15.482 Healthcare Finance
Spring 2017

Andrew W. Lo, MIT

Unit 2, Part 2: Genentech and Herceptin Funding Example

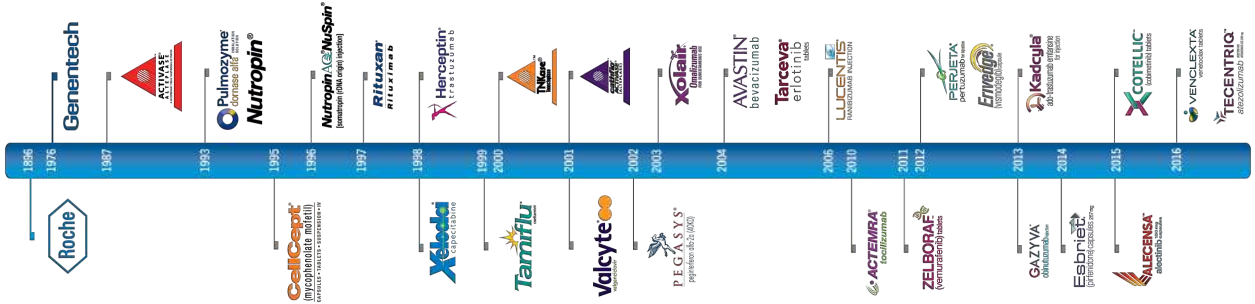
Unit Outline

- Capital Budgeting
- Alternatives to NPV
- Mini-Case: Genentech and Herceptin

Mini-Case: Genentech and Herceptin

Genentech

- Genentech founded in 1976 by Robert Swanson and Dr. Herbert Boyer based on recombinant DNA technology
- Cloned first human protein (1977), human insulin (1978), human growth factor (1979), etc.
- 1980 Genentech IPO'd, raising $35 million ($35 to $88 in an hour)
- 1990 Roche acquires majority ownership in Genentech, completed acquisition in 2009



Genentech

February 5, 1990

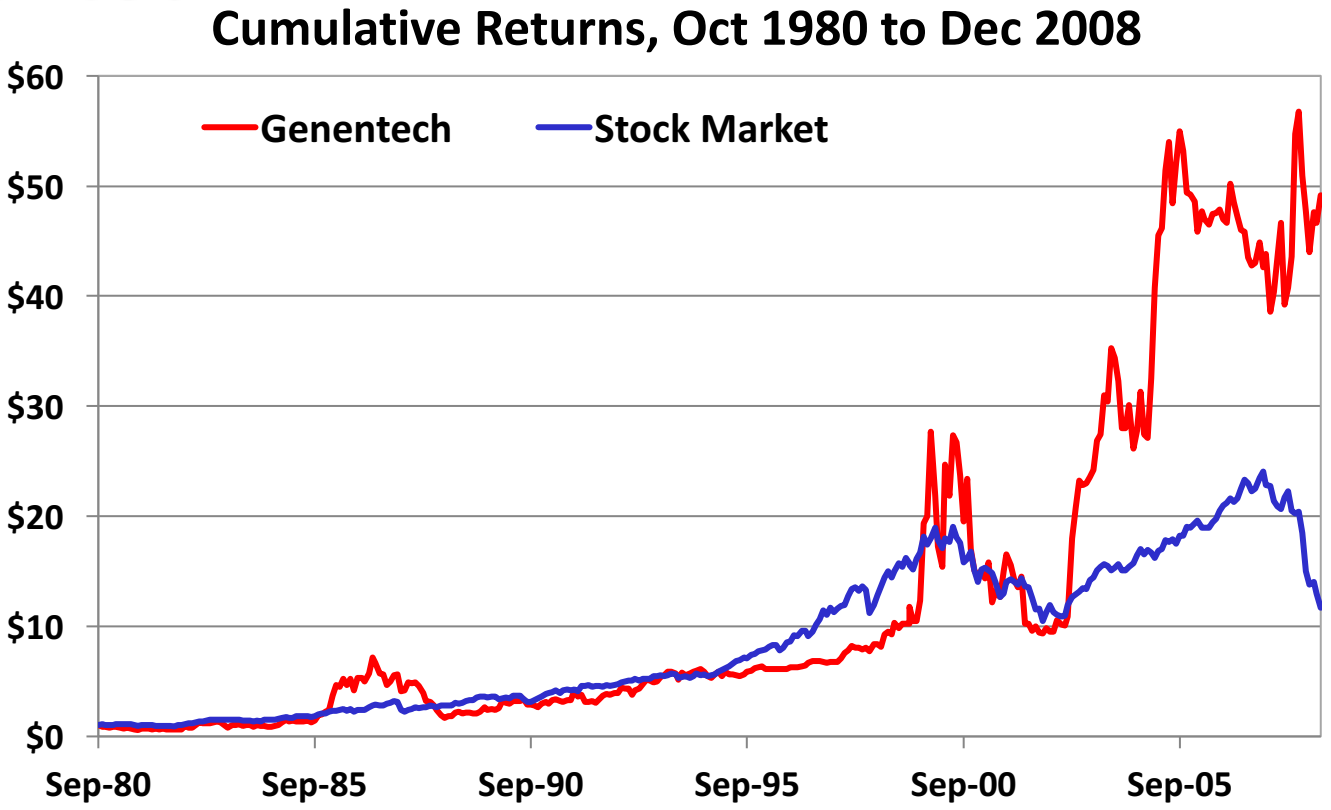
Genentech-Roche Deal May Spur Similar Ties

By ANDREW POLLACK, Special to The New York Times

SAN FRANCISCO, Feb. 4— The agreement announced Friday in which a large Swiss drug company will buy a majority stake in the biotechnology pioneer Genentech Inc. could be the start of a wave of similar transactions, some industry analysts said this weekend.

Some scientists like the deal because it will provide more money for research and will shield Genentech from the Wall Street pressures that had been forcing the company to curtail some of the researchers' freedom. But others were worried. "Some people think the company has sold out," Mr. Weisbrod said.

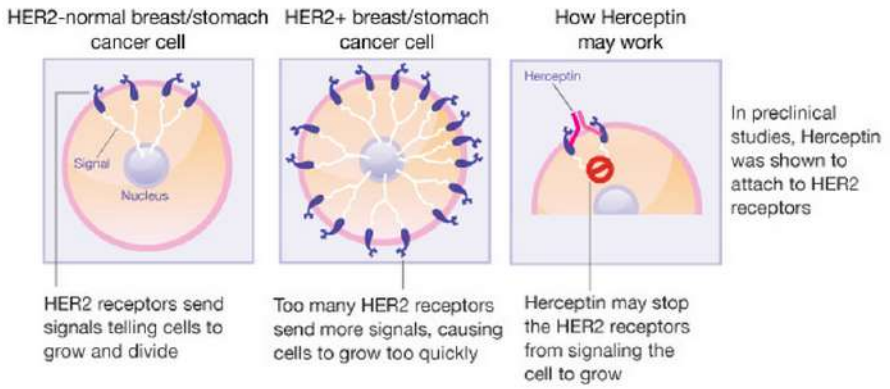
Genentech

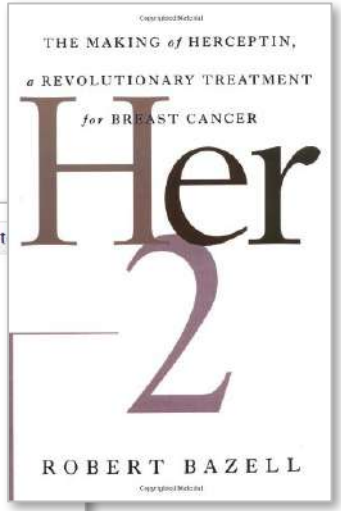


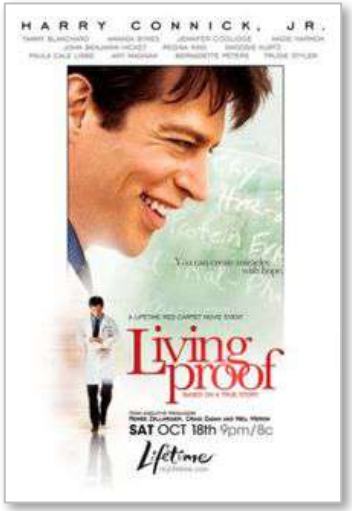
Herceptin

Herceptin®
trastuzumab

How Herceptin may work[1,2]







Herceptin

Herceptin® (Trastuzumab) Development Timeline

Basic Research

Preclinical

Phase I
Phase II

Phase III

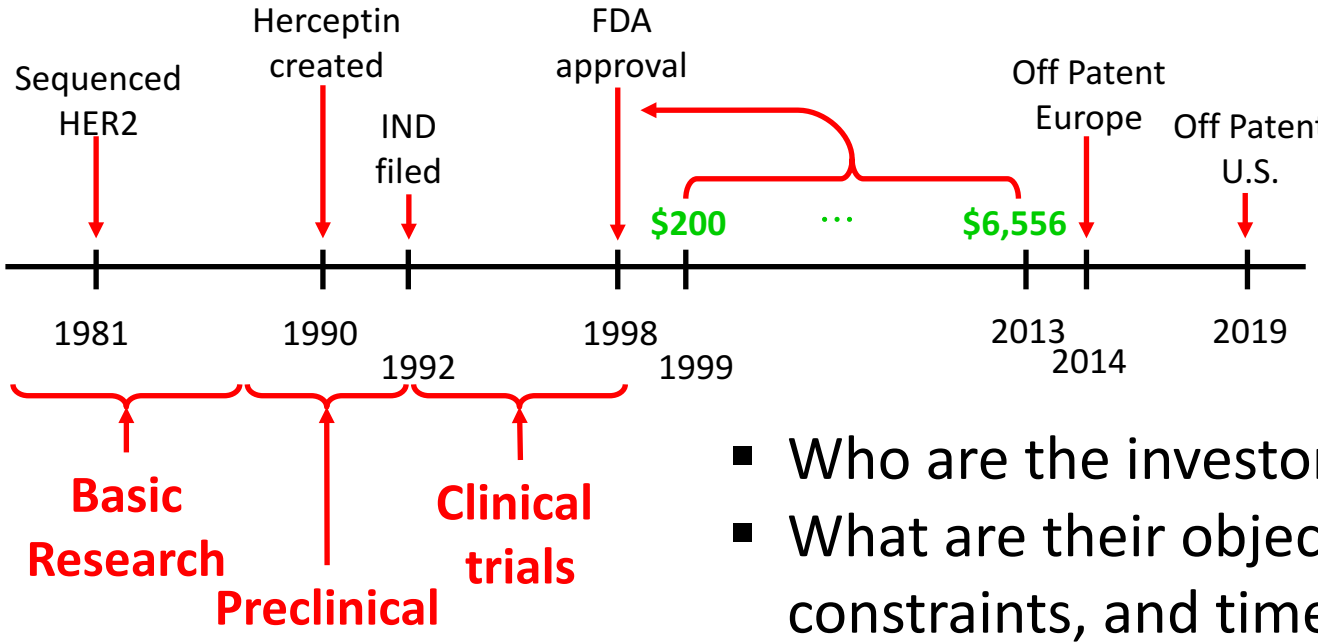
Date	Event
1975	Georges Köhler and César Milstein, scientists at the Medical Research Council, Laboratory of Molecular Biology (Cambridge, UK), discovered the potential of using antibodies in vitro to fight disease.
1976	The research of Michael Bishop and Harold Varmus at the University of California 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 Seeburg, in collaboration with Mike Waterfield at the Imperial Cancer Research Fund and Joseph Schlessinger 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 system. Further proof of concept was the demonstration by the Genentech and 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 651, 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.

Phase III

Source: gene.com (10/20/14)

Herceptin

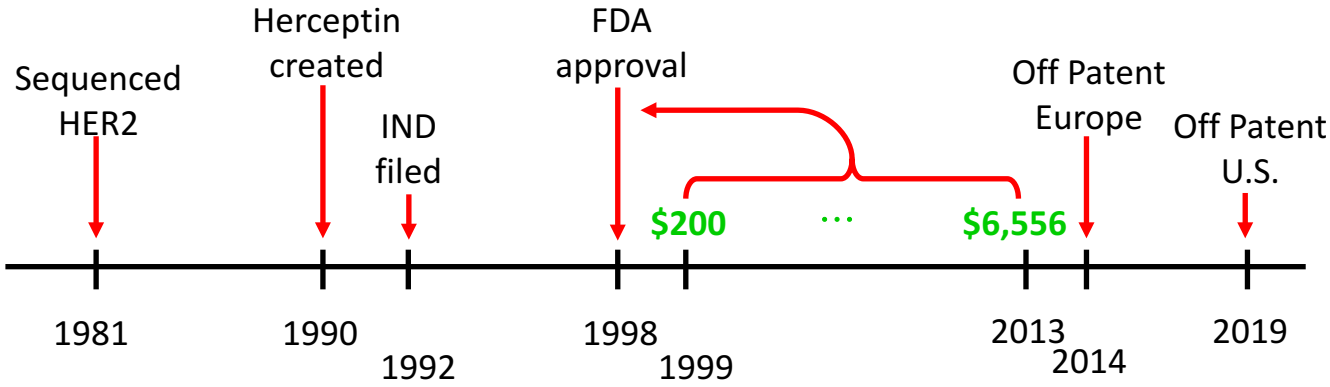
Approximate Herceptin Timeline



- Who are the investors?
- What are their objectives, constraints, and timelines?

Herceptin

Approximate Herceptin Timeline



Components of NPV Calculation:

- PV(Costs from 1981 to 1998)
- PV(Revenues from 1999 to 2013)
- PV(Revenues from 2014 to 2019)
- PV(Revenues from 2020 forward)

Additional Factors:

- Scientific risk
- Business risk
- Financing risk
- Legal risk

Herceptin

Herceptin Worldwide Annual Sales

k	Year	CHF Sales (M)	USD/CHF	USD Sales (M)	1/(1+R)^k , R = 5%	10%	15%	40%
1	1999	CHF 300	0.665	$ 200	0.95	0.91	0.87	0.71
2	2000	CHF 540	0.592	$ 320	0.91	0.83	0.76	0.51
3	2001	CHF 806	0.592	$ 477	0.86	0.75	0.66	0.36
4	2002	CHF 1,007	0.642	$ 647	0.82	0.68	0.57	0.26
5	2003	CHF 1,177	0.743	$ 874	0.78	0.62	0.50	0.19
6	2004	CHF 1,435	0.805	$ 1,155	0.75	0.56	0.43	0.13
7	2005	CHF 2,146	0.802	$ 1,722	0.71	0.51	0.38	0.09
8	2006	CHF 3,927	0.798	$ 3,133	0.68	0.47	0.33	0.07
9	2007	CHF 4,852	0.833	$ 4,043	0.64	0.42	0.28	0.05
10	2008	CHF 5,092	0.923	$ 4,701	0.61	0.39	0.25	0.03
11	2009	CHF 5,266	0.921	$ 4,852	0.58	0.35	0.21	0.02
12	2010	CHF 5,429	0.959	$ 5,207	0.56	0.32	0.19	0.02
13	2011	CHF 5,253	1.128	$ 5,924	0.53	0.29	0.16	0.01
14	2012	CHF 5,889	1.065	$ 6,274	0.51	0.26	0.14	0.01
15	2013	CHF 6,079	1.078	$ 6,556	0.48	0.24	0.12	0.01
16	2014	CHF 6,275	0.955	$ 5,992	0.46	0.22	0.11	0.00
17	2015	CHF 6,538	0.963	$ 6,295	0.44	0.20	0.09	0.00

PV-1998 (5%)	**CHF 35,243**	**$ 32,498**
PV-1998 (10%)	**CHF 21,270**	**$ 19,159**
PV-1998 (15%)	**CHF 13,567**	**$ 11,912**
PV-1998 (40%)	**CHF 2,770**	**$ 2,131**

Herceptin

Herceptin Worldwide Annual Sales

k	Year	CHF Sales (M)	USD/CHF	USD Sales (M)	1/(1+R)^k , R = 5%	10%	15%	40%
18	2016	CHF 6,734	0.985	$ 6,635	0.95	0.91	0.87	0.71
19	2017	CHF 6,936	1.006	$ 6,976	0.91	0.83	0.76	0.51
20	2018	CHF 7,144	1.006	$ 7,185	0.86	0.75	0.66	0.36
21	2019	CHF 7,359	1.006	$ 7,401	0.82	0.68	0.57	0.26
22	2020	CHF 5,887	1.006	$ 5,921	0.78	0.62	0.50	0.19
23	2021	CHF 4,709	1.006	$ 4,737	0.75	0.56	0.43	0.13
24	2022	CHF 3,768	1.006	$ 3,789	0.71	0.51	0.38	0.09
25	2023	CHF 3,014	1.006	$ 3,031	0.68	0.47	0.33	0.07
26	2024	CHF 2,411	1.006	$ 2,425	0.64	0.42	0.28	0.05
27	2025	CHF 1,929	1.006	$ 1,940	0.61	0.39	0.25	0.03
28	2026	CHF 1,543	1.006	$ 1,552	0.58	0.35	0.21	0.02
29	2027	CHF 1,235	1.006	$ 1,242	0.56	0.32	0.19	0.02
30	2028	CHF 988	1.006	$ 993	0.53	0.29	0.16	0.01
31	2029	CHF 790	1.006	$ 795	0.51	0.26	0.14	0.01
32	2030	CHF 632	1.006	$ 636	0.48	0.24	0.12	0.01
33	2031	CHF 506	1.006	$ 509	0.46	0.22	0.11	0.00
34	2032	CHF 405	1.006	$ 407	0.44	0.20	0.09	0.00

PV-1998 (5%)	CHF 78,981	$ 76,356
PV-1998 (10%)	CHF 56,707	$ 54,674
PV-1998 (15%)	CHF 43,103	$ 41,498
PV-1998 (40%)	CHF 18,190	$ 17,541

Assumption: After 2019, sales decline by 20% per year

Herceptin

Does Upfront Investment Justify Potential Profits?

- Large investment over a lengthy period
- Risk is high at the start, but declines over time
- Profits are potentially significant, but very difficult to predict
- Risk and uncertainty: side effects, FX, competitors, etc.
- Cost of capital is key for: (1) discounting future profits; and (2) ongoing financing costs
- Careful financing can yield highly profitable drugs whereas poor financing can generate huge losses

Herceptin

Nature Reviews Drug Discovery 12(2013), 737–738.

NEWS & ANALYSIS

FROM THE ANALYST'S COUCH

Pharmaceutical forecasting: throwing darts?

Myoung Cha, Bassel Rifai and Pasha Sarraf

Image from fckncg/Alamy