Oncology
Changing Market Dynamics
February, 2010
Oncology – a new market dynamic on the horizon

Historically, oncology has been an area of significant sales growth due to favorable factors, such as a cooperative FDA, premium pricing, and prevalent off-label usage.

However, we see signs of change…

- New drugs and indications are crowding the market
- Payors are having a greater impact on drug utilization
  - “Traditional” tools such as tiered co-payments, prior authorization and step-edits are being used more aggressively throughout the industry
- The industry is responding as well with price caps and pay for performance arrangements

Overall, we believe industry participants need to pay close attention to these signals, and position themselves for a new market dynamic.
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Oncology agents have experienced exceptional market growth

Overview

- Oncology products have grown at more than double the rate of global pharmaceuticals, with a CAGR of 8.39% during 2004–08
- Reasons for the robust growth of the oncology market:
  - Increased use of targeted therapeutics, including more patients accessing modern targeted therapies in emerging markets
  - Premium pricing for targeted brands as compared to cytotoxic therapies and antihormonal therapies
  - Longer treatment duration for patients due to longer survival and adjuvant treatment
  - Earlier detection of disease with the availability of new screening procedures

Note: Projections are extrapolated based on IMS prediction of 3-6% of CAGR till 2012; we have assumed a CAGR of 4.5% till 2012

Source:
- b“Top 15 Global Therapeutic Classes”, IMS Health, March 2009
- c“IMS Health forecasts double-digit growth of cancer drugs”, IMS Health Website, May 15, 2008
- e“Nuovifarmacie vecchitrend diconsumo: unapanoramicaeuropea”, IMS Presentation
- f“Booming oncology market redefines relations between manufacturers and healthcare payers, providers”, Pharmaceutical Commerce Magazine, August 2008
- g“IMS Health Lowers 2009 Global Pharmaceutical Market Forecast to 2.5 – 3.5 Percent Growth”, IMS Press Release, April 22, 2009
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Recent events raise the possibility that this market dynamic is changing

1. New drugs and new indications are crowding the market

2. Payors are more aggressive in managing Biologics

3. New Pricing Pressures

4. Shift to orals enables traditional utilization controls
The pipeline for new targeted therapies is significant

Note: Late Stage Pipeline includes only those drugs which are either in Phase III or pre-registration stage of development
Source: Grail Research; PharmaProjects database (accessed in August 2009)
Many compounds focus on the same biology

Competitive intensity is increasing as companies target similar mechanisms

### Current Level of Competition

<table>
<thead>
<tr>
<th>EGFR Antagonist</th>
<th>Expected Near Term Competition</th>
<th>Expected Long Term Competition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herceptin (trastuzumab)</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>ERBITUX (cetuximab)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vectibix (panitumumab)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| VEGFR Antagonist | | |
|-----------------| | |
| AVASTIN (bevacizumab) | 2 | 12 |

| Tyrosine Kinase Inhibitors | | |
|---------------------------| | |
| Tarceva (erlotinib) | 9 | 9 |
| Nexavar (sorafenib) tablets | | |
| Tykerb (lapatinib) | | |

Note: The dates mentioned in the chart are approval dates and not the launch dates; ¹Represents the number of molecules in phase III / Pre-registration / Registration stage of development for relevant indications; ²Represents the number of molecules in phase I / II of development; Above mentioned data represent the primary pharmacology action for the marketed and pipeline molecules (a molecule can target more than one receptors; however, we have only considered the primary target in this analysis)

Sources: FDA website, Company website; PharmaProjects database; Grail Analysis
Adding indications to existing drugs increases competition

Expansion of existing agents

- **Gleevec**: 5 Early Stage, 13 Late Stage, 1 Approved
- **Avastin**: 5 Early Stage, 10 Late Stage, 2 Approved
- **Revlimid**: 1 Early Stage, 2 Late Stage, 13 Late Stage, 2 Approved
- **Erbitux**: 2 Early Stage, 3 Late Stage, 10 Late Stage, 1 Approved
- **Sutent**: 2 Early Stage, 5 Late Stage, 8 Late Stage, 1 Approved
- **Tykerb**: 1 Early Stage, 3 Late Stage, 7 Late Stage, 1 Approved
- **Tarceva**: 2 Early Stage, 3 Late Stage, 4 Late Stage, 1 Approved
- **Nexavar**: 2 Early Stage, 2 Late Stage, 3 Late Stage, 1 Approved
- **Vectibix**: 1 Early Stage, 2 Late Stage, 3 Late Stage, 1 Approved
- **Torisel**: 1 Early Stage, 3 Late Stage, 1 Approved
- **Herceptin**: 1 Early Stage, 1 Late Stage, 1 Late Stage, 1 Approved
- **Rituxan**: 1 Early Stage, 1 Late Stage, 1 Approved

Note: Late Stage pipeline include molecules in registration / pre-registration / phase III of development. Early Stage pipeline include molecules in phase I or II of development.

Source: PharmaProjects; Clinical Trials Website; Company Websites; “Top 20 Cancer Brands”, Datamonitor
Many indications will soon have multiple targeted therapies

### LATE STAGE PIPELINE

<table>
<thead>
<tr>
<th>Year</th>
<th>Lymphoma</th>
<th>Breast Cancer</th>
<th>Leukemia</th>
<th>NSCLC</th>
<th>Colorectal Cancer</th>
<th>Kidney Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>Rituxan (CD20 antagonist)</td>
<td>Herceptin (EGFR Antagonist)</td>
<td>Mylotarg (DNA antagonist)</td>
<td>Iressa (TKI)</td>
<td>Avastin (VEGFR Inhibitor)</td>
<td>Nexavar (B-raf kinase inhibitor)</td>
</tr>
<tr>
<td>1998</td>
<td>Zevalin (DNA antagonist)</td>
<td></td>
<td>Gleevec (Bcr-Abl inhibitor); Campath (Lymphocyte inhibitor)</td>
<td>Tarceva (TKI)</td>
<td>Erbitux (EGFR Antagonist)</td>
<td>Sutent; Nexavar; Aflibercept; Vectibix (EGFR Antagonist)</td>
</tr>
<tr>
<td>2000</td>
<td>Bexxar (DNA antagonist)</td>
<td></td>
<td></td>
<td>Avastin (VRGF Antagonist)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>Velcade (Proteasome inhibitor)</td>
<td>Tykerb (TKI)</td>
<td>Sprycel (Bcr-Abl inhibitor)</td>
<td>Tarceva (TKI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td></td>
<td>Avastin (VRGF Antagonist)</td>
<td>Tassigna (Bcr-Abl inhibitor)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td></td>
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<tr>
<td>2004</td>
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<td>2005</td>
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<td>2006</td>
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<td>2007</td>
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<tr>
<td>2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>Revlimid; Torisel; Campath; Afutuzumab; Galiximab; Ofatumumab; Enzastaurin</td>
<td>Sutent; Ramucirumab; BSI-201; Pazopanib; Herceptin-DM1; Omnitarg; Neratinib; BIBW-2992</td>
<td>Revlimid; Rituxan; Alvocidib; Midostaurin; Lestaurnib; Lumiliximab; Genasense; Ofatumumab; Zanesta; Bosutinib</td>
<td>Erbitux; Sutent; Nexavar; Aflibercept; Vadimezan; Telcyta; Figitumumab; Motesanib; Pazopanib; Recentin; BIBW-2992; Enzastaurin; Zactima; Vargatef</td>
<td>Tarceva; Sutent; Aflibercept; Brivanib Alaninate; Recentin</td>
<td>Axitinib; Pazopanib; Anyara; Rencarex</td>
</tr>
</tbody>
</table>

Note: Late Stage Pipeline includes only those drugs which are either in Phase III or pre-registration stage of development

Source: Grail Research; PharmaProjects database (accessed in August 2009)
More aggressive use of utilization tools is underway

<table>
<thead>
<tr>
<th>Management strategy</th>
<th>Commercial health plans</th>
<th>Medicare advantage plans</th>
<th>Managed Medicaid plans</th>
<th>PBMs$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of plans using the tool in 2008</td>
<td>Incremental % of plans to use the tool in 2011</td>
<td>% of plans using the tool in 2008</td>
<td>Incremental % of plans to use the tool in 2011</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td>36.4%</td>
<td>14.5%</td>
<td>43.5%</td>
<td>17.4%</td>
</tr>
<tr>
<td>Step Therapy</td>
<td>14.5%</td>
<td>23.6%</td>
<td>13.0%</td>
<td>30.4%</td>
</tr>
<tr>
<td>Prior Authorization by Diagnosis</td>
<td>56.4%</td>
<td>7.3%</td>
<td>60.9%</td>
<td>13.0%</td>
</tr>
<tr>
<td>Prior authorization by test results</td>
<td>34.5%</td>
<td>21.8%</td>
<td>21.7%</td>
<td>30.4%</td>
</tr>
<tr>
<td>Coinsurance cost share</td>
<td>29.1%</td>
<td>12.7%</td>
<td>56.5%</td>
<td>13.0%</td>
</tr>
</tbody>
</table>

Note: $^1$PBM is Pharmacy benefit management; $^2$Survey group include Commercial health plans (N=55), Medicare Advantage plans (N=23), Managed Medicaid plans (N=17), PBMs (N=11)

The cost of cancer therapy is increasing as patients shift to newer, more expensive therapies

New drugs cost more and are increasing share

Utilization of Newer therapies is increasing

New Therapies cost more

The Cost of Treating Cancer is Increasing

Source: 

"The Oncology Pipeline: Maturing, Competitive, and Growing?", Oncology Business Review, Sep 2008; "Limits on Medicare's Ability to Control Rising Spending on Cancer Drugs", NEJM Article, February 5, 2009; "Managed Care Oncology Magazine, Q3 2008 Issue"
At the same time, drug benefits may seem modest relative to cost

Some of the newly-approved brands cost USD 150-500K per life year gained

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Indication</th>
<th>Year of Approval</th>
<th>Incremental Benefit</th>
<th>Incremental Cost of Therapy (USD)</th>
<th>Cost / Life Year Gained (LYG) (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avastina(^a)</td>
<td>Roche</td>
<td>Breast Cancer</td>
<td>2008</td>
<td>4 months survival</td>
<td>50,000</td>
<td>150,000</td>
</tr>
<tr>
<td>Tykerb(^b)</td>
<td>GSK</td>
<td>Breast Cancer</td>
<td>2007</td>
<td>0.127 months survival</td>
<td>21,484</td>
<td>169,165</td>
</tr>
<tr>
<td>Ixempra(^c)</td>
<td>BMS</td>
<td>Breast Cancer</td>
<td>2007</td>
<td>1.96 months survival</td>
<td>30,900</td>
<td>189,184</td>
</tr>
<tr>
<td>Avastin(^b)</td>
<td>Roche</td>
<td>Non-small Cell Lung Cancer</td>
<td>2006</td>
<td>2.3 months survival</td>
<td>66,270–80,343</td>
<td>345,757–419,181</td>
</tr>
<tr>
<td>Tarceva(^b)</td>
<td>OSI Pharmaceuticals / Roche</td>
<td>Pancreatic Cancer</td>
<td>2005</td>
<td>0.4 months survival</td>
<td>12,156–16,613</td>
<td>364,680–498,390</td>
</tr>
<tr>
<td>Erbitux(^b)</td>
<td>BMS</td>
<td>Colorectal Cancer</td>
<td>2004</td>
<td>1.44 months survival</td>
<td>21,954</td>
<td>182,950</td>
</tr>
</tbody>
</table>

Notes: \(^1\)LYG costs have been derived
Source: \(^a\)New York times; \(^b\)American Society of Clinical Oncology (ASCO); \(^c\)Journal of Clinical Oncology
This has led to a new and public discussion about the cost/benefit of these new therapies.

Commentary in the press

**New York Times, July 2008** - Cost effectiveness of Avastin - “It’s absolutely critical that we start having a public discussion,” said Barbara Brenner, executive director of Breast Cancer Action, an advocacy group. “I think of Avastin as a model that is showing us where the problem is.”

**Bloomberg News, June 2009** - “Eli Lilly & Co.’s tumor-fighter Erbitux doesn’t prolong lung cancer patients’ lives enough to justify its $80,000 cost, U.S. scientists said in commentary published today. Erbitux added to other cancer drugs extends survival about 1.2 months more than chemotherapy alone, making the price too high for a ‘marginal benefit,’ commentary in the Journal of the National Cancer Institute said.”

**Medscape, May 2009** - ‘Ixabepilone (Ixempra) for metastatic breast cancer is an example of a cancer drug that adds ‘a small benefit at a high cost,’ says an editorial in the May 1 edition of the Journal of Clinical Oncology. The editorial accompanies a new cost-efficacy study in the same issue of the journal that found that the addition of ixabepilone to capecitabine (Xeloda) adds about $31,000 to the overall medical costs of metastatic breast cancer while providing about 1 more month of ‘quality-adjusted’ survival.”

**The Independent, August 2008** - “The National Institute for Health and Clinical Excellence (NICE) issued draft guidance rejecting the drugs Sutent (sunitinib), Avastin (bevacizumab), Nexavar (sorafenib) and Torisel (temsirilimus)”

“The guidance rejects the drugs because they are not cost effective.”

**The Wall Street Journal, March 2009** - “Expert advisers in the U.K. are sticking with their view that GlaxoSmithKline’s Tykerb is too costly to justify routine use in women with advanced breast cancer. The British government’s National Institute for Health Effectiveness, or NICE, put out a final appraisal that said Tykerb hadn’t ‘demonstrated that it was cost effective’ in comparison with other treatments. It put forth a similar view last summer.”

Sources:

Companies are reacting with price caps...

Examples of price cap initiatives

- Genentech capped Avastin at USD 55,000/year for patients with a household income less than $75,000 a year\(^d\)

- Patients who spend over USD 10,000/month become eligible for free or discounted drugs through a charitable program\(^a\)

- In Oct. 2006, Genentech announced a price cap on Avastin based on a patient’s income\(^a\)

- In Sept. 2006, Amgen instituted a price cap on Vectibix at $4,000 per dose (20% lower than BMS’s Erbitux)\(^d\)

- In May 2006, BMS announced a price cap on Erbitux for patients that reach a monthly threshold

- The UK government (NICE) uses cost/benefit analysis in evaluating drugs\(^c\)

- A threshold of GBP 30,000 per quality-adjusted life year (QALY) is used in evaluating drugs for reimbursement\(^c\)

- If patients spend more than 5% of their annual gross income on copayments, then they become eligible for free drugs through an assistance program\(^b\)

Sources: 
\(^a\)“Contracting, rebating, risk-sharing – IMS Conference hears about more innovative approaches to pricing”, IMS Global Insights; 
\(^b\)“Managed Care Best Practices in Oncology Management”, Conference report, November 2006; 
\(^d\)“Top Of The Cancer Market?”, Forbes, October 2006
... and pay for performance arrangements

*Drug companies are increasingly offering discounts to insurers based on drug performance rather than quantity of drug utilized*¹

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**Pay for Performance Examples**

- In 2001 Pfizer convinced the State of Florida to put all its drugs on the state's Medicaid formulary. In return Pfizer agreed to rebate a portion of drug costs if its drugs failed to generate long-term cost savings across the healthcare systemᵃ
  - This model worked for Pfizer, enabling the company to avoid up-front discounts and back-end rebates, while saving the State of Florida USD 41.9MM in other healthcare costsᵃ

- In 2007, after the NHS in Britain decided not to pay for the cancer drug Velcade, Johnson & Johnson offered a money-back guarantee if Velcade failed to reduce tumors by at least 25%ᵇ,c
  - Through this Pay for Performance strategy, the NHS designated Velcade as cost-effective for up to four cycles of treatmentᶜ

- In 2007, United Healthcare entered into a risk sharing agreement with Genomic Health. The company sells Oncotype DX®, a USD 3,460 genetic test that determines whether an early-stage breast cancer patient would benefit from chemotherapyᶜ
  - United Healthcare agreed to pay for the test for 18 months, on grounds that it would seek a price negotiation if the test failed to have the intended medical impactᶜ

- In 2009, in response to a negative UK NICE appraisal, Merck offered to refund the primary care cost of its drug Erbitux, if a patient did not respond within 6 weeksᵈ

- In 2009, when Tarceva was declared cost ineffective by NICE, Roche offered a rebate for the cost difference between Tarceva and the incumbent NSCLC treatmentᵈ

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¹Pay for Performance is more popular in Europe. US, insurers have less leverage with drug makers because of tough state regulations and marketplace pressures.

Companies are also conducting head-to-head trials in order to demonstrate superiority for their agent over alternatives. 

The crowded market is resulting in increased pressure on drug companies to conduct head-to-head trials to prove that their product is better than the competitor’s product.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Condition</th>
<th>Trial Sponsor</th>
<th>Expected Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zactima vs Tarceva&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Second line NSCL Cancer</td>
<td>Astrazeneca</td>
<td>Results were expected in September 2009; Regulatory submissions withdrawn</td>
</tr>
<tr>
<td>Recentin vs Avastin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>First line metastatic Colorectal Cancer</td>
<td>Astrazeneca</td>
<td>May 2011</td>
</tr>
<tr>
<td>Sutent vs. Avastin&lt;sup&gt;1,b&lt;/sup&gt;</td>
<td>First line metastatic Breast Cancer</td>
<td>Pfizer</td>
<td>Halted in June 2009</td>
</tr>
<tr>
<td>Sprycel vs Gleevec&lt;sup&gt;2,c&lt;/sup&gt;</td>
<td>First line CML</td>
<td>Bristol-Myers Squibb</td>
<td>Complete</td>
</tr>
<tr>
<td>Tykerb vs Herceptin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Adjuvant Breast Cancer</td>
<td>GlaxoSmithKline</td>
<td>May 2013</td>
</tr>
</tbody>
</table>

Note: <sup>1</sup> Trial halted in June 2009 as better survival rates could not be established; <sup>2</sup> FDA approved Sprycel for treatment of CML since the study established better survival rates in Gleevec-resistant patients. The drug fulfills the need for second line treatment. 

Source: <sup>a</sup>Clinicaltrial.gov, <sup>b</sup>“Pfizer halts Sutent breast-cancer trial”, fiercepharma.com, June 2009; <sup>c</sup>“FDA Grants Full Approval For SPRYCEL For The Treatment Of Adults With Chronic Myeloid Leukemia”, MedicalNewsToday, May 2009.
Greater use of oral therapeutics is changing oncology

Unlike the overall industry, orals are gaining share in Oncology

Percentage of Worldwide Rx & OTC Pharmaceutical Sales from Biotech vs. Conventional Technology

Share of Biologics Within Top 100 Products

Oncology Market for Targeted Therapies: Biologics vs. Conventional Technology

Oral oncologics are managed using traditional utilization tools...

Traditional tools such as tier status, prior authorization, quantity limits and co-payments are being adopted for oral oncologics

Formulary Status of Oral Oncology Brands

<table>
<thead>
<tr>
<th>Drug</th>
<th>% of Plans with Drug on Formulary</th>
<th>Primary Tier Placement</th>
<th>% of Plans: Prior Authorization</th>
<th>% of Plans: Quantity Limits</th>
<th>Primary Cost-Sharing Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleevec</td>
<td>100%</td>
<td>4</td>
<td>70%</td>
<td>29%</td>
<td>26% - 35%</td>
</tr>
<tr>
<td>Sutent</td>
<td>100%</td>
<td>4</td>
<td>62%</td>
<td>32%</td>
<td>26% - 35%</td>
</tr>
<tr>
<td>Tarceva</td>
<td>100%</td>
<td>4</td>
<td>62%</td>
<td>32%</td>
<td>26% - 35%</td>
</tr>
<tr>
<td>Thalomid</td>
<td>100%</td>
<td>4</td>
<td>68%</td>
<td>25%</td>
<td>26% - 35%</td>
</tr>
<tr>
<td>Tykerb</td>
<td>100%</td>
<td>4</td>
<td>74%</td>
<td>42%</td>
<td>26% - 35%</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>100%</td>
<td>1</td>
<td>0%</td>
<td>2%</td>
<td>$ 0 - $10</td>
</tr>
</tbody>
</table>

Note: 1Selected drugs include Gleevec, Sutent, Tarceva, Thalomid, Tykerb and Tamoxifen (Data from November 2008 for Medicare Part D plan)
... and this trend is increasing over time

PDP’s are increasing the use of traditional utilization tools such as prior authorization and co-payments

PDP’s\(^1\) Requiring Prior Authorization, 2006–2009\(^a\)

- PDPs are increasing the use of prior authorization to control access to branded cancer drugs\(^a,b\)
  - However, the administrative burden of obtaining prior authorization is high, and the process is time-consuming for payers and providers\(^b\)

% Coinsurance Amount, 2006-2009\(^a\)

- PDPs are shifting the cost burden to the patients by gradually increasing co-insurance amounts for brand-name oral anticancer drugs\(^a\)

Note: \(^1\)PDP’s are Prescription Drug Plans; \(^2\)2006 data omitted for Tykerb because the Food and Drug Administration (FDA) approved the drug in March 2007
Source: \(^a\)"Cost Sharing for Cancer Patients in Medicare, 2009", Avalere Health and American Cancer Society Cancer Action Network, December, 2008; \(^b\)"Oncology trends report", NCCN
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Case Studies: Close But Not Yet

- We are clearly seeing different dynamics in the oncology market than we have historically.

- However, we have not yet seen significant competition driven solely by pricing. This is a scenario which could emerge when there are multiple, largely equivalent agents available in the marketplace.

- To date, potential competitive situations (Erbitux vs Vectibix, Nexavar vs Sutent and Tykerb vs Herceptin) have resolved quickly with clear winners based on clinical data, labeling, and physician preference (not payor pressure).
## Case Study 1 – Vectibix position to displace the similar Erbitux was thwarted by clinical data

### Erbitux vs Vectibix

#### Scenario at Launch

- Erbitux was launched by BMS/Imclone in 2004 for metastatic colorectal cancer patients\(^1\)
- Vectibix was launched in September 2006 by Amgen for metastatic colorectal cancer patients\(^2\)
  - Analysts expected that Vectibix would replace Erbitux as a treatment for colon cancer\(^a,b\)
- Both Vectibix and Erbitux are antibody-based therapies that are administered intravenously; however Vectibix had a few potential advantages
  - More convenient (every other week) administration and lower cost (20% discount) compared to Erbitux\(^b\)
  - Lower frequency of infusion reactions (1% compared to 3% for Erbitux)\(^i,j\)
- Sales of Vectibix in 2006 (Oct-Dec) were USD 39MM and the company was upbeat about the future\(^c\)
- Analysts at Merrill Lynch predicted that Vectibix would eventually take 60% of Erbitux’s market. They also lowered their projected sales figures for Erbitux for 2008-2010\(^d\)

#### What Happened?

- In March 2007, Amgen discontinued a trial of Vectibix due to 231 cases of death or disease progression. Vectibix sales in the second quarter of 2007 fell from USD 51MM to USD 46MM\(^e,f\)
- Erbitux maintained steady growth even after the launch of Vectibix
  - The total number of patients treated with Erbitux increased in October 2007, and market share rose to 14.8% in that month\(^g\)
  - Vectibix did not show any month-to-month market share increase (in October 2007) and was underperforming according to analysts\(^g\)
- In 2009, label changes for both Erbitux and Vectibix were implemented; these are expected to narrow the eligible pool of patients for both the drugs by up to 40%\(^h\)

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**Note:**

- \(^1\)Approved as a single agent for EGFR-expressing metastatic colorectal cancer after failure of both irinotecan- and oxaliplatin-based regimens or in patients who are intolerant to irinotecan-based regimens OR used in combination with irinotecan, EGFR-expressing metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy
- \(^2\)Approved as a single agent for the treatment of metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy regimens
- Source: \(^a\)Press release, September 27, 2006, Amgen company website; \(^b\)“Vectibix Will be EGFR Antibody of Choice for Colon Cancer Therapy”, October 6, 2006, GLG group website; \(^c\)Analyst conference summary of Amgen quarter results, January 27, 2007, Openicon website; \(^d\)“Amgen wins approval for colorectal cancer drug”, September 28, 2006, Marketwatch website; \(^e\)“Amgen Discontinues Vectibix(TM) Treatment in PACCE Trial Evaluating Vectibix(TM) as Part of Triple Combination Regimen”, March 23, 2007, Biotechnology-europe website; \(^f\)Press Release, July 26, 2007, Pfizer company website; \(^g\)Monthly oncology regimen report through September 2007, Rodman & Renshaw, Inc., October 22, 2007; \(^h\)“New US labelling for Erbitux and Vectibix recommends against their use for large subset of colorectal cancer patients”, July 20, 2009, Scripnews website; \(^i\)“Vectibix(R) Now Available For The Treatment Of Advanced Colorectal Cancer In Belgium”, October 03, 2008, Medicalnewstoday website; \(^j\)Erbitux website
Case Study 2 – In another potential head-to-head battle, physicians chose Sutent over Nexavar

Nexavar vs Sutent

Scenario at Launch

- Nexavar was launched by Bayer/Onyx in December 2005 for advanced renal cell carcinoma
- Sutent was launched by Pfizer in 2006 for the same indication
- Direct competition was expected:
  - Datamonitor forecasted Nexavar revenues would reach USD 122MM and Sutent would reach USD 179MM by 2010
  - Although Nexavar had a first-to-market advantage, Sutent was expected to have superior efficacy
  - Nexavar on the other hand, was expected to have better tolerability – side-effects were limited mainly to blistering and rashes
- Cost of treatment was similar for both Sutent and Nexavar at USD 4,600 per treatment/month

What Happened?

- Sutent rapidly captured over 50% market share in renal cell carcinoma for all lines of therapy (July 2006)
  - Sutent became the standard therapy for first-line treatment of mRCC after launch
  - Nexavar competed more successfully in second line therapy with 35.1% patients receiving Sutent and 32.4% receiving Nexavar (October 2007)

Renal Cell Carcinoma Market share (All stages/ All lines)

Note: 1 Sutent is a kinase inhibitor indicated for the treatment of: (i) Gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate (ii) Advanced renal cell carcinoma; 2 Nexavar is a kinase inhibitor indicated for the treatment of advanced renal cell carcinoma

Case Study 3 – Tykerb could not displace Herceptin without more data and a better label

Tykerb vs Herceptin

Scenario at Launch

- Herceptin was the first targeted therapy to be launched for the treatment of breast cancer in 1998
- Tykerb (oral therapy) was launched in 2007 as combination therapy with capecitabine (Xeloda), for the treatment of patients with advanced or metastatic breast cancer (mBC) with HER2 over-expression and who progressed on prior therapy including an anthracycline, a taxane, and Herceptin
  - Tykerb was approved in a second or third line setting
  - At the time of launch, GSK marketed Tykerb as a more convenient and user-friendly oral therapy
- Expectations for Tykerb were mixed at the time of launch:
  - Some analysts expected the drug to achieve blockbuster status by 2010. Analysts assumed that drug would be effective in difficult to treat patients and patients with brain metastases, Tykerb was expected to gain share in first line and adjuvant settings.
  - Others predicted Tykerb’s use would be limited until it demonstrated significant benefits when added to Herceptin.
  - Analysts forecasted Tykerb sales to reach USD 104 MM in 2008
- At the time of launch, analyst expected the biggest sales opportunity for Tykerb to be in the adjuvant setting in the breast cancer market

What Happened?

- Tykerb reported modest global sales of USD 145.3MM in 2008
  - Sales were far behind Herceptin’s, which recorded global sales of USD 1.82 billion in 2008
- Factors contributing to Tykerb’s limited revenues were:
  - In August 2007, a study conducted by Decision Resources suggested that oncologists did not prefer Tykerb as a replacement for Herceptin. Instead they were only using it as an alternative for Herceptin-refractory patients in the treatment of advanced breast cancer
  - 58% of oncologists opined that they would favor IV Herceptin over Tykerb because the administration of IV drugs remains an important source of income for their practice
- To boost revenues from Tykerb in breast cancer, the company decided to expand use of Tykerb in an adjuvant setting:
  - As of April 2007, GSK was studying Tykerb for its application in adjuvant breast cancer: “We are dedicated to the further study and development of Tykerb in a variety of settings, including adjuvant breast cancer as well as in other solid tumor types”
    - Paolo Paoletti, MD, Oncology Medicine Development Center,GSK
  - GSK launched a head-to-head trial of Tykerb versus Herceptin in adjuvant breast cancer in 2008. Results for this trial are expected by May 2013
  - In April 2009, GSK submitted an application to expand Tykerb use for first-line treatment of metastatic breast cancer

Note: 1Reported as £ 62 million, conversion factor used as on November 16, 2009
Source: *Analysts raise NPVs of Promacta and Rezonic; Tykerb still star of GSK oncology pipeline*, Goliath Business News, July 2007; *Bear Stearns report September 21, 2007; *PR News wire August 14, 2007; *GSK Annual Report, 2008; Grail analysis; *Drugs @ FDA; *Clinicaltrial.gov; *komenozark.org; *Genentech Website; *GSK press release; *Tykerb Approved for Metastatic HER2+ Breast Cancer*, cancernetwork.com, April 2007; *Glaxo's Tykerb still has some convincing to do*, Evaluate Pharma, March 2008
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- While direct, payor-driven competition among oncology agents has not yet arrived, manufacturers need to be prepared for changes in the oncology market.

- Manufacturers may want to conduct head-to-head trials, or define market subsets where they can demonstrate superiority to potential alternative agents.

- Manufacturers may also want to consider scenarios where there are multiple agents with similar therapeutic profiles available for a given indication.
For More Information Contact:

Grail Research
(info@grailresearch.com)