Business Intelligence Analysis: Focus on Renal Cell Carcinoma

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Larry Gorkin, president of Gorkin & Cheddar Consulting, provides thought-provoking rhetoric through his myriad of written reports. Larry has agreed to present new and upgraded versions through Stelerix.com. Larry specializes in the critical review of competitive landscapes for developmental drugs and launched products to treat 27 chronic and diverse disease states, including non-small cell lung cancer, acute coronary syndrome, type 2 diabetes, rheumatoid arthritis, and Alzheimer’s disease. The aim is to determine which developmental drugs can be viable competitors in a particular indication. He has also analyzed decision-making by the United Kingdom’s National Institute for Health and Clinical Excellence (NICE) regarding cost effectiveness of agents to treat these and other disorders. He also wrote content for economic models of cost effectiveness for critical decision-making (e.g., shift from Phase II to Phase III, licensing opportunities). Prior to starting his own firm, Larry, a clinical psychologist by training, spent over 13 years developing his analytic skills at Pfizer, from 1996 to 2009.

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Question: What Percent of Current Revenue of Bayer/Onyx’s Nexavar (sorafenib) is generated by the Renal Cell Carcinoma Indication versus the Hepatocellular Carcinoma Indication, utilizing Pfizer’s Sutent (sunitinib) as a Historical Control?

Executive Summary

This report set out to explore what percent of current revenue of Bayer/Onyx’s Nexavar (sorafenib) is generated by the advanced renal cell carcinoma (RCC) indication versus the advanced hepatocellular carcinoma (HCC) indication, utilizing Pfizer’s Sutent (sunitinib) as a historical control. Nexavar was approved commercially to treat RCC, and then received supplemental labeling to treat HCC. Both Sutent and Nexavar have failed to demonstrate significant efficacy the “big four” solid tumors (i.e. lung, female breast, prostate and colorectal), and Sutent has failed in HCC, more commonly known as liver cancer.

Following launch within months of one another (circa the first quarter of 2006, 1Q06), the global revenue for Nexavar and Sutent was comparable in 2010, with totals of $1.07 billion for Sutent versus $934 dollars for Nexavar. The relative difference is about 15% from Sutent to Nexavar, and slightly higher the other way. Epidemiology would suggest that approximately 90% of the patients prescribed Sutent would be diagnosed with advanced RCC, given two other approvals in rare cancers: the digestive cancer, gastrointestinal stromal tumor, GIST, and pancreatic neuroendocrine tumors (NET) cancer.

Nexavar, in contrast, has two vital streams of potential revenue, from RCC and HCC. Given that Sutent failed in a head-to-head study versus Nexavar in the treatment of advanced HCC (Bloomberg.com, 4/23/10), one might assume that HCC is a significant contributor to Nexavar but not to Sutent revenue. Given that market share data (cf. IMS analysis) is unreliable involving branded drugs with multiple indications, arguably the best test of this line hypothesis would be to test the slope of revenue increases for Nexavar, in terms of changes before and after the approval of HCC in 4Q07, and relative to the historical control of revenue from Sutent.
One would have expected a divergence in the slopes, reflecting the additional revenue from the HCC indication. Instead, there was an initial “bump”, but no sustained, marked stream of revenue following the HCC indication for Nexavar. Indeed, in 1Q11, Bayer provided a conservative prospective regarding limited growth for Nexavar in 2011 (jpmorgan/Vosser, 3/23/11).

The percentage of 2010 revenue for Nexavar from RCC versus HCC was estimated based on data involving US market share and line of therapy usage (discounting that branded drugs with multiple indications yield less reliable results), greater competition from newer agents, global epidemiology, Pfizer detailed global revenue data for Sutent, clinical response rates to targeted therapies, and the novel slope analysis of quarterly global revenue changes pre- and post-HCC approval for Nexavar. Accordingly, Nexavar revenue in the US was estimated at $145 million, about 25% of total sales. The bulk, from international sales, were then derived, recognizing that RCC is more prevalent and HCC is less prevalent in the US than internationally. An additional $361 million in international sales of Nexavar was in RCC. Given total 2010 sales for Nexavar were $934 million, this implied that $428 million (45.8%) was derived from the HCC indication, with $506 million (54.2%) of Nexavar global revenue in 2010 derived from RCC. Given the associated variability in estimates, the contributions to revenue of Nexavar are not likely to represent a statistically significant difference.

The report notes the growing importance of emerging markets in Asia, wherein 2/3 of the 600,000 annual cases of liver cancer are diagnosed. Not as quickly as some express, but by the end of this decade, higher rates of HCC in Asia, and the increasing ability of the Asian governments or their residents to pay out-of-pocket, may propel markedly higher global sales of Nexavar relative to Sutent.

**Background**

**Nexavar**

Nexavar (sorafenib) is a multikinase inhibitor targeting a number of serine/threonine and receptor tyrosine kinases. Inhibition of these systems inhibits division and growth of tumor cells and potentiates cellular apoptosis.}

Mechanism of Action, Nexavar:

Nexavar is a multikinase inhibitor targeting a number of serine/threonine and receptor tyrosine kinases. Nexavar inhibited the kinase activity of both C-RAF and B-RAF. Inhibition of these systems inhibits division and growth of tumor cells and potentiates cellular apoptosis.
Sutent

Pfizer’s Sutent (sunitinib) is an oral, multiple tyrosine kinase inhibitor of fms-like tyrosine kinase 3 (Flt3), Kit, vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) receptors. Anti-cancer effects are generated via these targeted mechanisms that include anti-angiogenesis, as well as anti-proliferative effects on cancer cells (Polyzos, 2008).

Sutent is indicated to treat a pair of oncology indications: advanced renal cell carcinoma (RCC) and gastrointestinal stromal tumors (GIST) refractory to or following relapsed treatment with Novartis’ Gleevec (imatinib). The recommended initial dose regimen is 50-mg once daily for four weeks, followed by two weeks off-treatment. Dose may be adjusted up or down in 12.5-mg increments, based on patient response and tolerability. Sutent is patent protected in the US until at least 2020, according to Pfizer (reuters.com, 6/16/10)

Approach to Problem Solving

In an ideal world, one would be able to access affordable data on market share of Bayer/Onyx’s Nexavar in each approved disease indication, RCC as well as HCC, not only in the US, but in key international markets. The major company that complies such market share data is IMS, which is quite successful at collecting prescription data from pharmacies, sorting it by physician, and then selling this info (with patient info encrypted) to pharmaceutical companies. With such information, one could determine market share, and total scripts written for each indication, by clinical line of treatment, adjusting based on knowledge when a particular disease indication was launched in a particular market. With accurate information on drug pricing and patient compliance in each key market, one could derive tenable estimates of the combined revenue generated by each drug, in each indication. Alternatively, the drug manufacturer could provide a detailed presentation in its quarterly earning statement of sales of each drug in each key market, and separated by disease indication in the case of drugs such as Nexavar, with two key commercial approvals.

This is not an ideal world, though, and most companies consider these data proprietary. Accordingly, companies do not often share this level of detail publicly, in their quarterly earning statements. IMS and similar companies that collect information on more than 70% of all prescriptions filled in US pharmacies (thehealthcareblog.com/Laffel, 1/21/11), have been successful at sorting these data by physician, and then selling this info (with patient info encrypted) to pharmaceutical companies.
In contrast, IMS does not generate reliable and valid data when attempting to differentiate a launched drug with two or more indications, particularly sold under the same commercial and generic names, such as Bayer’s Nexavar to treat RCC and HCC, in terms of what sales are allocated accurately to each particular indication. Thus, there is little reason to trust IMS data in terms of allocations of Nexavar market share to RCC and HCC, – which is good, since without a budget, we didn’t have access to such information.

Other factors are relevant, given that a high percentage of the use of drugs and biologics in cancer care is off-label, according to the highly influential organization on cancer drug reimbursement, the National Comprehensive Cancer Network (nccn.org, 9/13/10). Off-label use, if relevant, serves to exacerbate the problems alluded to in terms of reliable allocations of market share of drugs within a particular disease indication.

Instead, a less direct approach was undertaken to estimate the percentage of total sales of Nexavar attributable to RCC, by evaluating quarterly revenue pre- and post-approval of the HCC indication from launch to the end of 2010, the last quarter for which data are available currently. Pfizer’s Sutent, an oral therapeutic also approved in RCC, with no indication to treat HCC, served as a historical control that was launched at the same time as Nexavar. The epidemiology of the two cancers, RCC and HCC, were evaluated, in terms of parameters that tend to influence patient numbers prescribing patterns across time and geography. From these cross-currents, a reasonable estimate of the contributions of RCC, relative to HCC, to revenue generated by Bayer/Onyx’s Nexavar was generated.

**Nexavar Revenue and Key Events**

- $841 million in 2009 [24% growth in 2010; dailymarkets.com, 2/25/11]
- 2Q09: Japanese approval to treat liver cancer (insciences.org, 5/20/09)
- $678 million in 2008 [82% growth in 2008; onyx.com, 2/23/09]
- 3Q08: Chinese approval to treat liver cancer (onyx-pharm.com, 7/28/08)
- $372 million in 2007 [125% growth in 2007; onyx.com, 2/23/09]
- 4Q07: United States (US) FDA approval to treat liver cancer (drugs.com, 11/19/07)
- European Union (EU) approval to treat liver cancer (onyx-pharm.com, 10/30/07)
- $165 million in 2006 [onyx-pharm.com, 2/15/07]
- 4Q05: US FDA approval in advanced renal cell carcinoma (drugs.com, 12/20/05)

1 From personal experience with IMS, et al., major reliability problems emerged when drugs had multiple indications, and the attempt was made to allocate drug prescriptions to particular disorders (e.g., methotrexate for use in cancer versus rheumatoid arthritis).
Sutent Revenue and Key Events

2010 Revenue: $1.07 billion [14% growth in 2010; sanfranciscogate.com, 2/16/11]

2009 Revenue: $964 million [14% growth in 2009; thepharmaletter.com, 4/26/10]

1Q09: the National Institute for Health and Clinical Excellence (NICE), in the United Kingdom, reverses its decision and recommends Sutent as cost effective in the treatment of advanced renal cell carcinoma (wsj.com/Rubinstein, 3/11/09).

2008 Revenue: $847 million [46% growth in 2008; medicalnewstoday.com, 3/13/09], including $254 million in the US

2007 Revenue: $581 million [165% growth in 2007; money.cnn.com, 2/12/08]

2Q07: US FDA approved new labeling for Sutent, which includes first-line treatment of renal cell carcinoma, based on improved progression-free survival (medicalnewstoday.com, 2/09/07)

2006 Revenue: $219 million [money.cnn.com, 2/12/08]

1Q06: US FDA approval to treat advanced renal cell carcinoma and gastrointestinal stromal tumors (GIST) after disease progression on, or intolerance to Novartis’ Gleevec (imatinib; cancer.gov, 1/26/06)

Renal Cell Carcinoma

**Sutent Efficacy:** In a trial of 750 patients with previously untreated, metastatic RCC in a multicenter, randomized, Phase III trial to receive either repeated 6-week cycles of sunitinib (at a dose of 50 mg given orally once daily for 4 weeks, followed by 2 weeks without treatment) or interferon alfa (IFN-α; at a dose of 9-MU given subcutaneously three times weekly). The primary end point was progression-free survival (Motzer, et al., 2007). There were 96 events (25.6 percent) of progression/death on Sutent, as compared with 154 events (41.1 percent) on IFN-α. Median PFS was 47.3 weeks (95 percent CI 42.6, 50.7) for Sutent-treated patients and 22.0 weeks (95 percent CI 16.4, 24.0) for patients treated with IFN; the hazard ratio was 0.415 (95 percent CI .320, 0.539, p<0.000001). Subsequently, Sutent has been shown to prolong overall survival in patients with the advanced disease by nearly five months compared to interferon-alpha (26.4 months vs. 21.8 months; inpharm.com/Tonarelli, 11/25/10).

**Nexavar Efficacy:** In an international, multi-center, randomized, double-blind, placebo-controlled, Phase III trial, 769 patients with RCC were enrolled. Subjects received 400-mg of the drug, or placebo, twice daily, with progression-free survival (PFS) as the primary outcome (http://www.medicineonline.com/drugs/N/2631/ NEXAVAR-sorafenib-tablets-200-mg.html). Trial data demonstrated significant efficacy in prolonging PFS, compared to placebo (167 days vs 84 days). This corresponded to an estimated hazard ratio (risk of disease progression for Nexavar compared to placebo) of 0.44. Interim overall survival data yielded a risk of death hazard ratio of 0.72 (Nexavar vs. placebo), which did not meet statistical significance, given the relatively small sample size.
Epidemiology: RCC arises in the renal cortex and comprises 80% to 85% of all kidney cancers (Huang, et al., 2008). In 2010, approximately 58,000 individuals in the US will be diagnosed with RCC, and about 13,000 will die from the disease (Jemal, et al., 2010). In the US, in contrast, an estimated 4,500 to 6,000 new cases of GIST disorders are diagnosed annually (pharmanews.eu.com, 1/11/11).


If RCC is diagnosed at an early stage, when the cancer is still confined to the kidney, the 5-year survival rates are relatively good at 60 to 75% (http://www.nlm.nih.gov/medlineplus/ency/article/000516.htm#Causes,%20incidence,%20and%20risk%20factors, accessed 20 November 2007). However, if the cancer has already spread to distant sites, the 5-year survival rate is less than 5%. Unfortunately, because kidney cancer is often asymptomatic, the majority of patients are diagnosed at later disease stages. Approximately 12,000 die from the disease annually.

Worldwide, the prevalence of RCC is a bit lower than in the US, at 2% of all cancer cases (Figlin, 2006). Of the approximate 86,000 new cases of kidney cancer occurring each year in Europe, the majority are RCC and of these about 30% present with metastatic disease (thepharmaletter.com, 4/02/07).

Sutent and Nexavar Efficacy in Other Solid Tumors

Sutent has been tested and failed in the treatment of several solid tumors, as depicted in Table 1 (motleyfool.com/Orelli, 9/28/10), and a corresponding Table 2 was assembled for Nexavar. The reliability of the two drugs in terms of their failures in the “big four” solid tumors (i.e., lung, female breast, prostate, and colorectal) is indeed...impressive. Whereas Sutent has succeeded in a smaller cancer indication, GIST, Nexavar succeeded in a more moderate indication, HCC.
### Table 1. Clinical Outcomes for Sutent in Several Cancer Indications

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Estimated New Cases, 2010</th>
<th>Status of Sutent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>21,000</td>
<td>Approved for a rare stomach cancer called gastrointestinal stromal cancer after Novartis' Gleevec.</td>
</tr>
<tr>
<td>Kidney and renal pelvis</td>
<td>58,240 (85% RCC)</td>
<td>Approved for advanced kidney cancer.</td>
</tr>
<tr>
<td>Pancreas</td>
<td>43,140</td>
<td>Positive results for a rare type called pancreatic neuroendocrine tumors.</td>
</tr>
<tr>
<td>Breast</td>
<td>209,060</td>
<td>Failed multiple trials on its own and in combination with other drugs.</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>222,520</td>
<td>Failed to extend lung cancer survival when combined with Roche and OSI Pharmaceuticals' Tarceva.</td>
</tr>
<tr>
<td>Liver and intrahepatic bile duct</td>
<td>24,120</td>
<td>Trial in liver cancer stopped early because it wasn’t as efficient as Bayer and Onyx Pharmaceuticals' Nexavar.</td>
</tr>
<tr>
<td>Prostate</td>
<td>217,730</td>
<td>Failed.</td>
</tr>
</tbody>
</table>

Source: American Cancer Society

### Table 2. Clinical Outcomes for Nexavar in Several Cancer Indications

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Estimated New Cases, 2010</th>
<th>Status of Nexavar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>21,000</td>
<td>Not approved.</td>
</tr>
<tr>
<td>Kidney and renal pelvis</td>
<td>58,240</td>
<td>Approved for advanced kidney cancer.</td>
</tr>
<tr>
<td>Pancreas</td>
<td>43,140</td>
<td>Not Approved. Ongoing Nexavar and everolimus trial for patients who do not respond to gemcitabine hydrochloride.</td>
</tr>
<tr>
<td>Breast</td>
<td>209,060</td>
<td>Failed multiple trials on its own and in combination with other drugs.</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>222,520</td>
<td>Failed to extend lung cancer survival when combined with gemcitabine and cisplatin.</td>
</tr>
<tr>
<td>Liver and intrahepatic bile duct</td>
<td>24,120</td>
<td>Approved for advanced liver cancer.</td>
</tr>
<tr>
<td>Prostate</td>
<td>217,730</td>
<td>Failed.</td>
</tr>
</tbody>
</table>

Pfizer’s Sutent has been found to generate a significant clinical benefit among patients with advanced pancreatic islet cell tumors, as demonstrated by increased progression-free survival, as compared to placebo (247wallstreet.com, 3/12/09). In a Phase III trial, Sutent more than doubled the time-period patients were free from disease progression or death (pharmatimes.com, 12/03/10). The progression-free survival for Sutent was 11.4 months versus 5.5 months for placebo (N = 171; Niccoli, et al., 2010).

Based on the above clinical results, the European Commission has approved Sutent (sunitinib) for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumors, with disease progression in adults (netcancerday.org, 12/02/10). This is the first treatment to be approved for pancreatic NET in 25 years.

Population based studies have assessed the incidence of pancreatic NETs as 0.2-0.4 per 100,000 (Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours, British Society of Gastroenterology & BMJ (2005); Gut 2005; 54(Supplement 4):iv1-iv16; doi:10.1136/gut.2004.053314). Based on all these findings, about 90% of the patients utilizing Sutent should be diagnosed with RCC.

**Nexavar Efficacy in the Hepatocellular Carcinoma (HCC/Liver Cancer)**

In the first quarter of 2007 (1Q07), Nexavar’s trial as a treatment for liver cancer was halted early due to increased efficacy of the experimental treatment, Nexavar, relative to placebo (bayer.com, 2/12/07). The approval of Nexavar was based on positive results from the international Phase III, placebo-controlled Sorafenib HCC Assessment Randomized Protocol (SHARP) trial, (which demonstrated that Nexavar extended overall survival by 44 percent among 602 patients with HCC (HR=0.69; p=0.0006) versus placebo (Llovet, et al., 2008). In the study, median overall survival was 10.7 months in Nexavar-treated patients compared to 7.9 months in those taking placebo. No demonstrable differences in the rates of serious adverse events were observed, with the most common effects being diarrhea and hand-foot skin reactions.
Sutent Efficacy: In contrast to the results reported by Bayer/Onyx, Pfizer had rather disappointing findings with regard to Sutent to treat liver cancer. An independent Data Monitoring Committee halted the Pfizer-sponsored trial, based on a higher number of serious adverse events observed in the Sutent arm, as compared to the Nexavar arm of the study (Sun 1170 trial; drugs.com, 4/22/10). In terms of efficacy, Sutent failed to demonstrate non-inferiority to Nexavar in this indication. The Sutent results leave Nexavar as the only approved medication for advanced liver cancer.

Epidemiology: HCC is a cancer that originates in the liver, not as the result of metastatic tumors that migrate to the liver from other parts of the body. The only potentially curative treatment for HCC is surgery, but only a small proportion of patients will be eligible for this due to finding that most patients are diagnosed in stage IV/metastatic disease, when surgery is not an option.

In 2010, an estimated 24,120 cases of liver cancer and hepatic bile duct were diagnosed and 18,190 patients died with this diagnosis during the year (http://www.cancer.org/Research/CancerFactsFigures/CancerFactsFigures/cancer-facts-and-figures-2010). The five-year relative survival rates for liver cancer, across stages, is only 13%, according to the SEER Cancer Statistics (Horner, 2006, 2009). The five-year survival for a patient diagnosed with metastatic HCC is under 10% (epvantage.com, 4/26/10).

The incidence of HCC is much higher in Asia than in the US or Europe. More than 600,000 cases of liver cancer diagnosed worldwide annually. Over 2/3 of these are in China, South Korea, Japan and Taiwan.

In Japan, for example, approximately 40,000 people are diagnosed with liver cancer each year and approximately 36,000 people die from the disease. Thus, primary liver cancer is the third leading cause of cancer-related death in Japan.
Other Treatments for Advanced Renal Cell Carcinoma

The market for branded kidney cancer drugs has become highly competitive. Besides Nexavar and Sutent, approved within a few months of one another in 4Q05 and 1Q06, respectively, several drugs have been added to the mix in recent years. In 2Q07, Pfizer’s Torisel was approved to treat RCC in the US, and in Europe in 3Q07 (bloomberg.com, 9/20/07). Roche’s Avastin was approved for RCC in the US in 4Q07 and in the US in 3Q09 (roche.com, 8/03/09), Novartis’ Afinitor was approved in the US in 1Q09 (novartis.com, 3/30/09), and in 3Q09 in the EU (novartis.com, 8/06/09), and GlaxoSmithKline’s Votrient in the US (4Q09; fda.gov, 10/19/09), and conditional approval in the EU, contingent upon the results of a head-to-head trial versus Pfizer’s Sutent (inpharm.com, 6/16/10).

Afinitor: In 1Q09, Afinitor (everolimus), an mTor inhibitor, was approved as an oral treatment of advanced RCC, after failure of treatment with sunitinib or sorafenib (novartis.com, 3/30/09). The approval is based on data that showed Afinitor, when compared with placebo, more than doubled the time without tumor growth or death in patients with advanced kidney cancer (4.9 vs. 1.9 months, respectively; Afinitor prescribing information, East Hanover, NJ: novartis.com, 2010.) and reduced the risk of disease progression or death by 67% (hazard ratio=0.33 with 95% confidence interval 0.25 to 0.43; p<0.0001). If used “on-label”, Afinitor would threaten neither these market leaders, since the Novartis drug is designated second-line, after the Pfizer and/or Bayer drugs have failed clinically.

Avastin: The Roche monoclonal antibody, a vascular endothelial growth factor (VEGF) inhibitor, has multiple indications, several which deliver blockbuster revenue (e.g., advanced forms of colorectal cancer, non-squamous non-small cell lung cancer, breast cancer), but RCC is not considered one of them. Progression-free survival in the pivotal Phase III study (AVOREN) was nearly twice as long with Avastin plus interferon versus interferon only (i.e., 10.2 months vs. 5.4 months, respectively; Rini, et al., 2008).

Torisel: Pfizer’s Torisel (temsirolimus), an mTor inhibitor (mammalian target of rapamycin), is a pro-drug, administered by infusion. Torisel is the first targeted RCC therapy proven to extend median overall survival versus interferon-alpha, an active comparator, in this patient population (drugs.com, 7/30/07). In a three-arm, phase III clinical trial of 626 patients with advanced RCC and poor prognosis, who had received no prior systemic therapy, Torisel significantly increased median overall survival by 49%, as compared to interferon-alpha (10.9 months vs. 7.3 months, respectively, p=0.0078).

The active ingredient in Torisel is very similar to sirolimus, the active ingredient in Rapamune, a medicine used to prevent organ rejection in patients who have had a kidney transplant, and used in Johnson & Johnson’s coated stent, Cypher (jnj.com, 9/27/10).
**Votrient**: GSK’s Votrient (pazopanib) was approved on the basis of a Phase III trial in which the overall median progression-free survival was 9.2 months with Votrient, and 4.2 months with placebo (Sternberg, et al., 2010). Treatment-naïve patients who received Votrient experienced 11.1 months of median progression-free survival versus 2.8 months with placebo (gsk.com, 11/20/10).

**Market Access**

**United States**

**Formulary Status**

In a brief review of the 2011 formularies at three of the largest health maintenance organizations (HMOs) in the United States (Aetna, Cigna, United Healthcare), Sutent and Nexavar are similarly categorized, as specialty drugs. On the Cigna Commercial formulary, though, Sutent had preferred status as compared to Nexavar being relegated to “non-preferred” status. Although costs were not provided at the formulary website (https://secure.cigna.com/cgi-bin/customer_care/member/drug_list/DrugList.cgi, accessed 3/22/11), presumably the co-pay charged the patient is higher for Nexavar than Sutent in this example.

**Market Share**

It is estimated over 30% of RCC cases in the US are diagnosed at Stages III or IV, and therefore relevant to on-label use of Sutent and Nexavar.

Nearly 80% of the population fails to respond to current therapeutics.

By July 2006, Sutent had captured more than 50% market share in RCC in the US, across all lines of therapy (http://www.slideshare.net/kaileshg/oncology-changing-market-dynamics, accessed 3/2/10). In the following year, market share varied slightly with Sutent varying between 52% and 56%, and Nexavar even “tighter”, between 33% and 34%. Given the lack of revenue established for newer approved treatments, this would suggest that these results remain viable, perhaps adjusted downward by only about 10%. An analysis of RCC by Decision Resources evaluated market share by line-of-treatment.

In 2009, reportedly, four targeted agents competed in second-line treatment of advanced RCC. Nexavar was the market leader, with a 47% market share, Torisel had 15%, Afinitor had 14%, and Avastin had 11% market share (inpharm.com/Tonarelli, 11/25/10). The competition notwithstanding, Nexavar and Sutent continue to dominate the US market, with a combined 67% market share in the treatment of renal cell carcinoma (researchandmarkets.com, 3/01/10).
**Europe**

Although the NICE rejections of Nexavar in terms of RCC and HCC implies that access to the NHS will be difficult, other countries in Europe have approved Nexavar for the treatment of liver cancer. Nexavar is approved for the most common type of liver cancer in France, Germany, Spain, Italy, and Romania (reuters.com, 11/18/09).

**South Korea**

Effective starting in 2011, the national health insurance in South Korea has indicated that the government will reimburse patients for use of Nexavar for 50% of the cost of treatment for advanced liver cancer (bnc.bayer.com, 1/20/11). Although Nexavar had been approved in South Korea since 2006, as a treatment for RCC, with health insurance coverage, this was not the case for the Nexavar in the HCC indication. Approval was granted in 1Q08, but until this year, Korean patients were burdened with the full cost of more than three million Korean Won (2658 USD or 2030 EUR) per month.

**India**

Bayer and Onyx experienced a large setback in India in 2Q10, when a local company, Cipla, launched a generic version of Nexavar, at 1/10th the price of the branded version in India (moneycontrol.com, 4/08/10). The drug is Soranib and we are launching it at less than Rs 28,000 per month of treatment versus the corresponding Bayer price of Rs 2,80,000. After a two- year delay, the Delhi High Court ruled against Bayer, paving the way for generic competition.

**Cost of Treatments**

**United States**

Based on the wholesale acquisition cost (WAC) of Sutent (sunitinib), which is $6,412 for a 30-count bottle of 50-mg capsules, the average monthly cost is $4,275, or $5,985 for the six-week treatment cycle (fdcreports.com, 1/30/06). This equates to an annual cost of $51,890. The WAC for Nexavar (sorafenib) is $4,333 for a one-month supply. A more recent estimate for Nexavar was reportedly still $4,300 per month (usatoday.com/Szabo, 7/11/06), for a comparable annual cost of $51,600.

As for other targeted treatments, the dose of Avastin used in the Phase III advanced RCC trial was 10-mg/kg q2weeks (Rini, et al., 2008), which was the same regimen used for Avastin in the advanced colorectal cancer trial (Hurwitz, et al., 2004), leading to the initial approval of Avastin. This dosing is associated with a cost of Avastin was $52,800 annually at the time of the initial launch (medicalnewstoday.com, 6/15/05). In contrast, Avastin treatment for other cancers, such as advanced breast cancer, has a dosing regimen that is associated with a greater than $80,000 annual cost (seekingalpha.com, 1/07/11).

Torisel, used as a second-line treatment, would be priced lower, at $30,000 annually (bloomberg.com/Rappaport, 4.06/07).
United Kingdom

In the UK, the University of Birmingham’s The National Horizon Scanning Centre Research Programme analyzed Pfizer’s Torisel for NICE (12/10). The costs provided in this document were the six-week cycle costs for four of the branded drugs approved to treat advanced RCC:

<table>
<thead>
<tr>
<th>Drug</th>
<th>6-Week Cycle Cost (£)</th>
<th>Annual Cost (£)</th>
<th>Annual Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer’s Torisel</td>
<td>£3,720</td>
<td>£32,240</td>
<td>$49,830*</td>
</tr>
<tr>
<td>Roche’s Avastin</td>
<td>£5,982 to £6,117</td>
<td>£51,864 to £53,034</td>
<td>$80,161 to $81,969</td>
</tr>
<tr>
<td>Pfizer’s Sutent</td>
<td>£3,139</td>
<td>£27,215</td>
<td>$42,063</td>
</tr>
<tr>
<td>Bayer’s Nexavar</td>
<td>£4,471</td>
<td>£38,764</td>
<td>$59,913</td>
</tr>
</tbody>
</table>

*Conversion of pounds to dollars based on 0.647 average for 2010 (http://www.irs.gov/businesses/small/international/article/0,,id=206089,00.html, accessed 3/23/11)

One is struck by the increased cost of Avastin in the UK as compared to the US. In contrast, because of the risk-sharing scheme adopted by Pfizer in the UK, the cost of Sutent is lower than in the US.

National Institute for Health and Clinical Excellence (NICE) Appraisal of Drug Treatments at the “End of Life”

The NICE is the cost-effectiveness “gate-keeper” for the United Kingdom’s National Health Service (NHS), the government program for England and Wales. Cost-effectiveness is the additional cost of one year of healthy life (expressed as the cost per quality adjusted life year, or QALY, gained). NICE typically recommends the NHS to use treatments when they fall within a range from £20-30,000 per QALY. This can be extended to between £40-50,000 per QALY for treatments, used when a patient is close to death and which can extend life for more than 3 months (nice.org.uk/TAG #189, 5/26/10).

In 4Q08, the NICE released guidance that the health technology assessment (HTA) group would evaluate treatments aimed at the “end of life”, with a more liberal standard (http://kidneycancerresource.com/index.php/N.I.C.E._%28Stuff%29_04-Nov-08).

That is, incremental cost-effectiveness ratios higher than the £30,000 per quality-adjusted life-year (QALY), the cut-off used conventionally by NICE for endorsement of cost effectiveness, among treatments that meet the following criteria:

1. patients with a short life expectancy, normally less than 24 months;
2. sufficient empiric evidence that the treatment does extend life, usually at least an additional three months, compared with current NHS treatment (bbc.uk.org, 1/02/09; http://news.bbc.co.uk/2/hi/health/7808644.stm); and
3. the drug is utilized in a patient population normally not exceeding 7,000 new patients annually, and does not have approval for other indications with numbers that exceed this criterion value (http://kidneycancerresource.com/index.php/N.I.C.E._%28Stuff%29_04-Nov-08).
Implications for Pfizer’s Sutent to Treat Renal Cell Carcinoma

Based on this new guideline regarding the “end-of-life”, in 1Q09, The NICE released new guidelines regarding Pfizer’s Sutent (sunitinib), along with Roche’s Avastin (bevacizumab), Bayer/Onyx’s Nexavar (sorafenib), and Wyeth’s Torisel (temsirolimus), regarding the treatment of advanced and/or metastatic renal cell carcinoma (RCC), among patients suitable for immunotherapy, who had a good ECOG performance status of 0 or 1 (NICE Technology Appraisal Guidance #169, 3/09). Among these branded treatments, only Sutent was recommended as a first-line treatment option for such RCC patients. Nexavar was rejected by NICE, as discussed in the next section, as was Affinitor. The NICE review of Torisel was terminated in 4Q10, once Pfizer reportedly failed to provide the relevant cost-effectiveness data (inpharm.com/Adams, 12/24/10).

This was a reversal of the previous draft of the NICE guidance in 2007, which acknowledged that Sutent is clinically effective in advanced RCC, but at £3,500 per month (prweek.com.uk, 9/01/09), did not represent a cost effective use of NHS resources (timesonline.com, 8/07/08). In response, Pfizer reduced the price of Sutent by 5% in the UK, and further reduced the price by providing one cycle/course of the treatment free of charge to every eligible patient in the UK. These moves, in retrospect, seemed intended to facilitate this reappraisal (wsj.com/Rubenstein, 3/11/09). That is, one six-week cycle of Sutent costs £3,139 (28 tablets of 50-mg) in the UK, equivalent to about $5,000 US. The average annual cost in the UK for a patient administered Sutent is £24,168 (this price includes one free treatment cycle, and is equivalent to $40,000 US). As an aside, the British pricing of Sutent is approximately 30% less than corresponding price at the time of the US launch, which had a $4,333 monthly wholesale acquisition cost (ihsglobalinsight.com, 2007).

A pricing strategy, in which the first cycle of Sutent was not charged to the NHS, was applied to the newer model (NICE TAG #169, 3/09). The revised model by NICE concluded that the OS advantage for Sutent, relative to IFN-α, produced an ICER of £54,366 (NICE TAG #169, 3/09). These results were consistent with the NICE analysis of PFS, with an adjusted ICER of £35,235 for Sutent versus IFN-α, based on a median PFS of 11 months in the Sutent arm, as compared to 5.2 months in the IFN-α arm (HR = 0.488, 95% CI = 0.406 to 0.586, p<0.000001).

In a post-hoc analysis, Pfizer noted that patients who received only one line of treatment (i.e. no subsequent treatments after stopping their sunitinib or IFN-alpha therapy) revealed that Sutent almost doubled the time patients were alive, as compared to interferon-alpha (28.1 months vs. 14.1, respectively; inpharm.com/Tonarelli, 11/25/10). Given that clinical practice in the UK generally supports funding for only one-line of treatment for advanced RCC, this was an important finding. The NICE evaluation committee was persuaded that the ICER for Sutent was less than £50,000 per QALY gained.
NICE Evaluation of Nexavar to Treat Renal Cell Carcinoma

In contrast, adjusting for the “end of life” recommendation did not yield a decision change in terms of the cost effectiveness of Avastin, Nexavar, or Torisel to treat advanced RCC as either first-line or second-line medications (NICE Technology Assessment #178, 3/09). Bayer argued that the “end-of-life” criteria should apply to Nexavar, along with Sutent, in the treatment of RCC (www.nice.org.uk/nicemedia/live/11817/43164/43164.pdf). Not only because of the epidemiology of RCC, but Nexavar has been shown to substantially increase both progression free and overall survival in patients with RCC who have failed prior cytokine therapy (Escudier, et al., for the TARGET Trial investigators, 2007). The economic analysis presented indicated to Bayer that the mean increase in life is between 30% and 37% (equivalent to at least an additional 5 months of life in the TARGET trial). But the overall survival results were not significantly different in Escudier, et al. (2007), and the analysis was confounded given the differential movement of placebo patients to Nexavar. Therefore non-empiric assumptions were made by Bayer and incorporated into the economic model. Accordingly, the academic firm that analyzed Nexavar to treat RCC for NICE derived ICER estimates that exceeded the £50,000 criterion discussed for end-of-life approvals. That is, Nexavar’s incremental cost per QALY was between £62,256 (for the prior cytokine group) and £72,546 (for the overall TARGET group).

NICE Evaluation of GSK’s Votrient to Treat Advanced Renal Cell Carcinoma

In 1Q11, NICE approved a second drug, GSK’s Votrient (pazopanib), in the first-line treatment of advanced RCC, who are of Eastern Cooperative Oncology Group (ECOG) performance status 0-1, on the basis that GSK provides the agreed patient access scheme, including a 12.5% discount on the list price of Votrient (thepharmaletter.com, 2/24/11). In addition, GSK proposed to the NICE a potential partial rebate, conditional upon the outcome of the COMPARZ trial, a head-to-head, albeit open-label study versus the current standard of care (Pfizer’s Sutent). This is a study of 876 patients with advanced RCC who are randomized to either Sutent (50-mg/day for four weeks, followed by two weeks off, in 6-week cycles) or Votrient (800-mg/day continuous treatment). The five-year study, which has progression-free survival as the primary outcome, began in 8/08, and is sponsored by GSK (clinicaltrials.gov #NCT00720941).
NICE Evaluation of Nexavar in the Treatment of Hepatocellular Carcinoma

In 2Q10, NICE did not recommend Bayer’s Nexavar as cost effective in the treatment of hepatocellular carcinoma (HCC), the most common form of liver cancer, among patients for whom surgery or locoregional therapies of the tumor (e.g., radiofrequency ablation or chemoembolization) have failed or are not suitable (nice.org.uk/TAG #189, 5/26/10). The high cost of Nexavar in the UK, approximately £2,900 per month, is equivalent to $4,877 US per month. This is actually higher than the corresponding US pricing of Nexavar. Notwithstanding that the normal life expectancy for such HCC patients is less than 24 months, and thus the median longevity meets one of the criteria for “end-of-life” NICE approval. In contrast, the clinical trial evidence for Nexavar, as evaluated by NICE’s “independent” advisory committee, indicated that Nexavar increased survival by an average of 2.8 months, which is slightly below the three-month criterion for the “end-of-life” evaluation. Indeed, NICE argued that half of the patients who gained clinical benefit with Nexavar, received less than this amount of additional life, implying a skewed distribution. Therefore, NICE argued that the “marginal benefit” in clinical efficacy did not warrant a recommendation of cost effectiveness.

At an additional cost of £27,000 ($38,850 US) per patient for the 2.8 months of additional life, this extrapolates to ICER equivalent to $166,500 per QALY. Although Bayer had offered a “buy-three-get one-free” deal, this 25% discount was insufficient to alter the NICE directive (fiercepharma.com, 5/26/10). As noted, Nexavar also failed the NICE evaluation in terms of cost effectiveness in the RCC indication.

Recently, the UK’s Health Secretary, Andrew Lansley, noted that £200million saved from National Insurance contributions will be used towards funding of cancer drugs by NHS patients, but the specifics of this program have not been illuminated (dailymail.co.uk, 5/26/10). The article noted that the hope is that some of the funding would be applied to Nexavar in these two cancers. The Daily Mail write-up noted that NICE claims that the agency is approving more drugs under End of Life policies to benefit small numbers of terminally ill patients, but figures last month showed it had failed to fully recommend any of 15 cancer medicines assessed since November 2008, when the “end-of-life” perspective was announced initially. As we have documented in this report, a dramatic reversal in NICE’s evaluation of Pfizer’s Sutent to treat RCC is attributed directly to the emergence of NICE’s “end-of-life” guidance.
Revenue Generated by Branded Targeted Drugs to Treat Renal Cell Carcinoma

Using the 1991–2007 SEER (Surveillance, Epidemiology and End Results)-Medicare and 1996–2007 MarketScan Commercial Claims and Encounter (CCAE) and Medicare Supplemental databases, patients with RCC were analyzed in terms of costs, including drug treatments, normalized to $US, year 2009 values (Shih, et al., 2011). The annual cost to treat patients with RCC who received targeted therapies was 3- to 4-fold greater than the corresponding cost to treat RCC patients who received other therapies. Results from the multivariate analysis showed that, after controlling for potential confounders, the annual medical cost was $31,000 to $65,000 higher for RCC patients treated with targeted therapies, with the largest increase observed among the non-elderly patients.

Revenue for Particular Drugs to Treat Renal Cell Carcinoma in 2010

As noted earlier, Sutent generated $1.07 billion in worldwide revenue in 2010, and Nexavar recorded a corresponding total of $934 million. While noting in the approach that pharmaceutical companies generally do not provide detailed analyses of revenue generation for a particular drug, including the focus of this report, Bayer/Onyx’s Nexavar, our “control drug”, Sutent, however, has been presented with more detailed information by Pfizer in recent quarterly releases. Not by disease indication, but for Sutent such information is regarded as irrelevant, since sales in the RCC indication represents the overwhelming majority of sales, as compared to GIST or the new pancreatic cancer subgroup indications. From the 4Q10 earning release (pfizer.com, 2/01/11), comes the following data regarding components of Sutent global revenue:

<table>
<thead>
<tr>
<th>Component</th>
<th>4Q10</th>
<th>4Q09</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developed Europe</td>
<td>$114</td>
<td>$138</td>
</tr>
<tr>
<td>Developed Rest-of-World</td>
<td>$40</td>
<td>$28</td>
</tr>
<tr>
<td>Emerging Markets</td>
<td>$69</td>
<td>$46</td>
</tr>
<tr>
<td>United States</td>
<td>$72</td>
<td>$81</td>
</tr>
<tr>
<td>Total</td>
<td>$295</td>
<td>$293</td>
</tr>
</tbody>
</table>

Results indicate that although the total global revenue for Sutent essentially was unchanged from 4Q09 to 4Q10, the pattern of revenue generation was markedly different for the quarters, one year apart. While revenue shrank in the US and Developed Europe, sales rose in the Developed Rest-of-World and in Emerging Markets. While this dramatic shift would arguably be expected for Nexavar, given the known increasing rates of liver cancer in emerging markets, such as China, and in the predominant country in the Developed Rest-of-World, Japan. But this was not confirmed empirically, given the lack of information forthcoming from Bayer/Onyx; just a vague claim of increased Nexavar sale in the Asia-Pacific region, involving Japan and China, in 4Q10 (market intellisearch.com, 3/18/11). This is a theme that will be salient when interpreting the results.
Avastin generated the equivalent of $5.97 billion in global sales in 2010 (bernstein.com/Anderson, 7/20/10). With six oncology indications, RCC is not considered one of the major indications, which include advanced colorectal cancer, non-squamous non-small cell lung cancer, and advanced breast cancer. The ongoing attempt by the FDA to rescind approval of Avastin to treat advanced breast cancer has led to the speculation that $1 billion in Avastin sales is derived from breast cancer (bernstein.com/Anderson, 7/20/10). Avastin is also approved to treat pancreatic cancer, and glioblastoma (a form of brain cancer), as well RCC, as relatively smaller opportunities. Finally, there is the “hidden” revenue from off-label use of Avastin in the treatment of age-related macular degeneration (AMD). Thus, attempts to carve up Avastin revenue into its components are highly likely to be unreliable in the treatment of age-related macular degeneration, given all the “moving parts.”

In the 4Q10 earning release from Pfizer, Torisel is not listed separately; in contrast, 35 other drugs from Pfizer and Wyeth legacy are presented. The absence of Torisel suggests trivial sales for this agent in RCC. But the related drug, Rapamune, is listed, and generated $388 million in 2010 (pfizer.com, 2/01/11). It is not clear if all this revenue is from transplant organ rejection, or includes the Torisel revenue derived from RCC as well. While $388 million seems large for an organ transplant drug, note that Pfizer now receives royalties on Rapamune from JNJ, as the drug constitutes the coating in the successful “coated stent”, sold commercially as Cypher (jnj.com, 9/27/10). These results tend to support that Torisel revenue is not contained within Rapamune sales. Instead, Torisel, as an injected drug when an oral version of the mTor inhibitor mechanism is available (cf. Novartis’ Afinitor), is likely a small contributor to revenue.

Afinitor generated $243 million in 2010, including $80 million in 4Q10, in the treatment of advanced kidney cancer (deutschebanc.com/Race, 3/21/11). In contrast, GSK’s Votrient was a trivial contributor to the RCC market as well, with only 38 million pounds, equivalent to $58.7 million US, generated in 2010 (gsk.com, 2/03/11). The combined revenue from the newer agents accounts for about ¼ of the revenue of the combined market leaders, $2 billion Sutent or Nexavor.
Analyses to Determine the Contribution of Liver Cancer to Revenue for Nexavar

Revenue data for Nexavar and Sutent were collected on a quarterly basis from 1Q06, at the time of launch, until as recently as 4Q10. As noted earlier, Nexavar was not approved for treatment of HCC until 1Q08. Thus, data prior to this compares the relative revenues generated by treatment of RCC only. Notably, while GIST revenues are included in all Sutent figures, they were deemed to be negligible in the contribution to total Sutent revenue given the rarity of the condition. Indeed, in the “Estimated New Cancer Cases and Deaths by Sex for All Sites, US, 2010, GIST did not have its own “line” but was presumably included in the generic heading of cancers involving “other digestive organs”. The insignificance is further amplified when the growing incidence of RCC is taken into consideration relative to the incidence of GIST.

2 Estimated new cases are based on 1995-2006 incidence rates from 44 states and the District of Columbia as reported by the North American Association of Central Cancer Registries (NAACCR), representing about 89% of the US population. Estimated deaths are based on data from 1969 Mortality Data, 1990-2007 National Center for Health Statistics, Centers for Disease Control and Prevention.
Data after 1Q08 compares sales of Nexavar and Sutent where Nexavar has approval for HCC and RCC, while Sutent is approved for HCC and the fiscally irrelevant GIST. Nexavar and Sutent were both plotted on the same revenue vs. time axis. Four linear regressions were performed to test the hypothesis that HCC was a major contributor to Nexavar. The result that would support this hypothesis is an increase in the slope of the regression of Nexavar revenue following 1Q08.

Sutent revenue over the period was modeled as: $y = 13.27x + 44.46$ ($R^2 = 0.901$). Revenue volatility increased significantly following 3Q08, reducing the accuracy of the correlation, somewhat. Nexavar revenue over the period was also regressed, and modeled as: $y = 12.57x + 16.7$ ($R^2 = 0.964$). The lower slope coefficient for Nexavar is indicative of consistently slower revenue growth, relative to Sutent. However, the higher $R^2$ value in the Nexavar model points to lower revenue volatility.

Given that the Nexavar approval in liver cancer was the first for this indication in the past 30 years (nytimes.com/Pollack, 6/04/07), one hypothesis is that approval for the HCC indication allowed Nexavar to fill a small backlog of unmet need, thereby padding sales, as Sutent revenues, driven by RCC alone, suffered. This effect was short-lived, though, and was expected, given the relatively small size of the HCC market. Indeed, an initial strong launch into the liver cancer market by Nexavar had shown signs of slowing in 1Q09 (thestreet.com/Feruerstein, 2/24/09). The reversion to volatility a year and a half later, and indeed reduced revenues, seems to further suggest that a small area of unmet need in the treatment of HCC padded Nexavar revenues in the latter half of 2008.

Two more regressions were modeled on Nexavar revenues. The first linear regression modeled revenue figures in the first half of the period, wherein Nexavar was only approved for the treatment of RCC. This was marked by a period of fast and consistent growth, and the equation $y = 3.392x + 19.75$ ($R^2 = 0.974$). This is to be expected, given the large area of unmet need at the time. As expected, the Sutent data is similar, albeit at a consistently higher revenue base, over the same time-frame.

Following 1Q08, Nexavar revenue was modeled by the equation $y = 2.451x + 151.2$ ($R^2 = 0.886$). The reduced slope coefficient, relative to the period prior to 1Q08, represents much slower revenue growth. Further, the reduced $R^2$ value points to increased volatility relative to 1Q06 to 4Q07, despite the approval for the treatment of HCC in the latter half of the period.
Of particular interest are the remarkably different profiles of Nexavar revenue between 2Q08 and 4Q09, and the quarterly data collected in 2010. In the first instance, Nexavar growth appears robust, and familiar of the previous regression, characterized by a strong linear trend upwards. Also of note, is that Sutent revenue growth began to suffer as early as 3Q09. This seems to confirm the previously postulated notion that Nexavar sales remained robust during 2008 because of a small pocket of unmet need; in the meantime, Sutent sales suffered possibly due to a worsening global credit environment, at a time when the wealthy had been paying for their expensive drugs. Recall, it wasn’t until 2009 that Sutent received a recommendation of acceptable cost-effectiveness from the UK’s NICE, which is arguably the most influential of the HTA organizations worldwide (nature.com, 11/01/10). However, any relief provided by new market opportunities for Nexavar, were quickly saturated. The quarterly data collected in 2010 shows a volatile revenue picture that looks remarkably reminiscent of Sutent two years earlier.

Interpreting the Data Findings with regard to Contributions to Nexavar Revenue
Following launch within months of one another, the global revenue for Nexavar and Sutent was comparable in 2010, with totals of $1.07 billion for Sutent versus $934 dollars for Nexavar. The relative difference is about 15% from Sutent to Nexavar, and slightly higher the other way. The bulk of the revenue for Sutent should be attributed to RCC, as a minority of patients would be diagnosed with GIST or pancreatic NET, approved recently for Sutent in Europe. The epidemiology would suggest that approximately 90% of the patients prescribed Sutent would be diagnosed with advanced RCC.

The more complex task, the raison d’etre for this report, is to estimate the contribution of RCC and HCC to global Nexavar sales. The complexity is, in part, because global sales are shifting to Asia, which is salient given the markedly higher rates of HCC in Asia as compared to the US and Europe. Accordingly, several lines of evidence were utilized, including comparing the sales of Sutent, which shares labeling to treat RCC with Nexavar, as a natural, historic control group. The bulk of revenue for Sutent was from RCC, rather than GIST or a sub-population of pancreatic cancer patients, particularly given the reliable set of failures in the solid tumors (e.g., NSCLC, breast, prostate, and colorectal). These results would tend to discourage off-label use in other cancers.

Nexavar, in contrast, has two vital streams of potential revenue, from RCC and HCC. Given that Sutent failed in a head-to-head study versus Nexavar in the treatment of advanced HCC (Bloomberg.com, 4/23/10), one might assume that HCC is a significant contributor to Nexavar but not to Sutent revenue. Indeed, there are several lines of evidence that support that Sutent is more dominant in RCC, including that Sutent received first-line labeling for RCC treatment in the US, whereas Nexavar did not. Sutent's once-daily regimen seems to have a dosing advantage over Nexavar, a twice-daily mediation. Additionally, Sutent offers a two-week "drug holiday", in terms of dosing, as compared to the continuous use of Nexavar.
Sutent was ultimately approved for the treatment of advanced RCC by the influential HTA, the UK’s NICE, an institute established to determine the cost effectiveness of medications used within the NHS. The NICE “reversal of fortune” with regard to Sutent has not been applied to Nexavar, arguably because Pfizer was more willing to discount the price Sutent than Bayer was willing to discount the price of Nexavar. In any event, Nexavar has been rejected by NICE in both RCC and HCC. This difference in the status of these competitive drugs is important because of the influence that NICE has in other markets, outside the UK. On the other hand, Avastin recorded nearly $6 billion in global sales in 2010 in the absence of receipt of any NICE recommendation of cost effectiveness for any approved indication.\(^3\) Ironically, the closest that Avastin is to a NICE recommendation of cost effectiveness is off-label in the treatment of AMD, a license and recommendation that Roche is not seeking (myvisiontest.com, 1/21/11).

The contribution of other branded drugs is essentially nonexistent in HCC, where Nexavar has been the only approved drug in decades. In contrast, several branded drugs have been approved to treat advanced RCC, although their contribution has been muted, relative to Sutent and Nexavar. Revenue contributions of other branded drugs to RCC sales are regarded as minimal. Although Avastin generated nearly $6 billion in 2010, and is approved in advanced RCC, the blockbuster contributors of $1 billion or more are assumed to be from advanced colorectal cancer, advanced NSCLC, and advanced breast cancer. Smaller contributions to Avastin revenue are from pancreatic cancer, glioblastoma, and off-label use to treat AMD, as well as RCC.

In terms of the US market, market share of the two drugs in RCC has slipped from about 87% to about 67% from 2006 to 2009, if such market share data are credible. But based on the Pfizer revenue data, only about 25% of Sutent revenue is derived in the US, noteworthy for a drug that costs tens of thousands of dollars annually.

These results lead one to key international sites to explain revenue generation for Sutent and Nexavar. Given that the epidemiology of the two disorders points to greater rates of HCC in Asia than in the US, but lower rates of RCC in Asia than in the US, these findings would lead one to conclude that the bulk of global revenue for Sutent should be generated among patients with RCC, whereas the bulk of Nexavar global revenue should be recorded in HCC. Anecdotally, in 4Q10, Nexavar reportedly increased sales in the Asia-Pacific region, led primarily by Japan and China (market intellisearch.com, 3/18/11). There was no mention of differentially greater sales in the RCC versus HCC indication.

\(^3\) Ironically, the closest that Avastin is to a NICE recommendation of cost effectiveness is off-label in the treatment of AMD, a license and recommendation that Roche, or its international partner, Novartis, is not seeking (myvisiontest.com, 1/21/11). Novartis sells a related drug, Lucentis, for 15 times the price of Avastin in AMD, and this ratio is low compared to the 40-difference noted in the US (consumerreports.org, 5/09).
It seems that the best test of this line hypothesis would be to test the slope of revenue increases for Nexavar, in terms of changes before and after the approval of HCC in 4Q07, and relative to the historical control of revenue from Sutent. Based on plots of revenue from launch in 1Q06 to the latest quarter, 4Q10, it seems that the slope of revenue change for Nexavar before the approval of the HCC indication to the corresponding slope after approval of the HCC indication. Moreover, there was no striking change in the slope of the Nexavar revenue plot as compared to that of Sutent (which failed in HCC).

One would have expected a divergence in the slopes, reflecting the additional revenue from the HCC stream. Instead, there was an initial “bump”, but no sustained, marked insurmountable revenue following the HCC indication for Nexavar. Indeed, in 1Q11, Bayer provided a conservative perspective regarding limited growth for Nexavar in 2011 (jpmorgan/Vosser, 3/23/11). Bayer pointed to the increasing competition to Nexavar in RCC, as Novartis’ Afinitor gains some traction as a second-line treatment, following Sutent failure. Moreover, the cost effectiveness recommendation granted recently to GSK’s Votrient opens another avenue for competitive disadvantage.

The US market share data in RCC, which has a 2 : 1 ratio in favor of Sutent over Nexavar in RCC, combined with the finding that 90% of Sutent revenue is from RCC, and the US represents ¼ of the 2010 revenue of $1.07 billion for Sutent, can be used to derive estimates of RCC contributions to both Sutent and Nexavar revenue in the US. The estimates are $241 million is derived for Sutent in the US, with half that amount, $121 million allocated to Nexavar in RCC from the US. Given that 80% of patients do not respond clinically, and the tenuous nature of such market share data from IMS, et al. for drugs with multiple indications, then second- and third-line treatments in RCC must be given greater emphasis. Accordingly, Nexavar revenue will be increased by 20%, to $145 million.

Based on the epidemiology, and Sutent advantageous pricing in the UK and NICE endorsement, we assume that Nexavar achieves only 40% of international revenue derived by Sutent in RCC. This is offset by the bias towards additional lines of therapy, and the lack of differential slopes in revenue change over time; accordingly, Nexavar is estimated at 50% of estimated international sales of Sutent in RCC. Since Sutent generated another $722 million internationally from RCC, then an additional $361 million is derived for international sales of Nexavar in RCC. Given that 2010 revenue for Nexavar was $934 million, this would suggest that $428 million (45.8%) was derived from the HCC indication, whereas $506 million (54.2%) of Nexavar global revenue in 2010 was derived from RCC. Given the variability in estimates, the contributions of RCC and HCC to global Nexavar revenue are not likely to represent a statistically significant difference.

The discussion about the emerging Asian presence in pharmaceutical sales provides an opportunity to write on a topic that deserves its own report, but will be reviewed briefly. That is, the “gold rush” by the pharmaceutical companies to mine emerging markets, and the reality of the short-term results of such excavations.
Growing Importance of the Asian Emerging Markets in the Prescribing of Nexavar relative to Sutent

In recent years, the focus is on emerging nations for growth of the pharmaceutical industry, as IMS expects an aggregate growth rate of between 15% to 17% for 17 emerging markets in 2011. The corresponding rate in Europe and Western Europe is 5% growth or less. Combined sales of these emerging markets are estimated at $170 billion to $180 billion in 2011 (reuters.com/Berkrot, 10/07/10). Global pharmaceutical revenue is expected to reach $890 billion; thus, emerging markets represent only about 15% of worldwide revenue.

Table 2. Summary of Major Geographies Sales and Growth Estimates

<table>
<thead>
<tr>
<th>Market</th>
<th>2011 Sales ($US Billion)</th>
<th>Growth from 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worldwide</td>
<td>$890</td>
<td>5-7%</td>
</tr>
<tr>
<td>United States</td>
<td>$325</td>
<td>3-5%</td>
</tr>
<tr>
<td>5 Major European</td>
<td>$140</td>
<td>1-3%</td>
</tr>
<tr>
<td>Japan</td>
<td>$98</td>
<td>5-7%</td>
</tr>
<tr>
<td>17 Emerging Markets</td>
<td>$175</td>
<td>15-17%</td>
</tr>
<tr>
<td>China (inc in the 17 EM)</td>
<td>$50</td>
<td>25-27%</td>
</tr>
</tbody>
</table>

China

According to Decision Resources, the drug market to treat liver cancer in China is expected to triple by 2014 (biospectramasia.com, 9/08/10), from a baseline of $53 million in 2009. Fueling this growth will be greater access to medical care among an increasingly drug-treated patient population, and a rising number of higher-income HCC patients willing-to-pay for more-efficacious and costly Western brands of targeted agents, such as Bayer's Nexavar. Liver cancer drugs, manufactured by international firms, accounted for 54% of total sales in China in 2009. This percentage is likely to increase to 68% of total sales in 2014, according to the analysis.

While this level of increase, a tripling of sales, with Nexavar likely to be beneficiary of most of this dramatic increase in China, the impact on global Nexavar sales by 2014 is not likely to be so striking. Earlier, it was established that worldwide Nexavar sales were nearly at $1 billion in 2010 (dailymarkets.com, 2/25/11), and increasing at about $100 million annually. Accordingly, even if Chinese sales increase markedly to $150 million in 2014, given the projected increase of global Nexavar revenue to $1.5 billion in 2014, the contribution of China to worldwide sales increases from 6% in 2009 to 10% in 2014. While a marked 67% increase in relative growth, a less impressive 4% change in absolute growth.

This is not to indicate that the growing importance of Asia is mistaken, only that as these trends continue in China, India and Japan, it will not be until the next decade that the impact of Asian sales will be demonstrated more strikingly. That is, the combination higher rates of HCC in cancer, and the increasing ability of these government or their residents to pay out-of-pocket, is likely to propel markedly higher global sales of Nexavar relative to Sutent.
Implications for Roche:

Roche expects a global regulatory submission by mid-2012, about a two-year delay from the initial submission. Roche committed a more important misgaging of the US regulatory body, that is, recognizing the shifting tides of greater reliance on OS versus PFS, and the need for adequate control groups for regulatory approval.

References


