Proposed mechanism of action

Multiple effects of specific VEGF inhibition with Avastin

The mechanism of action of Avastin has been elucidated in preclinical models. Its clinical significance is unknown.

**Indications**

Avastin in combination with paclitaxel, pegylated liposomal doxorubicin or topotecan is indicated for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who received no more than 2 prior chemotherapy regimens.

Avastin, either in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by Avastin as a single agent, is indicated for the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Avastin in combination with paclitaxel and cisplatin or paclitaxel and topotecan is indicated for the treatment of persistent, recurrent, or metastatic carcinoma of the cervix.

Avastin is indicated for the treatment of metastatic renal cell carcinoma in combination with interferon alfa.

Avastin is indicated for the first-line treatment of unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer in combination with carboplatin and paclitaxel.

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.

Limitation of Use: Avastin is not indicated for adjuvant treatment of colon cancer.

Please see accompanying full Prescribing Information, including **Boxed WARNINGS**, and select additional important safety information throughout this piece.
As demonstrated in preclinical models:

**VEGF is a pro-angiogenic factor that is present throughout tumor progression**

![Tumor progression and metastases diagram]

While expressed in normal tissues, VEGF also is present at physiologically relevant levels in tumors. VEGF is also known as a vascular permeability factor and may increase vessel permeability and promote other angiogenic effects.

A VEGF ligand binds to receptors on endothelial cells to help drive angiogenesis.

As secondary pathways emerge over time, VEGF continues to be expressed and remains an important anti-angiogenic target.

In addition, VEGF expression is stable, making targeting of this pathway a viable strategy.

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**Boxed WARNINGS**

**Gastrointestinal (GI) perforation**
- Serious and sometimes fatal GI perforation occurs at a higher incidence (up to 3.2%) in Avastin-treated patients compared to controls. Discontinue Avastin for GI perforation.

**Surgery and wound healing complications**
- The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients.
- Discontinue in patients with wound dehiscence. Discontinue at least 28 days prior to elective surgery.
- The appropriate interval between termination of Avastin and subsequent elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has not been determined.
- Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed.

**Hemorrhage**
- Severe or fatal hemorrhage, hemoptysis, GI bleeding, CNS hemorrhage, epistaxis, and vaginal bleeding are increased in Avastin-treated patients. Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis.

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**As demonstrated in preclinical models:**

**Avastin directly binds VEGF to inhibit angiogenesis**

![Vegetative cell diagram]

Avastin is designed to directly bind to VEGF extracellularly to prevent interaction with VEGF receptors (VEGFRs) on the surface of endothelial cells, and may thereby inhibit VEGF’s angiogenic activity.

The VEGFR family is primarily responsible for pro-angiogenic VEGF signaling.

The mechanism of action of Avastin has been elucidated in preclinical models. Its clinical significance is unknown.

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As demonstrated in preclinical models:
Avastin may exert certain effects to inhibit tumor growth and development.6,17-27

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Proposed early and later effects of Avastin6,17,22,25,27-30

- The impact of the individual effects of VEGF inhibition may vary over time.17,30
- Sustained VEGF inhibition may be an important strategy to maintain tumor regression.25,27-30

**Axitinib clinical trials designed for continuous VEGF suppression**

- Pivotal clinical trials with Avastin have been designed to maintain VEGF inhibition until disease progression or unacceptable toxicity.13
  - This strategy includes instances in which the accompanying combination therapy is modified and/or discontinued.1

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Boxed WARNINGS

- **Gastrointestinal (GI) perforation**
  - Serious and sometimes fatal GI perforation occurs at a higher incidence in Avastin-treated patients compared to controls
  - The incidences of GI perforation ranged from 0.3% to 3.2% across clinical studies
  - Discontinue Avastin in patients with GI perforation

- **Surgery and wound healing complications**
  - The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients
  - Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. The appropriate interval between termination of Avastin and subsequent elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has not been determined
  - Discontinue Avastin at least 28 days prior to elective surgery and in patients with wound healing complications requiring medical intervention

- **Hemorrhage**
  - Severe or fatal hemorrhage, including hemoptysis, GI bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving Avastin. Across indications, the incidence of grade ≥3 hemorrhagic events among patients receiving Avastin ranged from 0.4% to 6.9%
  - Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis (≥1/2 tsp of red blood)
  - Discontinue Avastin in patients with serious hemorrhage (ie, requiring medical intervention)

**Additional serious adverse events**

- Additional serious and sometimes fatal adverse events with increased incidence in the Avastin-treated arm vs control included
  - GI fistulae (up to 2% in metastatic colorectal cancer and ovarian cancer patients)
  - Non-GI fistulae (<1% in trials across various indications; 1.8% in a cervical cancer trial)
  - Arterial thromboembolic events (grade ≥3, 2.6%)
  - Proteinuria (nephrotic syndrome, <1%)

- Additional serious adverse events with increased incidence in the Avastin-treated arm vs control included
  - GI-vaginal fistulae occurred in 8.3% of patients in a cervical cancer trial
  - Venous thromboembolism (grade 3–4, up to 10.6%) in patients with persistent, recurrent, or metastatic cervical cancer treated with Avastin
  - Hypertension (grade 3–4, 5%–18%)
  - Posterior reversible encephalopathy syndrome (PRES) (<0.5%)

- Infusion reactions with the first dose of Avastin were uncommon (<3%), and severe reactions occurred in 0.2% of patients

- Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin

- Avoid use in patients with ovarian cancer who have evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction

**Pregnancy warning**

- Based on the mechanism of action and animal studies, Avastin may cause fetal harm
- Advise female patients that Avastin may cause fetal harm, and to inform their healthcare provider of a known or suspected pregnancy
- Advise females of reproductive potential to use effective contraception during treatment with Avastin and for 6 months after the last dose of Avastin
- Advise nursing women that breastfeeding is not recommended during treatment with Avastin
- Avastin may impair fertility

**Most common adverse events**

- Across indications, the most common adverse reactions observed in Avastin patients at a rate >10% and at least twice the control arm rate were
  - Epistaxis
  - Headache
  - Hypertension
  - Rhinitis
  - Proteinuria
  - Taste alteration
  - Dry skin
  - Rectal hemorrhage
  - Exfoliative dermatitis
  - Back pain
  - Lacrimation disorder

- Across all studies, Avastin was discontinued in 8.4% to 21% of patients because of adverse reactions

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

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