



## **Chronology**

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### **Genentech's BioOncology Timeline: A History of Leadership and Innovation in BioOncology**

#### **1976**

Genentech founded by Robert Swanson and Dr. Herbert Boyer.

#### **1984**

Data published in Nature report the cloning of the gene encoding EGFR (epidermal growth factor receptor, HER1) and identify it as a gene known to cause cancer in chickens.

#### **1985**

Data published in Science report cloning of the gene encoding HER2 (human epithelial growth factor receptor 2).

#### **1986**

Interferon alpha-2a licensed to Hoffmann-La Roche, Inc. as Roferon®-A, which is approved by the FDA for the treatment of hairy cell leukemia.

#### **1987**

Dennis Slamon at UCLA and Genentech scientists publish data demonstrating correlation between HER2 amplification and progression of breast cancer in Science.

#### **1989**

Napoleone Ferrara and Genentech scientists identify and clone the gene encoding VEGF (vascular endothelial growth factor). Data published in Science magazine.

Data published in Molecular and Cellular Biology demonstrate that an antibody directed against HER2 has anti-proliferative effects in human breast tumor cells.

#### **1990**

Genentech scientists humanize an antibody against HER2.

#### **1991**

First anti-HER2 antibody tested in humans.

#### **1992**

Data published in the Proceedings of the National Academy of Sciences report the successful humanization of anti-HER2 antibody, setting the foundation for the

development and commercialization of Herceptin® (Trastuzumab).

### **1993**

Phase II trials of Herceptin commence.

Data published in Nature demonstrate that an antibody targeted against VEGF can suppress tumor growth in animal models.

### **1994**

Phase II Herceptin trial completed.

### **1995**

Genentech signs collaboration with IDEC (now known as Biogen Idec) to develop IDEC's anti-CD20 monoclonal antibody, C2B8 (now known as Rituxan® [Rituximab]), for the treatment of relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma (NHL).

Pivotal Phase III trial of Rituxan initiated in patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL.

Initiation of pivotal Phase III trial to evaluate the efficacy and safety of adding Herceptin to initial treatment with chemotherapy regimens in women with metastatic disease who had not previously been treated with chemotherapy.

Establishment of access program for Herceptin ensures that the investigational therapy is available to breast cancer patients with no other therapeutic alternatives.

### **1996**

Positive data from the pivotal Phase III clinical trial of Rituxan as a single agent therapy for relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL presented at the American Society of Hematology (ASH) annual meeting.

Successful humanization of an antibody targeted against VEGF. Data published in Cancer Research.

### **1997**

Launch of BioOncology initiative, focused on commercializing Genentech's diverse oncology pipeline.

FDA approves Rituxan for the treatment of relapsed or refractory low-grade or follicular CD20-positive, B-cell NHL, the first new drug for this disease in a decade and the first therapeutic antibody to receive FDA approval for cancer.

Phase I trials of Avastin® (bevacizumab), a humanized antibody targeted against VEGF, commence.

## **1998**

Herceptin receives Fast-Track designation from the FDA for the treatment of metastatic breast cancer.

FDA approves Herceptin in combination with paclitaxel for the first-line treatment of HER2-positive metastatic breast cancer, and as a second- and third-line therapy as a single agent. Herceptin was the first therapeutic antibody targeted to a cancer-related molecular marker to receive FDA approval.

Establishment of marketing agreement for Herceptin with Roche.

Establishment of collaboration with Dako to develop HER2 diagnostic test for breast cancer.

Phase II trials of Avastin commence.

## **2000**

Initiation of Avastin Phase III clinical trial program for the first-line treatment of metastatic colorectal cancer.

Initiation of Phase III trials to evaluate the safety and efficacy of adding Herceptin to chemotherapy in the adjuvant setting in women with early-stage HER2-positive breast cancer.

## **2001**

FDA approves expanded uses of Rituxan to include re-treatment after an initial course, weekly dosing for eight weeks and the treatment of bulky disease.

Data from pivotal Phase III Herceptin trial in HER2-positive metastatic breast cancer patients published in the New England Journal of Medicine.

FDA approves addition of increase in median survival data to Herceptin product labeling.

Agreements entered with OSI Pharmaceuticals and Roche to co-develop and commercialize Tarceva. The development of Tarceva is Genentech's second program targeted to the HER signaling pathway.

Initiation of Phase I clinical trials of 2C4 antibody, Genentech's third program targeted to the HER signaling pathway, in patients with non-HER2-positive cancers.

## **2002**

FDA approves inclusion of FISH (fluorescence in situ hybridization) gene amplification test for HER2 gene in Herceptin product labeling.

Tarceva® (erlotinib) receives Fast-Track designation from the FDA for the treatment of chemotherapy-naïve Stage III/IV non-small cell lung cancer patients.

New England Journal of Medicine publishes data from the Phase III GELA LNH98-5 study demonstrating that Rituxan plus CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy may offer previously-untreated patients the potential for a significant improvement in event-free and overall survival compared to CHOP alone – represents the first improvement in survival in this patient population in more than 25 years.

### **2003**

Phase III Avastin data in metastatic colorectal cancer presented at the ASCO annual meeting demonstrating that the study met all of its primary and secondary efficacy endpoints and proved the "anti-angiogenic" hypothesis that tumors need oxygen and nutrients to live and that vascular endothelial growth factor (VEGF) is a central mediator of this process.

Biologics License Application filed with the FDA for approval of Avastin as a treatment for first-line metastatic colorectal cancer in combination with 5-FU-based chemotherapy and given Fast-Track designation.

Phase III study (E4494) data, presented at the American Society of Hematology (ASH) annual meeting, show that adding Rituxan to chemotherapy in patients with diffuse large B-cell, CD20-positive NHL (DLBCL) significantly prolonged progression-free survival.

### **2004**

Avastin approved by the FDA in combination with intravenous 5-Fluorouracil-based chemotherapy as a treatment for patients with first-line metastatic cancer of the colon or rectum.

Tarceva approved by the FDA for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has progressed after one or more courses of chemotherapy.

Phase III data from the study E1496, presented at the ASCO annual meeting, showed that Rituxan therapy given over a two-year period in patients with low grade or follicular NHL who had achieved a response or demonstrated stable disease to first-line CVP (cyclophosphamide, vincristine and prednisone) chemotherapy significantly extended progression-free survival.

### **2005**

FDA grants Priority Review status to supplemental Biologics License Application (sBLA) for Rituxan for the treatment of DLBCL in combination with CHOP or other anthracycline-based chemotherapy regimens in previously untreated patients.

Tarceva approved by the FDA in combination with gemcitabine chemotherapy for the treatment of locally advanced, inoperable or metastatic pancreatic cancer in patients who have not received previous chemotherapy.

Data from Phase III study of Avastin plus paclitaxel and carboplatin chemotherapies met its primary endpoint of improving progression-free survival in first-line non-squamous non-small cell lung cancer.

Data from Phase III study of Avastin plus paclitaxel chemotherapy met its primary endpoint of improving progression-free survival for first-line treatment of metastatic breast cancer.

Results from a joint analysis of two Phase III clinical trials evaluating the potential use of Herceptin in the adjuvant setting presented at the ASCO annual meeting. Herceptin, in combination with chemotherapy, was shown to reduce the risk of breast cancer recurrence, the primary endpoint, by 52 percent in women with early-stage HER2-positive breast cancers, compared to those patients who received chemotherapy alone.

Supplemental Biologics License Application filed with the FDA for Avastin plus chemotherapy in patients with metastatic colorectal cancer who were previously treated with 5-fluorouracil (5-FU)-based and irinotecan chemotherapy.

## **2006**

FDA approves expanded use of Rituxan for the first-line treatment of (previously untreated) patients with diffuse large B-cell, CD20-positive, NHL (DLBCL – a type of NHL), in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or other anthracycline-based chemotherapy regimens. Supplemental Biologics License Application (sBLA) filed with the FDA for Avastin plus chemotherapy for front-line treatment of metastatic breast cancer.

FDA approves Avastin in combination with intravenous 5-fluorouracil-based chemotherapy for second-line treatment of patients with metastatic carcinoma of the colon or rectum.

FDA approves Rituxan for the first-line treatment of follicular, CD20-positive, B-cell non-Hodgkin's lymphoma in combination with CVP (cyclophosphamide, vincristine and prednisolone) chemotherapy and for the treatment of low-grade, CD20-positive, B-cell non-Hodgkin's lymphoma in patients with stable disease or who achieve a partial or complete response following first-line treatment with CVP chemotherapy.

FDA approves Avastin 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). Genentech also

announces that it plans to initiate a first-of-its-kind program to cap the overall expense of Avastin to \$55,000 per year per eligible patient for any FDA-approved indication.

FDA approves 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.

### **2008**

FDA approves 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.

### **2009**

FDA approves Avastin plus interferon-alfa for people with metastatic renal cell carcinoma, the most common type of kidney cancer.

### **2010**

FDA approves Rituxan in combination with fludarabine and cyclophosphamide (FC) for people with previously untreated and previously treated CD20-positive chronic lymphocytic leukemia (CLL).

FDA approves Tarceva for patients with advanced-stage non-small cell lung cancer (NSCLC) whose cancer has not spread or grown after initial treatment with certain types of chemotherapy.

For the full prescribing information for Tarceva and the full prescribing information and Boxed Warnings for Rituxan, Herceptin, and Avastin please visit <http://www.gene.com>.