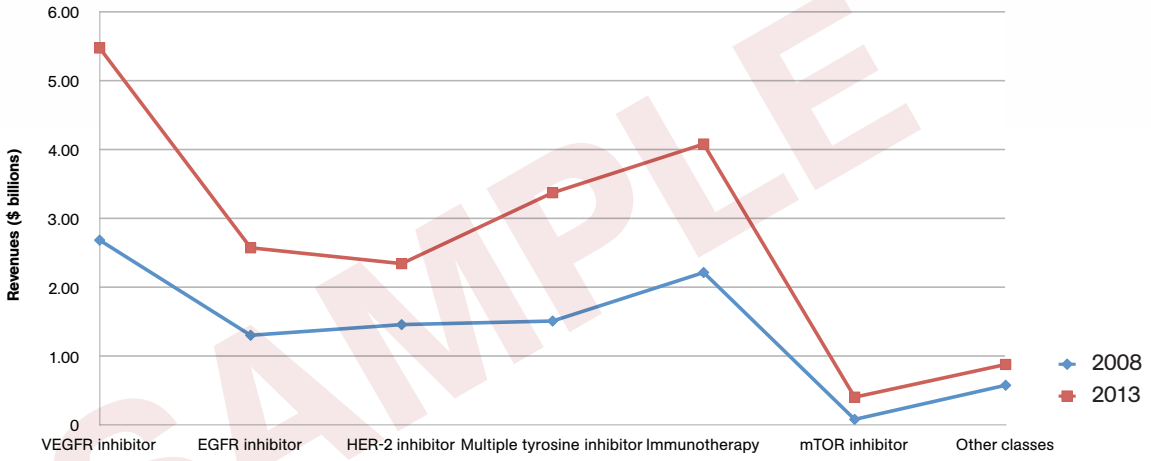
Immunotherapy

Rituxan, the first targeted drug, is the major driver for the immunotherapy segment with 2008 sales being more than $2.0 billion in the Unites States just for cancer treatment. Rituxan is mainly used in the treatment of non-Hodgkin's lymphoma. Bexxar and Zevalin are radioimmunotherapy agents and their contribution to this segment is minimal compared to the revenues generated by Rituxan. FDA approval for use of Rituxan in chronic lymphocytic leukemia as 1st line and for relapsed CLL is currently pending. Once Rituxan receives approval from the FDA on treating CLL, its demand will increase and so will the revenues and growth rate. With regards to Bexxar and Zevalin, their market share will continue to remain more or less the same and they will not threaten the sales of Rituxan.

By the end of the forecast period 2013, the immunotherapy segment of the targeted drugs will see a slight decrease in its market share, to 22 percent from 23 percent in 2008, mainly because of higher growth rates seen in other segments.

Figure 8. Targeted Therapeutics Market, Revenue Projection, 2008 and 2013



Rituxan

Introduction

Rituxan (rituximab) is the first targeted cancer drug approved by the FDA. It was approved in 1997 and since then has been a pioneer in the targeted therapy area for cancer treatment. Rituxan is approved by the FDA for treatment of various non-Hodgkins lymphoma and rheumatoid arthritis. It was developed by IDEC Pharmaceuticals, and now is marketed by Biogen Idec (Biogen acquired Idec Pharmaceuticals in 2003) and Genentech in the United States. After the acquisition of Genentech by Swiss drugmaker Roche, Rituxan is now marketed by Roche and Biogen Idec. Prior to the acquisition, Genentech held the marketing rights for Rituxan in the United States and Japan while Roche marketed it in Europe and remaining areas as MabThera.

Mechanism of Action (MoA)

Rituxan is a humanized, monoclonal antibody and belongs to the immunotherapy class of targeted drugs. Drugs belonging to this class attack the cancerous cells by stimulating the defense mechanism of the body. Rituxan binds itself to a particular protein called CD20 which is present in the surface of B-cells. The body's defense mechanism identifies it as an antigen and attacks the cells with CD20. The new stem cells generated from the bone marrow do not contain CD20 therefore, healthy B-cells regenerate after treatment.

Indications: Current and Future

Table 32. Rituxan : Current Indications, 2009

INDICATIONS APPROVED	LINE OF THERAPY
Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin's Lymphoma	Single agent
Previously untreated follicular, CD20 positive B-cell non Hodgkin's lymphoma	Combination with CVP (cyclophosphamide, vincristine, pre-chemodnisone)therapy
Non-progressing, low grade, CD20 positive, B-cell non Hodgkin's lymphoma	Single agent after first-line CVP chemotherapy
Previously untreated diffuse large B-cell, CD20 positive non-Hodgkin's lymphoma	In combination with CHOP (cyclophosphamide, doxorubicin/hydroxydoxorubicin, Vincristine, prednisone) or other anthracycline based chemotherapy regimens
Rheumatoid Arthritis (RA)	In adult patients suffering from moderately to severe active RA, in combination with methotrexate

Table 33. Rituxan: Future Indications, 2009

INDICATION	PHASE	PROJECTED FILING DATE
Chronic lymphocytic leukemia (1st line)	Filed	
Chronic lymphocytic leukemia (relapsed)	Filed	
Indolent non-Hodgkin's lymphoma maintenance, 1st line	3	2010
Rituximab and bevacizumab Diffuse large B-cell lymphoma	3	Post-2012

Competition

Herceptin is used in the treatment of HER-2 positive breast cancer. HER-2 positive breast cancers are more aggressive than other breast cancer types. They are also relatively resistant to hormone therapy. Herceptin has been found to be very successful in treating HER-2 positive breast cancer. In this area, Herceptin competes with GSK's Tykerb which also targets the HER-2 receptors. Herceptin is administered intravenously while Tykerb is an oral drug. While Herceptin has been in the market for more than a decade, Tykerb was introduced only in 2007. Until then, Herceptin was more or less the standard treatment option for HER-2 positive breast cancer along with chemotherapy and surgery. Tykerb has a long way to go to reach a Herceptin's position.

Market Revenues

Herceptin is used only for the treatment of HER-2 positive breast cancer. Approximately 25 to 30 percent of breast cancers are HER-2 positive. This leads to a considerably small number of patients for whom Herceptin is useful. That is one of the main reasons why Herceptin revenues are much smaller than its other Genentech counterparts. Hence the cumulative revenue increase in Herceptin over last 3 years has been a mere 5.8 percent, which is average for a cancer drug.

Introduction of GSK's Tykerb has put additional pressure on Herceptin in terms of market revenue. Prior to being approved in combination with chemotherapy, Herceptin had to fight against chemotherapy treatment options. Herceptin is patent protected until 2019 and has no competition from generic versions during the forecast period.

The following table shows the revenue projection for Herceptin during the period 2006 to 2013. Herceptin is expected to show steady growth but not with fancy growth rates. Roche is expected to file for approval for Herceptin in metastatic gastric cancer by early 2010. It is estimated to receive FDA approval by 2011. The drastic increase in sales of Herceptin will not be seen as Herceptin is being prescribed quite often for same indication in off label settings. Another indication in the pipeline which may get approved during the forecast period is the use of Avastin with Herceptin for metastatic breast cancer. By the end of the forecast period, Herceptin is expected to garner $1.985 billion in the United States.

Table 37. Herceptin Revenues: United States 2006 to 2013

	2006	2007	2008	2009	2010	2011	2012	2013
Revenues ($millions)	1,234	1,287	1,382	1,490	1,610	1,740	1,865	1,985

Market Revenues

In January 2009, ImClone and BMS withdrew its application for approval of NSCLC using Erbitux after the FDA raised some questions regarding the pharmacokinetics of the drug. ImClone, now a part of Eli Lilly and BMS were trying to expand Erbitux scope by adding non small cell lung cancer (NSCLC) to its list of approved indications. Instead, the FDA asked for more data from the companies to support Erbitux's treatment of head and neck cancer. In similar lines, the CHMP (Committee for Medical Products for Human Use) rejected Merck KGaA's plea for approval of Erbitux for NSCLC. The company is planning to submit the application again for reconsideration. This time, it hopes to get approval for Erbitux, if not as a first line, then at least for particular tumor types or indications.

The global sales of Erbitux are close to $1.5 billion making it a blockbuster worldwide. In the United States it is marketed by ImClone (now a part of Eli Lilly) and BMS. Outside the United States, Erbitux is marketed by German drug maker Merck KGaA. The sales shown in the table below are the US sales and obtained from the BMS annual report.

The sales of Erbitux are expected to increase but not with very high growth rates. The rejection of NSCLC indication is a big blow to BMS and especially to Eli Lilly which has pinned high hopes on ImClone's oncology drugs. The drug may reach blockbuster status in the United States by 2012. Erbitux will lose its patent protection by 2017. Erbitux will face stiff competition from Vectibix in the colorectal cancer and head and neck cancer area once that indication is approved. Erbitux revenues decreased in 2009 due to the additional wild KRAS condition for patients. However, the sales are expected to pick up over the forecast period. By the end of the forecast period, 2013, Erbitux sales in the United States are expected to reach $1.180 billion.

Table 52. Erbitux Sales: United States, 2006 to 2013

	2006	2007	2008	2009	2010	2011	2012	2013
Revenues ($millions)	646	683	739	690	775	820	1,025	1,180