



Fact Sheet

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Genentech BioOncology: Translating Science into Life

Innovation in Oncology

Genentech BioOncology is dedicated to understanding the science behind cancer and translating this knowledge into the development of novel biologic therapies that target the underlying biologic pathways that cause cancer cells to grow and spread. Our mission is to create medicines that will transform cancer into either a curable illness or a chronic condition.

The company is the leading provider of anti-tumor targeted therapeutics in the United States. Genentech is conducting clinical development programs for Avastin[®] (bevacizumab), Herceptin[®] (Trastuzumab), Rituxan[®] (Rituximab) and Tarceva[®] (erlotinib), and markets all four products in the United States, either alone (Avastin and Herceptin) or with Biogen Idec, Inc. (Rituxan) or OSI Pharmaceuticals, Inc. (Tarceva).

Evolution: New Approaches to Cancer Therapy

A turning point in the understanding and treatment of cancer came in the late 1980s and early 1990s as new biologic tools allowed scientists to study cancer at the molecular and genetic levels. The work of many within the life sciences industry, academia and government laboratories identified the connection between specific biologic pathways and the growth and spread of cancer cells in the body.

This research suggested that targeting specific proteins within these pathways might inhibit the growth of cancer. Genentech and its collaborators provided the first validation of this theory through the development of a new class of cancer medicines called therapeutic antibodies.

Rigorous, Groundbreaking Science

The philosophy of Genentech BioOncology in focusing on both the basic biology of cancer and its application to therapeutics in oncology continues to drive our program of groundbreaking scientific discovery and the identification of novel targets and molecules for therapeutic development. Many approved biotechnology products originated from or are based on Genentech science. Some of our important achievements in cancer biology and treatment include:

- Independent discovery and cloning of the human epidermal growth factor receptor-2 gene (*her2/neu*) in 1985 simultaneously with two other research groups¹⁻³

- More than two decades of research into the biology of the HER family of receptors, including the discovery of the correlation of high HER2 levels with an aggressive form of breast cancer and the development of the first humanized monoclonal antibody directed at HER2^{4,5}
- Cloning of vascular endothelial growth factor (VEGF) in 1989, a key mediator of both tumor angiogenesis and the maintenance of existing tumor blood vessels^{6,7}
- Development of a humanized monoclonal antibody directed at VEGF⁸
- Investigating new ways to activate apoptosis, a natural process that eliminates damaged or abnormal cells, such as cancer cells

A History of “Firsts” for Patients

The scientific advances made by Genentech and its collaborators have led to a number of firsts in the treatment of cancer:

First FDA-approved therapeutic antibody for cancer in the U.S.

➔Rituxan plus CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) becomes the first treatment to improve survival for patients with first-line, diffuse large B-cell, CD20-positive, non-Hodgkin’s lymphoma since the introduction of the CHOP chemotherapeutic regimen more than 25 years ago^{9,10}

First FDA-approved therapeutic antibody targeted to a cancer-related molecular marker

➔Herceptin, in combination with chemotherapy, becomes the first targeted therapy to improve survival in advanced HER2-positive breast cancer patients¹¹

First FDA-approved anti-angiogenic cancer therapy

➔Avastin becomes the first FDA-approved anti-angiogenic therapy proven to extend survival, in combination with intravenous (IV) chemotherapy, in patients with first-line metastatic colorectal cancer¹²

➔Avastin becomes the first FDA-approved targeted therapy, in combination with IV chemotherapy, to extend median survival beyond one year in patients with first-line unresectable locally advanced recurrent or metastatic non-squamous non-small cell lung cancer¹²

First EGFR therapy FDA-approved for pancreatic and non-small cell lung cancer

➔Tarceva is the first EGFR targeted treatment to improve survival for patients with advanced pancreatic cancer in combination with gemcitabine, and advanced non-small cell lung cancer¹³

Please see page 4 for full indications and important

safety information, including Boxed Warnings for Rituxan, Herceptin and Avastin.

Genentech's FDA-approved products and late-stage clinical candidates have significant potential to improve cancer care. Importantly, there is great excitement about the prospect of combining some of these therapies to create entirely new treatment paradigms that are highly targeted and have the potential to inhibit multiple mechanisms that support tumor growth without the use of chemotherapy. Combining agents that target different cancer pathways is an active area of investigation for Genentech.

Multiple Approaches to Targeted Cancer Therapy

Cancer is a complex disease and is treated in a variety of ways. Genentech BioOncology is focusing on multiple approaches to targeted cancer therapy:

- Inhibiting tumor angiogenesis¹⁴⁻¹⁶
- Targeting cell signaling¹⁷⁻¹⁹
- Arming therapeutic antibodies²⁰⁻²⁴

We believe that this comprehensive approach can shut down the growth and spread of cancer cells. Our expertise in product and process development has allowed the company to employ multiple technology platforms in each of these approaches.

Inhibiting Tumor Angiogenesis

Angiogenesis is the process by which new blood vessels are formed. In the context of cancer, tumor angiogenesis is the creation of a network of blood vessels that supplies tumors with essential nutrients and oxygen and removes waste products.¹⁴

Agents that block vascular endothelial growth factor (VEGF) may have multiple effects on tumor angiogenesis, including:

- Causing existing blood vessels in the tumor to die^{15,16}
- Preventing new blood vessels from forming^{15,16}
- Making mature tumor vessels less leaky, thus facilitating the delivery of chemotherapy to tumor cells^{15,16}

Targeting Cell Signaling

Numerous cell-signaling pathways promote tumor cell growth and keep tumors alive.¹⁷ Agents that target cell signaling combat cancer by:

- Blocking pathways that promote tumor cell growth and survival¹⁷
- Activating pathways that tell the cell to self-destruct (undergo apoptosis)^{18,19}

Arming Therapeutic Antibodies

Therapeutic antibodies can be used to target specific proteins on the surface of cancer cells.¹¹ Genentech is creating “armed” antibodies to selectively kill cancer cells, using “stable” linkers to attach potent chemotherapy drugs to therapeutic antibodies.²⁰⁻²² The linker molecules potentially limit the release of the chemotherapy agent outside of the target cells, which may lessen the impact of chemotherapy on normal tissue.²²⁻²⁴

Safety Information

Rituxan

Indications

Rituxan is indicated for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma (NHL) as a single agent; for previously untreated diffuse large B-cell, CD20-positive, NHL in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or other anthracycline-based chemotherapy regimens; for previously untreated follicular, CD20-positive, B-cell NHL in combination with CVP (cyclophosphamide, vincristine and prednisolone) chemotherapy; and for the treatment of non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent, after first-line CVP chemotherapy.

Important Safety Information

Rituxan therapy does involve risks. **Life-threatening side effects related to Rituxan therapy include infusion reactions and kidney and skin problems, and progressive multifocal leukoencephalopathy (PML, a rare condition that causes nerve damage within the brain).** Serious side effects have occurred in patients treated with Rituxan including hepatitis B virus infections with related serious liver problems, other viral infections, heart problems, kidney failure, and stomach and bowel problems.

The most common adverse reactions observed in Rituxan infusions include fever, headache, chills and shakes, nausea, itching, hives, cough, sneezing, and throat irritation or tightness.

[Full Prescribing Information, including Boxed WARNINGS](#)

[Medication Guide \(79K/PDF\)](#)

Herceptin

Indications

Herceptin in combination with paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have not received chemotherapy for their metastatic disease.

Herceptin as a single agent is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease.

Herceptin, as part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel, is indicated for the adjuvant treatment of patients with HER2-overexpressing, node-positive breast cancer.

Herceptin, as a single agent, is indicated for the adjuvant treatment of HER2-overexpressing node-negative (ER/PR-negative or with one high-risk feature) or node-positive breast cancer, following multi-modality anthracycline-based therapy.

Important Safety Information

Herceptin treatment can result in heart problems, including those without symptoms (reduced heart function) and those with symptoms (congestive heart failure). Some patients have had serious infusion reactions and lung problems; fatal infusion reactions have been reported.

Worsening of low white blood cell counts associated with chemotherapy has also occurred. Herceptin can cause low amniotic fluid levels and harm to the fetus when taken by a pregnant woman. The most common side effects associated with Herceptin were fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, shortness of breath, rash, low white and red blood cells, and muscle pain.

Because everyone is different, it is not possible to predict what side effects any one person will have. Patients should talk to their doctor if they have questions or concerns about side effects.

[Full Prescribing Information, including Boxed WARNINGS](#)

Tarceva

Indication

Tarceva monotherapy is indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.

Results from two multicenter, placebo-controlled, randomized, Phase III trials conducted in first-line patients with locally advanced or metastatic NSCLC showed no clinical benefit with the concurrent administration of Tarceva with platinum-based chemotherapy, and its use is not recommended in that setting.

TARCEVA in combination with gemcitabine is indicated for the first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer.

Important Safety Information

There have been infrequent reports of serious Interstitial Lung Disease (ILD)-like events including deaths in patients taking Tarceva. Serious side effects (including deaths) in patients taking Tarceva include liver and/or kidney problems; gastrointestinal (GI) perforations (the development of a hole in the stomach, small intestine, or large intestine); and severe blistering skin reactions including cases similar to Stevens-Johnson syndrome. Patients taking Tarceva plus gemcitabine were more likely to experience bleeding and clotting problems such as heart attack or stroke. Eye irritation and damage to the cornea have been reported in patients taking Tarceva. Women should avoid becoming pregnant and avoid breastfeeding while taking Tarceva. Patients should call their doctor right away if they have these signs or symptoms: new or worsening skin rash; serious or ongoing diarrhea, nausea, loss of appetite, vomiting, or stomach pain; new or worsening shortness of breath or cough; fever; eye irritation. Rash and diarrhea were the most common side effects associated with Tarceva in the non-small cell lung cancer clinical study. Fatigue, rash, nausea, loss of appetite, and diarrhea were the most common side effects associated with Tarceva plus gemcitabine therapy in the pancreatic cancer clinical study.

[Full Prescribing Information](#)

Avastin **Indications**

Avastin, in combination with intravenous 5-fluorouracil-based chemotherapy, is indicated for first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum.

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

BOXED WARNINGS and Additional Important 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.

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.

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).

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 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.

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.

Avastin may impair fertility. Patients who are pregnant or thinking of becoming pregnant should talk with their 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.

In the first-line metastatic colorectal cancer 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 metastatic colorectal cancer 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%).

In the metastatic kidney cancer trial, the most common severe to fatal side effects that increased by 2% or more in people who received Avastin vs those in the comparison group included tiredness (13% vs 8%), weakness (10% vs 7%), too much protein in the urine (7% vs 0%), high blood pressure (6% vs 1%), and severe bleeding (3% vs 0.3%).

In the non-small cell lung cancer trial, the most common life-threatening to fatal side effects that increased by 2% or more in people who received Avastin vs those in the comparison group were reduced white blood cell counts (27% vs 17%), tiredness (16% vs 13%), high blood pressure (8% vs 0.7%), infection without reduced white blood cell counts (7% vs 3%), blood clots in the veins of the body (5% vs 3%), fever with reduced white blood cell counts (5% vs 2%), inflammation of the lungs (5% vs 3%), infection with severe or life-threatening reduced white blood cell counts (4% vs 2%), low sodium levels in the blood that could lead to seizure or coma.

[Full Prescribing Information, including Boxed WARNINGS](#)

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