

UNDERGOING SURGERY
Avastin should not be used for 28 days before or after surgery and until surgical wounds are fully healed

PREGNANT, THINK YOU ARE PREGNANT, PLANNING TO BECOME PREGNANT OR BREASTFEEDING
Data have shown that Avastin may harm your unborn baby. Use birth control while on Avastin. If you stop Avastin, you should keep using birth control for 6 months before trying to become pregnant. Taking Avastin could cause a woman’s ovaries to stop working and may impair her ability to have children. Breastfeeding while on Avastin may harm your baby and is therefore not recommended.

If you have any questions about your condition or treatment, talk to your doctor.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

Visit Genentech Access Solutions (www.GenentechAccessSolutions.com) for coverage and reimbursement support, patient assistance and information resources.

For full prescribing information including Boxed WARNINGS and other important safety information for Avastin, please visit www.avastin.com.
Study Specific Safety

STUDY ADVERSE EVENTS IN MCRC

In the first-line mCRC trial, the most common severe to life-threatening side effects that increased by 2% or more in people who received Avastin plus IFL (chemotherapy) vs IFL (chemotherapy) alone were weakness (10% vs 7%), abdominal pain (8% vs 5%), pain (8% vs 5%), high blood pressure (12% vs 2%), blood clots in the veins of the body (9% vs 5%), blood clots inside the abdomen (3% vs 1%), a brief loss of consciousness (3% vs 1%), diarrhea (34% vs 25%), constipation (4% vs 2%), reduced white blood cell counts (37% vs 31%), and reduced white blood cell counts that may increase the chance of infection (21% vs 14%).

In the second-line mCRC trial, the most common severe to life-threatening and fatal side effects that increased by 2% or more in people who received Avastin plus FOLFOX4 (chemotherapy) vs FOLFOX4 (chemotherapy) alone were diarrhea (18% vs 13%), nausea (12% vs 5%), vomiting (11% vs 4%), dehydration (10% vs 5%), blockage of the bowel (4% vs 1%), numbness and tingling in fingers and toes (17% vs 9%), nervous system disturbances (5% vs 3%), tiredness (19% vs 13%), abdominal pain (8% vs 5%), headache (3% vs 0%), high blood pressure (9% vs 2%), and severe bleeding (5% vs 1%).

STUDY ADVERSE EVENTS IN NSCLC

In an NSCLC clinical trial, the most common life-threatening to fatal side effects that increased by 2% or more in patients receiving Avastin plus paclitaxel and carboplatin (chemotherapies) compared with those patients receiving paclitaxel and carboplatin (chemotherapies) alone were lower than normal white blood cell count (27% vs 17%), tiredness (16% vs 13%), high blood pressure (8% vs 0.7%), infection without lower than normal white blood cell count (7% vs 3%), blood clots in the veins (5% vs 3%), fever with lower than normal white blood cell count (5% vs 2%), lung inflammation (5% vs 3%), infection with lower than normal white blood cell count (4% vs 2%), abnormally low sodium that could lead to seizure or coma (4% vs 1%), headache (3% vs 1%), and too much protein in the urine (3% vs 0%).

STUDY ADVERSE EVENTS IN MRCC

In one trial, severe to fatal side effects that increased by 2% or more in people with metastatic kidney cancer taking Avastin plus interferon alfa compared with interferon alfa alone were fatigue (13% vs 8%), weakness (10% vs 7%), too much protein in the urine (7% vs 0%), high blood pressure (6% vs 1%), and bleeding (3% vs 0.3%; this included nosebleeds, coughing up blood, bleeding of the gums, bleeding in the small and large intestines, and bleeding in the brain, stomach, respiratory tract, and skull).

STUDY ADVERSE EVENTS IN CERVICAL CANCER

In the CC trial, the most common severe to life-threatening side effects that increased by 2% or more in people who received Avastin plus chemotherapy compared to those receiving chemotherapy alone were abdominal pain (11.9% vs 9.9%), diarrhea (5.5% vs 2.7%), abnormal opening at or near the anus (3.7% vs 0%), pain at the anus or the rectum (2.8% vs 0%), urinary tract infections (8.3% vs 6.3%), skin infection (3.2% vs 0.5%), tiredness (14.2% vs 9.9%), high blood pressure (11.5% vs 0.5%), blood clot formation (8.3% vs 2.7%), low potassium (7.3% vs 4.5%), abnormally low sodium that could lead to seizure or coma (3.7% vs 1.4%), dehydration (4.1% vs 0.5%), lower than normal white blood cell count (neutropenia 7.8% vs 4.1%), lymphopenia (6.0% vs 3.2%), back pain (5.5% vs 3.2%), and pain in the lower part of your abdomen (5.5% vs 1.4%).

STUDY ADVERSE EVENTS IN PLATINUM-RESISTANT OVARIAN CANCER

In the prOC trial, the most common severe to life-threatening side effects that increased by 2% or more in people who received Avastin plus chemotherapy compared to those receiving chemotherapy alone were diarrhea (18% vs 13%), nausea (12% vs 5%), vomiting (11% vs 4%), dehydration (10% vs 5%), blockage of the bowel (4% vs 1%), numbness and tingling in fingers and toes (17% vs 9%), nervous system disturbances (5% vs 3%), tiredness (19% vs 13%), abdominal pain (8% vs 5%), headache (3% vs 0%), high blood pressure (9% vs 2%), and severe bleeding (5% vs 1%).

STUDY ADVERSE EVENTS IN PLATINUM-SENSITIVE OVARIAN CANCER

In a psOC study, the most common severe to life-threatening side effects that increased by 2% or more in people who received Avastin plus carboplatin and gemcitabine (chemotherapy) compared with those who received placebo plus chemotherapy were lower than normal platelet count (40.1% vs. 33.9%), nausea (4.5% vs. 1.3%), tiredness (6.5% vs. 4.3%), headache (3.6% vs. 0.9%), too much protein in the urine (9.7% vs. 0.4%), shortness of breath (4.5% vs. 1.7%), nosebleeds (4.9% vs. 0.4%) and high blood pressure (17.0% vs. 0.9%). Severe to life-threatening side effects of lower than normal red blood cell count (16.2% vs 18.9%) and white blood cell count (1.6% vs 4.3%) increased by 2% or more in the chemotherapy group compared to the Avastin plus chemotherapy group.

In a psOC study, the most common severe to life-threatening side effects that increased by 2% or more in people who received Avastin plus carboplatin and paclitaxel (chemotherapy) compared with those who received chemotherapy were high blood pressure (11.1% vs 0.6%), tiredness (7.7% vs 2.7%), fever and lower than normal white blood cell count (6.2% vs 2.7%), too much protein in the urine (8% vs 0%), abdominal pain (5.8% vs 0.9%), lower than normal blood sodium levels (3.7% vs 0.9%), headache (3.1% vs 0.9%) and pain in limbs (3.4% vs 0%).

References