Genentech
A Member of the Roche Group

Herceptin® (Trastuzumab) Development Timeline

Date	Event
1975	Georges Köhler and César Milstein, scientists at the Medical Research Council, Laboratory of Molecular Biology (Cambridge, UK), discovered the potential of using antibodies in vitro to fight disease.
1976	The research of Michael Bishop and Harold Varmus at the University of California San Francisco showed that disturbances in one or more members of a family of genes can lead to the transformation of a normal cell into a cancer cell.
1976	Genentech was founded by venture capitalist Robert A. Swanson and biochemist Dr. Herbert W. Boyer.
1981	Genentech scientists John McGrath and Art Levinson cloned and sequenced a portion of the human HER2 gene for the first time.
1984	Robert Weinberg and his team of scientists at the Massachusetts Institute of Technology discovered an unusual mutant rat gene encoding a tyrosine kinase that produced cancer features in transfected cells and named it "neu."
1984	Georges Köhler and César Milstein win the Nobel Prize in Medicine, "for theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies."
1984	Genentech scientists Axel Ullrich and Peter Seeberg, in collaboration with Mike Waterfield at the Imperial Cancer Research Fund and Joseph Schlesinger at the Weizmann Institute, published the complete human EGF-R sequence in *Nature*.
1985	Following work that began in the early 1980s, a Genentech team of scientists, including Axel Ullrich and Art Levinson, clone the first full-length human HER2 gene. This achievement is described in a paper published in *Science*.
1985	Stu Aaronson at the National Institute of Health showed that the HER2/neu gene is frequently amplified in human breast tumors.
1987	Michael Shepard, Axel Ullrich and their teams at Genentech developed mouse 4D5, the parent of Herceptin, simultaneous with the discovery by Dr. Dennis Slamon at UCLA, and colleagues at the University of Texas Health Science Center, that linked HER2 over-expression with a more aggressive type of breast cancer found in approximately 25 percent of patients. Further work by Shepard's group demonstrated that the 4D5 could suppress the growth of HER-over-expressing tumor cells, and also enhance their sensitivity to killing by the host immune

UCLA teams that radio-labeled 4D5 could localize to HER2-overexpressing tumors in patients.

1989 Michael Bishop and Harold Varmus were awarded the Nobel Prize in Medicine for their discovery that normal cells contain genes capable of becoming cancer genes.

1990 Len Presta, Paul Carter and Michael Shepard of Genentech create Herceptin by humanizing the 4D5 mouse antibody directed at HER2.

1992 Genentech filed an Investigational New Drug Application (IND) with the U.S. Food and Drug Administration (FDA) and Phase I clinical trials were initiated.

1993 Genentech initiated two Phase II clinical trials that evaluated the investigational anti-HER2 antibody as a single agent and in combination with chemotherapy in the relapsed setting.

1995 Genentech began enrollment of the Phase III pivotal trials for patients with HER2 over-expressing metastatic breast cancer.

- Pivotal trial 648, double-blind, placebo-controlled study of the investigational anti-HER2 antibody plus chemotherapy to include 450 women with newly diagnosed metastatic breast cancer
- Trial 649, study of the investigational anti-HER2 antibody as a single agent to include 200 women whose metastatic disease had failed to respond to one or two rounds of chemotherapy
- Trial 650, study of the investigational anti-HER2 antibody to include 200 women who had newly diagnosed metastatic breast cancer but did not want chemotherapy

Genentech worked closely with breast cancer patient advocates to design an expanded access program to ensure the investigational agent is available to patients with no other therapeutic alternatives.

Genentech advanced the construction of a new manufacturing facility that would produce the anti-HER2 antibody.

1996 Critical efforts are undertaken to enroll patients into the trials, including:

- Genentech clinicians and outside investigators spearheaded an amendment to the study protocol of pivotal trial 648 to include paclitaxel chemotherapy as an alternative to doxorubicin chemotherapy and traveled across the country to inform investigators to spur interest in the trial;
- Genentech and patient advocates worked together to publicize the trials to the breast cancer community.

March 1996 Researchers at Memorial Sloan Kettering co-authored a paper titled, "Phase II study of weekly intravenous recombinant humanized anti-p185HER2 monoclonal antibody in patients with HER2-neu-overexpressing metastatic breast cancer,"

	which showed that the antibody was clinically active in women with HER2 neu overexpressing metastatic breast cancer who had received prior therapy. The study provided evidence that targeting growth factor receptors caused regression of human cancer.
December 1996	Genentech initiated a partnership with diagnostics company DAKO to develop a commercial test to identify patients who overexpress the HER2 gene.
March 1997	Genentech completed enrollment of the Phase III pivotal trials for the anti-HER2 antibody (now known as Herceptin® (Trastuzumab)).
May 1998	Genentech submitted a biologic license application (BLA) for Herceptin, and DAKO submitted a pre-market approval (PMA) application to the FDA for approval of the diagnostic HercepTest. The FDA designated Herceptin as a "Fast Track" product for the treatment of metastatic breast cancer. **Herceptin treatment can result in heart problems, including those without symptoms (reduced heart function) and those with symptoms (congestive heart failure).**
May 1998	Results from a Phase III investigational clinical trial of Herceptin were presented at the American Society of Clinical Oncology (ASCO) annual meeting. Results showed that Herceptin, in combination with chemotherapy, increased time to disease progression and response rates. **Herceptin treatment can result in heart problems, including those without symptoms (reduced heart function) and those with symptoms (congestive heart failure).**
July 1998	Genentech and Roche signed a licensing agreement giving Roche exclusive marketing rights for Herceptin outside of the United States.
September 1998	Herceptin received FDA approval for use in women with metastatic breast cancer who have tumors that overexpress the HER2 protein. It is indicated for treatment of patients both as **first-line therapy in combination with paclitaxel chemotherapy and as a single agent for those who have received one or more chemotherapy regimens**. Dako's HercepTest is approved simultaneously to aid in the identification of patients for Herceptin treatment. Herceptin was the first therapeutic antibody targeted to a specific (HER2) cancer-related molecular marker to receive FDA approval. Herceptin treatment can result in heart problems, including those without symptoms (reduced heart function) and those with symptoms (congestive heart failure). The risk and seriousness of these heart problems were highest in people who received both Herceptin and a certain type of chemotherapy (anthracycline). Some patients have had serious infusion reactions and lung problems; fatal infusion reactions have been reported. In most cases, these reactions occurred during or within 24 hours of receiving Herceptin.
May 2000	Genentech issued a letter to healthcare providers about reports of serious adverse events, including hypersensitivity, infusion and pulmonary reactions.

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August 2000	European Commission approved Herceptin for the treatment of HER2-positive metastatic breast cancer.
December 2000	Enrollment of two Phase III clinical trials evaluating the potential use of Herceptin for the adjuvant treatment of early-stage HER2-positive breast cancer was initiated. Adjuvant therapy is given to women with early-stage (localized) breast cancer who have had initial treatment — surgery with or without radiation therapy — with the goal of reducing the risk of cancer recurrence and/or the occurrence of metastatic disease. The studies are sponsored by the National Cancer Institute (NCI), part of the National Institutes of Health, and conducted by a network of researchers led by the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the North Central Cancer Treatment Group (NCCTG).
March 2001	Further data from a pivotal Phase III clinical trial were published in the *New England Journal of Medicine* (NEJM) that showed a significant increase in survival for women with HER2-positive metastatic breast cancer who received Herceptin and chemotherapy over chemotherapy alone. **Herceptin treatment can result in heart problems, including those without symptoms (reduced heart function) and those with symptoms (congestive heart failure). The risk and seriousness of these heart problems were highest in people who received both Herceptin and a certain type of chemotherapy (anthracycline).**
March 2001	HERA, the third adjuvant trial of Herceptin, began enrollment.
December 2001	Genentech received FDA approval to include, in the product label, data that showed an improved median overall survival for women with HER2-positive metastatic breast cancer treated initially with Herceptin and chemotherapy, compared to chemotherapy alone (median 25.1 months compared to 20.3 months). 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.
December 2001	BCIRG 006, the fourth adjuvant trial of Herceptin, began enrollment.
August 2002	Genentech received FDA approval to include information about a breast cancer gene-detection test method called FISH (fluorescence in situ hybridization) in the Herceptin product labeling.
May 2005	Results from a joint analysis of the Phase III NSABP and NCCTG clinical trials evaluating the addition of Herceptin to standard adjuvant therapy for early-stage HER2-positive breast cancer were presented at the ASCO annual meeting. According to this 3-year planned joint analysis, Herceptin in combination with chemotherapy significantly reduced the risk of cancer recurrence.

	Some patients have had serious infusion reactions and lung problems; fatal infusion reactions have been reported. In most cases, these reactions occurred during or within 24 hours of receiving Herceptin.
August 2005	Genentech issued a letter to healthcare providers informing them of updated cardiotoxicity information related to the use of Herceptin, obtained from the Phase III NSABP study (B-31). **Herceptin treatment can result in heart problems, including those without symptoms (reduced heart function) and those with symptoms (congestive heart failure). The risk and seriousness of these heart problems were highest in people who received both Herceptin and a certain type of chemotherapy (anthracycline).** In one study with Herceptin and certain types of chemotherapy, an inadequate blood supply to the heart occurred.
February 2006	Based on results from the joint analysis of the NSABP and NCCTG trials, Genentech filed a supplemental Biologics License Application (sBLA) with the FDA for Herceptin for the adjuvant treatment of early-stage HER2-positive breast cancer.
November 2006	The FDA approved Herceptin as **part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel for the adjuvant treatment of patients with early-stage HER2-positive, node-positive breast cancer** based on the joint analysis of the NSABP and NCCTG studies. Herceptin can cause low amniotic fluid levels and harm to the fetus when taken by a pregnant woman. Patients should talk to their doctor if they are pregnant or become pregnant while taking Herceptin.
December 2006	Genentech submitted an sBLA with the FDA based on the global HERA study to potentially expand Herceptin's use in the adjuvant treatment of early-stage HER2-positive breast cancer.
June 2007	Genentech submitted two sBLAs to the FDA based on the global BCIRG 006 trial to potentially expand Herceptin's use in the adjuvant treatment of early-stage HER2-positive breast cancer.
January 2008	Based on the HERA one-year data, the FDA approved Herceptin as a **single agent for the adjuvant treatment of early-stage HER2-positive node-positive breast cancer or node-negative (ER/PR-negative or with one high-risk feature) following multi-modality, anthracycline-based therapy**. Herceptin also may be administered as a single agent in an every-three-week dosing schedule for one year. Patients receiving their first dose of Herceptin may have chills and fever as well as nausea, vomiting, pain, headache, dizziness, shortness of breath, low blood pressure, rash, and weakness.
May 2008	Based on the results of the BCIRG 006 study, the FDA approved two new Herceptin-containing regimens for the adjuvant treatment of early-stage HER2-positive node-positive or node-negative (ER/PR-negative or with one high-risk feature) breast cancer.

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