Avastin® (bevacizumab) is the first biologic medicine (not a chemotherapy) approved by the U.S. Food and Drug Administration (FDA) designed to inhibit angiogenesis. Angiogenesis is the growth of new blood vessels. This process helps a tumor grow and spread by connecting the tumor to the body’s blood supply.¹

Avastin is the first and only medicine to be FDA-approved for use in all of the following settings for people with metastatic colorectal cancer (mCRC):

- Previously untreated disease (first-line treatment) or previously treated disease (second-line treatment) in combination with intravenous (IV) 5-FU-based chemotherapy
- Second-line treatment in combination with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy following progression on a first-line Avastin-containing regimen
- Avastin is not approved for adjuvant treatment of colon cancer.

For all of these indications, prospective Phase III clinical trials have shown that Avastin plus chemotherapy helped people with mCRC live longer than chemotherapy alone.²

What is Colorectal Cancer?

CRC is the third most commonly diagnosed cancer in both men and women in the United States and the second leading overall cause of cancer deaths.³

Adenocarcinoma, which accounts for approximately 95 percent of CRC tumors, begins in the lining of the colon or rectum, and is preceded by colorectal polyps (adenomas; abnormal tissue growth).²

90% of CRCs occur in people age 50 and older.

FDA Approval History for Avastin in mCRC

- **2004**
  - Approved in combination with IV 5-FU-based chemotherapy for treatment of people with previously untreated mCRC
  - First biologic medicine to extend overall survival in first-line mCRC

- **2006**
  - Approved in combination with IV 5-FU-based chemotherapy for the treatment of people with previously treated mCRC
  - First biologic medicine to extend overall survival in second-line mCRC

- **2013**
  - Approved in combination with fluoropyrimidine-based chemotherapy for second-line treatment following progression with an Avastin-based regimen in people with mCRC
  - First and only biologic medicine specifically approved for people whose cancer worsened after initial treatment with an Avastin-based regimen

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

- Genentech continues to investigate Avastin in clinical studies.
- Visit www.clinicaltrials.gov to find information about ongoing Avastin clinical trials.
- Visit Genentech Access Solutions (www.GenentechAccessSolutions.com) for coverage and reimbursement support, patient assistance and information resources.
How Avastin May Work (Proposed Mechanism of Action)

1. Tumors and normal cells release a protein called vascular endothelial growth factor (VEGF), which stimulates the growth of new blood vessels — a process called angiogenesis.¹

2. These new vessels feed the growth of the tumor. They also provide a “highway” for tumor cells to spread to other parts of the body.¹

3. Avastin is a biologic medicine (not chemotherapy) designed to specifically bind to the VEGF protein.¹

4. Avastin may block the tumor’s ability to communicate with nearby blood vessels and may prevent the tumor from connecting to the blood supply.¹

5. Studies have shown that targeting the VEGF protein with Avastin may interfere with a tumor’s ability to grow and spread (metastasize).¹

Important Safety Information

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 there are any signs of 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 your 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; and vaginal bleeding. If you recently coughed up blood or had serious bleeding, be sure to tell your doctor.
Avastin Efficacy and Safety Profile in mCRC

**First-Line Treatment**

Avastin reduced the risk of death by 34 percent (HR=0.66, p<0.001), which is equivalent to a 52 percent improvement in overall survival.

<table>
<thead>
<tr>
<th>Study</th>
<th>Avastin + IFL</th>
<th>IFL N=402</th>
<th>N=411</th>
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<tbody>
<tr>
<td>Avastin2107</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median overall survival (mOS)</td>
<td>20.3 months</td>
<td>15.6 months</td>
<td></td>
</tr>
<tr>
<td>median progression-free survival (mPFS)</td>
<td>10.6 months</td>
<td>6.2 months</td>
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</tr>
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</table>

*Study information can be found on the next page

**Second-Line Treatment**

Avastin reduced the risk of death by 25 percent (HR=0.75, p=0.001), which is equivalent to a 33 percent improvement in overall survival.

<table>
<thead>
<tr>
<th>Study</th>
<th>Avastin + FOLFOX</th>
<th>FOLFOX N=286</th>
<th>N=291</th>
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</thead>
<tbody>
<tr>
<td>E3200 Study*</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>mOS</td>
<td>13.0 months</td>
<td>10.8 months</td>
<td></td>
</tr>
<tr>
<td>mPFS</td>
<td>7.3 months</td>
<td>4.7 months</td>
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</table>

**Second-Line Treatment After First-Line Avastin Progression**

Avastin reduced the risk of death by 19 percent (HR=0.81, p<0.0057), which is equivalent to a 23 percent improvement in overall survival.

<table>
<thead>
<tr>
<th>Study</th>
<th>Avastin + Chemotherapy</th>
<th>Chemotherapy N=409</th>
<th>N=411</th>
</tr>
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<tbody>
<tr>
<td>ML18147 Study*</td>
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<td></td>
</tr>
<tr>
<td>mOS</td>
<td>11.2 months</td>
<td>9.8 months</td>
<td></td>
</tr>
<tr>
<td>mPFS</td>
<td>5.7 months</td>
<td>4.1 months</td>
<td></td>
</tr>
</tbody>
</table>

Other Possible Serious Side Effects

- **KIDNEY PROBLEMS**
  These may be caused by too much protein in the urine and can sometimes be fatal.

- **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.

- **INFUSION REACTIONS**
  These were uncommon with the first dose (less than 3% of patients). 0.2% of patients had severe reactions.

- **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.

- **A PASSAGE BETWEEN TWO ORGANS**
  This type of passage—known as a fistula—does not form normally and can sometimes be fatal.

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**

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.
First-Line Treatment: AVF2107 Study

The approval of Avastin for first-line treatment of mCRC was based upon 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.

Second-Line Treatment Following Disease Worsening with First-Line Chemotherapy: E3200 Study

The approval of Avastin for second-line treatment of mCRC following disease worsening with first-line chemotherapy was based upon the results of the E3200 study, a Phase III, randomized, controlled study of Avastin plus FOLFOX chemotherapy compared to FOLFOX alone in 577 people that had progressed following previous treatment with chemotherapy.

Second-Line Treatment Following Progression with First-Line Avastin-Based Regimen: ML18147 Study

The approval of Avastin for second-line treatment of mCRC following progression with an Avastin-based regimen was based upon 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).

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.

- **BREAST-FEEDING OR PREGNANT**
  Avastin may harm a nursing child or a baby in the womb.

- **PLANNING TO BECOME PREGNANT**
  Taking Avastin could cause a woman's ovaries to stop working and may impair her ability to have children.

Avastin mCRC Indications:

- Avastin is indicated for the first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil–based chemotherapy.
- Avastin in combination with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy is indicated for the second-line treatment of patients with metastatic colorectal cancer who have progressed on a first-line Avastin-containing regimen.
- Avastin is not indicated for adjuvant treatment of colon cancer.

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

References