



Product Portfolio

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Genentech BioOncology Product Portfolio

Genentech is working to fundamentally change the way cancer is treated by developing a broad oncology portfolio of innovative targeted therapies designed to improve and extend the lives of cancer patients.

Marketed Products

Avastin® (bevacizumab)

Avastin is a therapeutic antibody that is believed to work by targeting and inhibiting the function of a natural protein called "vascular endothelial growth factor" (VEGF) that stimulates new blood vessel formation, a process known as angiogenesis. Researchers have shown in preclinical models that anti-VEGF agents like Avastin may work by causing the following changes to occur in the blood vessels supporting tumor growth (tumor vasculature):

- Regression of existing microvessels — helps arrest tumor growth and reduce tumor size
- “Normalization” of surviving mature vasculature — makes the tumor vasculature more conducive to effective anti-cancer therapy
- Inhibition of vessel growth and neovascularization (e.g., the sprouting of new micro-vasculature from existing vessels)

Avastin is currently approved for use in combination with intravenous 5-fluorouracil-based chemotherapy for first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum, and has been shown to extend survival in this patient population. Avastin is also approved in combination with carboplatin and paclitaxel for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer (NSCLC). It was the first anti-angiogenesis therapy approved by the U.S. Food and Drug Administration (FDA).

Based on data showing that VEGF may play a broad role in a range of cancers, Genentech is pursuing a broad development program for Avastin that currently includes more than 300 clinical trials in 20 different tumor types. Avastin is being evaluated in Phase III clinical trials for its potential use in adjuvant and metastatic colorectal, renal cell (kidney), breast, pancreatic, non-small cell lung, prostate and ovarian cancers.

Avastin Safety Profile

The most serious adverse events associated with Avastin across all trials were

GI perforation, wound healing complication, hemorrhage, non-GI fistula formation, arterial thromboembolic events, hypertensive crisis, reversible posterior leukoencephalopathy syndrome, neutropenia and infection, nephrotic syndrome, and congestive heart failure. Other serious bleeding events occurring in patients receiving Avastin across all indications include GI hemorrhage, subarachnoid hemorrhage, and hemorrhagic stroke. The most common grade 3–5 (nonhematologic) and 4–5 (hematologic) events that may have occurred in Avastin indications (first-line NSCLC, first- and second-line MCRC) included neutropenia, fatigue, hypertension, infection, hemorrhage, asthenia, abdominal pain, pain, deep vein thrombosis, intra-abdominal thrombosis, syncope, diarrhea, constipation, leukopenia, nausea, vomiting, dehydration, ileus, neuropathy–sensory, neurologic–other, and headache.

Herceptin® (Trastuzumab)

Herceptin is a targeted therapeutic antibody treatment for women with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer, an especially aggressive form of the disease that affects approximately one-fourth of women with breast cancer. Special testing is required to identify women who have HER2-positive breast cancer and who may be candidates for treatment with Herceptin.

Herceptin received FDA approval in September 1998 for use in women with metastatic breast cancer, who have tumors that overexpress the HER2 protein. It is indicated for weekly treatment of patients both in combination with paclitaxel and as a single agent in second- and third-line therapy. In clinical trials of HER2-positive metastatic breast cancer patients, Herceptin has shown a survival benefit when used in combination with chemotherapy. Nearly 400,000 women with HER2-positive metastatic breast cancer have been treated with Herceptin worldwide. In November 2006, the FDA approved Herceptin as part of a treatment regimen containing doxorubicin, cyclophosphamide and paclitaxel, for the adjuvant treatment of patients with HER2-positive, node-positive breast cancer. In January 2008, the FDA approved Herceptin, as a single agent, 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.

Herceptin Safety Information

Herceptin administration can result in sub-clinical and clinical cardiac failure manifesting as congestive heart failure and decreased left ventricular ejection fraction. Serious infusion reactions and pulmonary toxicity have occurred; fatal infusion reactions have been reported.

Exacerbation of chemotherapy-induced neutropenia has also occurred. Herceptin can cause oligohydramnios and fetal harm when administered to a pregnant woman. The most common adverse reactions associated with Herceptin use were fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia.

Rituxan® (Rituximab)

Rituxan, the first therapeutic antibody approved for cancer in the United States, targets and selectively depletes CD20, a protein found on the surface of B-cells. Normal B-cells are an important component of the immune system, but uncontrolled B-cell growth and replication can give rise to several types of blood cancers, such as non-Hodgkin's lymphoma (NHL). Rituxan works by binding to a specific protein (CD20 antigen) on the surface of B-cells. From there, it is believed that Rituxan works with the body's own immune system to attack and kill the marked B-cells. Rituxan does not target stem cells, B-cell progenitors in the bone marrow that lack the CD20 protein, allowing healthy B-cells to regenerate after treatment and return to normal levels within several months.

Rituxan is approved in the United States 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.

Rituxan Safety Information: The most important serious adverse reactions of Rituxan are **fatal infusion reactions, tumor lysis syndrome (TLS), severe mucocutaneous reactions, progressive multifocal leukoencephalopathy (PML)**, hepatitis B reactivation with fulminant hepatitis, other viral infections, cardiovascular events, renal toxicity, and bowel obstruction and perforation. The most common adverse reactions of Rituxan (incidence $\geq 25\%$) observed in patients with NHL are infusion reactions, fever, chills, infection, asthenia, and lymphopenia.

Tarceva® (erlotinib)

Tarceva is a small molecule designed to target the human epidermal growth factor receptor 1 (EGFR/HER1) pathway, which is one of the factors critical to cell growth in non-small cell lung cancer (NSCLC). EGFR/HER1 is a component of the HER signaling pathway, which plays a role in the formation and growth of numerous cancers. Tarceva is designed to inhibit the tyrosine kinase activity of the HER1 signaling pathway inside the cell, which may block tumor cell growth. Tarceva is the first and only HER1/EGFR-targeted therapy proven to prolong survival in advanced second-line NSCLC.

Tarceva is an oral tablet currently approved for use as a monotherapy in advanced non-small cell lung cancer for patients whose disease has progressed after one or more courses of chemotherapy (at a recommended dose of 150

mg/day). Results from two randomized, placebo-controlled clinical trials in first-line advanced NSCLC patients showed no clinical benefit with concurrent administration of Tarceva with doublet platinum-based chemotherapy (carboplatin and paclitaxel or gemcitabine and cisplatin) and its use is not recommended in that setting. Tarceva is also indicated in combination with gemcitabine for the treatment of locally advanced or metastatic pancreatic cancer in patients who have not received previous chemotherapy (at a recommended dose of 100 mg/day). Additional early-stage trials of Tarceva are being conducted in other solid tumors.

Tarceva Safety Information: There have been infrequent reports of serious Interstitial Lung Disease (ILD)-like events, including fatalities, in patients receiving Tarceva for treatment of NSCLC, pancreatic cancer or other advanced solid tumors. Cases of hepatic failure, hepatorenal syndrome, acute renal failure (all including fatalities), and renal insufficiency have been reported during use of Tarceva. In the pancreatic cancer trial, other serious adverse reactions associated with Tarceva plus gemcitabine and which may have included fatalities, were myocardial infarction/ischemia, cerebrovascular accident and microangiopathic hemolytic anemia with thrombocytopenia. When receiving Tarceva therapy, women should be advised against becoming pregnant or breastfeeding. Tarceva is pregnancy category D. The most common adverse reactions in patients with NSCLC receiving Tarceva monotherapy 150 mg were rash and diarrhea. The most common adverse reactions in patients with pancreatic cancer receiving Tarceva 100 mg plus gemcitabine were fatigue, rash, nausea, anorexia and diarrhea.

Pipeline Projects

Genentech's pipeline continues to grow and includes both breakthrough innovations and new indications for existing, well-understood products that may fight more than one disease or more than one form of a disease.

In oncology, we are focusing our efforts in four primary areas: HER signaling, anti-angiogenesis, apoptosis and B-cell biology. We are studying our marketed products Avastin, Herceptin, Rituxan and Tarceva in numerous new oncology indications as well as conducting combination trials including a Phase III trial of Avastin plus Tarceva in lung cancer. In addition, we are investigating a number of new molecules as cancer therapies. The following investigational agents are in clinical development in our oncology pipeline:

- Pertuzumab, the first in a new class of investigational agents known as HER dimerization inhibitors (HDIs), is being investigated in Phase II studies in combination with other therapies in ovarian cancer, and Phase III studies in combination with Herceptin in HER2-positive metastatic breast cancer are planned;
- Apo2L/TRAIL, a recombinant soluble human protein designed to selectively induce apoptosis (programmed cell death), is being evaluated

- in collaboration with Amgen in Phase I studies in combination with Rituxan in indolent NHL; and
- Trastuzumab-DM1, a HER2 antibody-drug conjugate which comprises a cell-killing agent linked to a HER2 therapeutic antibody that targets overexpression of the HER2 protein, is being evaluated in HER2-positive metastatic breast cancer.

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