Liver Cancer Therapeutics Market to 2018

Nexavar, the Only Approved Targeted Therapy for Advanced Disease, Continues to Dominate as Other Late Stage Trials Fail
GBI Research Report Guidance

- The report starts with an executive summary of the key points influencing liver cancer therapeutics in the top seven markets.
- Chapter two summarizes the scope of the report and contains the report guidance.
- Chapter three gives an overview of liver cancer, covering the symptoms, diagnosis and treatment options available for the disease.
- Chapter four gives an overview of the liver cancer therapeutics market, its drivers and barriers and the recent developments in the top seven markets.
- Chapter five estimates the market size of the US, the UK, France, Germany, Spain, Italy and Japan, and gives forecasts to 2018. A key analysis of the treatment usage pattern is also discussed.
- Chapter six gives details on the current pipeline analysis of the liver cancer market. The section also contains detailed analysis of the most promising pipeline products.
- Chapter seven analyzes the top companies operating in the liver cancer market and includes benchmarking and detailed profiles of the leading companies.
- Chapter eight discusses in detail the strategic consolidations that have taken place within the global liver cancer therapeutics market, looking at key licensing agreements.
The Liver Cancer Therapeutics Market is Forecast to Grow at a CAGR of 8.1% from 2011 to 2018

The liver cancer therapeutics market in the top seven markets (the US, the UK, Germany, France, Spain, Italy and Japan) was estimated at $XXm in 2011, having grown at a Compound Annual Growth Rate (CAGR) of XX% from 2004. Growth was driven by an increase in the patient volume and the Annual Cost of Therapy (ACT) per patient, which was itself due to the approval of Nexavar (sorafenib) in the US and Europe. The market is forecast to reach $XXm by 2018 at a CAGR of XX% from 2011. The anticipated launch of Eli Lilly’s ramucirumab (IMC-1121B), a monoclonal Antibody (mAb) in 2014; Celsion Corporation’s ThermoDox in 2014; and PrevOnco in 2015 will drive market growth.

Newer Techniques are Being Studied for Treating Liver Cancer

Hepatocellular Carcinoma (HCC) is usually detected late as symptoms tend to appear in the advanced stages of the disease. As a result, most patients have a poor prognosis. Poor diagnosis measures also affect the patient volume available for HCC treatment. New treatment options have recently been considered for treating HCC, and doctors are looking at advances in different types of neoadjuvant (before surgery) and adjuvant (after surgery) therapies that might help to increase survival rates. Chemotherapy, ablation, embolization and radiation therapy are examples of important types of neoadjuvant therapy.

New drugs are being developed that work differently from standard chemotherapy drugs, by targeting specific parts of cancer cells or their surrounding environment. Nexavar, which works by hindering new blood vessel and thereby tumor growth, is being studied for use in the early stages of cancer. Additionally, a newer approach to treatment is the use of a virus known as JX-XX, the same virus that was used to make the smallpox vaccine, but that has been altered so that it infects mainly cancer cells by causing them to die or make proteins that result in them being attacked by the body’s immune system, leaving normal cells unaffected.
Liver Cancer Therapeutics Market to 2018 - Introduction

Liver cancer is the third leading cause of death from cancer worldwide and the ninth leading cause of cancer deaths in the US (CDC, 2010). Disease symptoms usually appear in the late stage of the disease, leading to a low diagnosis rate that in turn affects the patient volume available for Hepatocellular Carcinoma (HCC) treatment. Disease awareness is also low and there are no mandatory screening guidelines for the diagnosis of HCC. Moreover, failure to recognize patients at risk of hepatitis B and/or C and a lack of public understanding of the disease means that knowledge of the risk factors is limited.

Early liver cancer often has no symptoms. Symptoms may include, but are not limited to, weight loss, lack of appetite, weakness, nausea and vomiting. Treatment is based on tumor size, location, and overall health. HCC is often unresectable, meaning that it cannot be removed surgically. Liver transplant and surgical resection are the curative treatment options for patients in the early stages of the disease which represent XX-XX% of cases. Many HCC patients (approximately XX%) are not eligible for curative treatments, either due to poor liver function or advanced disease. Other treatment options include embolization, chemotherapy, ablation, radiation and targeted therapy.

The current competition in the liver cancer market is weak, as Nexavar (sorafenib) is the only approved drug for advanced HCC with the exception of Miripla (miriplatin) in Japan. However, there are some molecules in Phase XX development as first-line and second-line treatments, which promise to influence the competitive landscape in the next two to three years. These molecules include Celsion’s ThermoDox, ImClone/Eli Lilly’s ramucirumab, Medigen/Progen’s muparfostat and Novartis’ Afinitor (everolimus).

The deal activity in the liver cancer therapeutics market is very low with no high-profile deals involving any major research-based partnerships or any of the most promising molecules. Licensing agreements were the most common type of deal that occurred between 2007 and October 2012 in the liver cancer therapeutics market.
4.2 Annual Cost of Therapy

The ACT for liver cancer was $XX in 2004 and grew at a CAGR of XX% to $XX in 2011. The increase was primarily due to the introduction of new blockbusters such as Nexavar and Miripla. The ACT for liver cancer therapeutics market will grow at a rate of XX% between 2011 and 2018 to $XX. Increased awareness and access and the expected launch of new products such as Ramucirumab, ThermoDox and PrevOnco will increase the ACT in the forecast period.

![Graph showing the annual cost of therapy for liver cancer therapeutics market from 2004 to 2018.]

Source: GBI Research

<table>
<thead>
<tr>
<th>Year</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>CAGR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT</td>
<td>$XX</td>
<td>$XX</td>
<td>$XX</td>
<td>$XX</td>
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<td>$XX</td>
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Source: GBI Research

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<th>Year</th>
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<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>CAGR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT</td>
<td>$XX</td>
<td>$XX</td>
<td>$XX</td>
<td>$XX</td>
<td>$XX</td>
<td>$XX</td>
<td>$XX</td>
<td>$XX</td>
<td>$XX</td>
</tr>
</tbody>
</table>

Source: GBI Research
6 Liver Cancer Therapeutics Market to 2018 - Pipeline Analysis

6.1 Introduction

The current competition in the liver cancer market is weak, as Nexavar is the only approved drug for advanced HCC, with the exception of Miripla in Japan. However, there are some molecules in Phase III as first-line and second-line treatments which promise to influence the competitive landscape in the near future. They include Celsion’s ThermoDox, ImClone/Eli Lilly’s ramucirumab Medigen/Progen’s muparfostat and Novartis’ Afinitor. These pipeline molecules are expected to have an impact on the HCC therapeutics market during the forecast period, boosting future competition. The HCC pipeline has been considerably weakened by the discontinuation or failure of several late-stage clinical trials. However, in recent late-stage clinical trials (such as BRISK-FL, PS) of one of the most promising molecules, BMS’ brivanib, was announced to be ineffective at meeting its end point (BMS, 2012a; 2012b). Other promising molecules such as Abbott’s linifanib, for which the late-stage trial has been terminated, and Onyx/Bayer’s Tarceva in combination with Nexavar failed to meet their end points (Onyx Pharmaceuticals, 2012a). The HCC pipeline includes several agents targeting angiogenesis-related pathways including mAbs and TKIs. Market growth is expected to be influenced by the ongoing shift from chemotherapy-based regimens to high-price targeted and biological agents.

Companies and research institutions are actively pursuing R&D activities for HCC treatment, and activity is expected to remain high during the 2011-2018 period. There are currently XX molecules in various stages of development, of which the majority are in Phase XX (XX%) and Preclinical (XX%). Late-stage molecules (Phase XX and Phase XX/XX) account for XX%, while Phase XX/XX and Phase XX constitute XX%. Discovery constitutes the remaining XX% of the HCC pipeline.

<table>
<thead>
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<th>Phase</th>
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<tr>
<td>I</td>
<td>XX%</td>
</tr>
<tr>
<td>II</td>
<td>XX%</td>
</tr>
<tr>
<td>II/III</td>
<td>XX%</td>
</tr>
<tr>
<td>III</td>
<td>XX%</td>
</tr>
<tr>
<td>Preclinical</td>
<td>XX%</td>
</tr>
<tr>
<td>Discovery</td>
<td>XX%</td>
</tr>
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</table>

Figure 20: Liver Cancer Therapeutics Market, Global, Pipeline Products, by Stage of Development, 2012

Source: GBI Research’s Proprietary Pipeline Database [accessed December 14, 2012]
<table>
<thead>
<tr>
<th>Development Stage</th>
<th>No. of Pipeline Products</th>
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<td>Phase III</td>
<td></td>
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<tr>
<td>Phase II/III</td>
<td></td>
</tr>
<tr>
<td>Phase II</td>
<td></td>
</tr>
<tr>
<td>Phase I/II</td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td></td>
</tr>
<tr>
<td>Preclinical</td>
<td></td>
</tr>
<tr>
<td>Discovery</td>
<td></td>
</tr>
<tr>
<td>Total no. of pipeline products</td>
<td></td>
</tr>
</tbody>
</table>

Source: GBI Research’s Proprietary Pipeline Database [accessed December 14, 2012]
9 Liver Cancer Therapeutics Market to 2018 - Appendix

9.1 Market Definitions

The global liver cancer therapeutics market refers to liver cancer in the top seven markets of the US, the UK, Germany, France, Spain, Italy and Japan.

Prevalence population: The prevalence population is the estimated number of people at any given point of time who are affected by liver cancer.

Diagnosis rate and population: The diagnosis rate is the percentage of the treatment-seeking population that is diagnosed with liver cancer, and the diagnosis population refers to the number of people that are diagnosed with liver cancer.

Prescription rate and population: The prescription rate is the percentage of the diagnosed population that is prescribed medication for liver cancer, and the prescription population refers to the number of people that are receiving medication for liver cancer.

9.2 Abbreviations

ACRG: Asia Cancer Research Group
ACT: Annual Cost of Therapy
ADCC: Antibody-Dependent Cellular Cytotoxicity
ADI: Arginine Deiminase
AFP: Alpha-Fetoprotein
ALT: Alanine Aminotransferase
ARD: Androgen Receptor Degradation
AST: Aspartate Aminotransferase
BGI: Beijing Genomics Institute
BSC: Best Supportive Care
CAGR: Compound Annual Growth Rate
CRC: Colorectal Cancer
DSP: Dainippon Sumitomo Pharma
DPD: Dihydropyrimidine Dehydrogenase
EEIFA: Ethyl Esters of Iodized Fatty Acids
EGFR: Epidermal Growth Factor Receptor
FDA: Food and Drug Administration
FGFR: Fibroblast Growth Factor Receptor
FLT-3: FMS-Like Tyrosine kinase 3
GM-CSFR: Granulocyte-Macrophage Colony Stimulating Factor Receptor
GPCR: G-Protein Coupled Receptor
GSK: GlaxoSmithKline
HBV: Hepatitis B Virus
HCC: Hepatocellular Carcinoma
HCV: Hepatitis C Virus
HDAC: Histone Deacetylase
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGS</td>
<td>Human Genome Sciences</td>
</tr>
<tr>
<td>IAP</td>
<td>Inhibitor of Apoptosis</td>
</tr>
<tr>
<td>IGF</td>
<td>Insulin-like Growth Factor</td>
</tr>
<tr>
<td>KSP</td>
<td>Kinesin Spindle Protein</td>
</tr>
<tr>
<td>LICR</td>
<td>Ludwig Institute for Cancer Research</td>
</tr>
<tr>
<td>mAb</td>
<td>monoclonal Antibody</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>mTOR</td>
<td>mammalian Target of Rapamycin</td>
</tr>
<tr>
<td>NDA</td>
<td>New Drug Application</td>
</tr>
<tr>
<td>PDGF</td>
<td>Platelet-derived Growth Factor</td>
</tr>
<tr>
<td>PDGFR</td>
<td>Platelet-derived Growth Factor Receptor</td>
</tr>
<tr>
<td>PEI</td>
<td>Percutaneous Ethanol Injection</td>
</tr>
<tr>
<td>PPI</td>
<td>Proton Pump Inhibitor</td>
</tr>
<tr>
<td>RCC</td>
<td>Renal Cell Carcinoma</td>
</tr>
<tr>
<td>RFA</td>
<td>Radiofrequency Ablation</td>
</tr>
<tr>
<td>RNAi</td>
<td>Ribonucleic Acid interference</td>
</tr>
<tr>
<td>SCLC</td>
<td>Small-Cell Lung Cancer</td>
</tr>
<tr>
<td>SEER</td>
<td>Surveillance and Epidemiology and End Results</td>
</tr>
<tr>
<td>SEGA</td>
<td>Subependymal Giant Cell Astrocytoma</td>
</tr>
<tr>
<td>SIRT</td>
<td>Selective Internal Radiation Therapy</td>
</tr>
<tr>
<td>STAT3</td>
<td>Signal Transducer and Activator of Transcription 3</td>
</tr>
<tr>
<td>TACE</td>
<td>Trans-Arterial Chemo-Embolization</td>
</tr>
<tr>
<td>TBI</td>
<td>TGF-beta receptor I</td>
</tr>
<tr>
<td>TGF-β</td>
<td>Transforming Growth Factor beta</td>
</tr>
<tr>
<td>TKI</td>
<td>Tyrosine Kinase Inhibitor</td>
</tr>
<tr>
<td>TRAIL</td>
<td>TNF-related apoptosis-inducing ligand</td>
</tr>
<tr>
<td>TROP</td>
<td>Trophoblast</td>
</tr>
<tr>
<td>TWEAK</td>
<td>Tumor Necrosis Factor-like Weak Inducer of Apoptosis</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular Endothelial Growth Factor</td>
</tr>
<tr>
<td>VEGFR</td>
<td>Vascular Endothelial Growth Factor Receptor</td>
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</tbody>
</table>
9.3 Bibliography

- Onyx Pharmaceuticals (2012a). Addition of Tarceva® (erlotinib) to Nexavar® (sorafenib) did not Provide Additional Benefit to Patients with Unresectable Liver Cancer Versus Nexavar alone in Phase 3 Trial.


### 9.4 Research Methodology

GBI Research’s dedicated research and analysis teams consist of experienced professionals with a pedigree in marketing, market research, consulting backgrounds in the medical devices industry, and advanced statistical expertise.

GBI Research adheres to the codes of practice of the Market Research Society (www.mrs.org.uk) and the Society of Competitive Intelligence Professionals (www.scip.org).

All GBI Research databases are continuously updated and revised.

#### 9.4.1 Coverage

The objective of updating GBI Research’s coverage is to ensure that it represents the most up-to-date vision of the industry possible.

Changes to the industry taxonomy are decided on the basis of extensive research of company, association and competitor sources.

Company coverage is based on three key factors: market capitalization, revenues, and media attention/innovation/market potential.

- An exhaustive search of 56 member exchanges is conducted, and companies are prioritized on the basis of their market capitalization.
- The estimated revenues of all major companies, including private and governmental, are gathered and used to prioritize coverage.
- Companies which are making the news, or which are of particular interest due to their innovative approach, are prioritized.

GBI Research aims to cover all major news events and deals in the medical industry, with its databases updated on a daily basis.

The coverage is further streamlined and strengthened with additional inputs from GBI Research’s expert panel (see below).
9.4.2 Secondary Research

The research process begins with exhaustive secondary research on internal and external sources being carried out to source qualitative and quantitative information relating to each market.

The secondary research sources that are typically referred to include, but are not limited to:

- Company websites, annual reports, financial reports, broker reports, investor presentations and US Securities and Exchanges Commission (SEC) filings.
- Industry trade journals, scientific journals and other technical literature
- Internal and external proprietary databases
- Relevant patent and regulatory databases
- National government documents, statistical databases and market reports
- Procedure registries
- News articles, press releases and webcasts specific to the companies operating in the market

9.4.3 Primary Research

GBI Research conducts hundreds of primary interviews each year with industry participants and commentators, in order to validate its data and analysis. A typical research interview fulfills the following functions:

- It provides first-hand information on the market size, market trends, growth trends, competitive landscape and future outlook
- Helps in validating and strengthening the secondary research findings
- Further develops the analysis team’s expertise and market understanding

Primary research involves email interactions, telephone interviews, and face-to-face interviews for each market, category, segment and sub-segment across geographies.

The participants who typically take part in such a process include, but are not limited to:

- Industry participants: CEOs, VPs, marketing/product managers, market intelligence managers and national sales managers
- Hospital stores, laboratories, pharmacies, distributors and paramedics
- Outside experts: Investment bankers, valuation experts, research analysts specializing in specific medical equipment markets
- Key Opinion Leaders: Physicians and surgeons specializing in different therapeutic areas corresponding to different kinds of medical equipment

The report consists of the following four major sections:

- Geographical Landscape
- Therapeutic Landscape
- Pipeline Analysis
- Competitive Analysis
9.5 **Therapeutic Landscape**

The revenues for each indication, by geography, are arrived at by utilizing the GBI Research market forecasting model. The global revenues for each indication are a summarized value of the revenues of all seven regions.

The annual cost of therapy for each indication is arrived at by considering the cost of the drugs, dosage of the drugs, and the duration of the therapy.

The generic share of the market for each indication is obtained by calculating the prescription share for generic drugs and the respective cost of treatment.

The treatment usage pattern, which includes quantitative data on diseased population, treatment-seeking population, diagnosed population and treated population for an indication, is arrived at by referring to various sources, as described below.

The marketed drugs section contains an overview of the drugs, their mechanism of action, efficacy and safety issues related to the drugs. The drugs profiled in this section are chosen based on estimated revenues and their mechanism of action.

GBI Research uses the epidemiology-based treatment flow model to forecast the market size for therapeutic indications.

### 9.5.1.1 Epidemiology-Based Forecasting

The forecasting model used at GBI Research makes use of epidemiology data gathered from research publications and primary interviews with physicians to represent the treatment flow patterns for individual diseases and therapies. The market for any disease segment is directly proportional to the volume of units sold and the price per unit.

\[ \text{Sales} = \text{Volume of units sold} \times \text{Price per unit} \]

The volume of units sold is calculated based on the average dosage regimen for that disease, the duration of treatment, and the number of patients who are prescribed drug treatment (the prescription population). The prescription population is calculated as a % of the population diagnosed with a disease (the diagnosis population). The diagnosis population is the population diagnosed with a disease expressed as a % of the population that is seeking treatment (the treatment-seeking population). The prevalence of a disease (diseased population) is the % of the total population who suffer from a disease/condition.

Data on treatment seeking rate, diagnosis rate and prescription rate, if unavailable from research publications, are gathered from interviews with physicians and are used to estimate the patient volumes for the disease under consideration. Therapy uptake and compliance data are fitted in the forecasting model to account for patient switching and compliance behavior.

To account for differences in patient affordability of drugs across various geographies, macroeconomic data such as inflation and GDP, and healthcare indicators such as healthcare spending, insurance coverage and average income per individual, are used.

Annual cost of treatment is calculated using product purchase frequency and the average price of the therapy. Product purchase frequency is calculated from the dosage data available for the therapies, and drug prices are gathered from public sources.

The epidemiology-based forecasting model uses a bottom-up methodology, and makes use of estimations in the absence of data from research publications. Such estimations may result in a final market value that is different from the actual value. To correct this ‘gap’, the forecasting model uses triangulation, with the help of base year sales data (from company annual reports, internal and external databases) and sales estimations.

### Analogous Forecasting Methodology

The analogous forecasting methodology is used to account for the introduction of new products, patent expiries of branded products, and the subsequent introduction of generics. Historic data for new product launches and generics penetration are used to arrive at robust forecasts. The increase or decrease of prevalence rates, treatment seeking rate, diagnosis rate and prescription rate are fitted into the forecasting model to estimate the market growth rate.
The proprietary model enables GBI Research to account for the impact of individual drivers and restraints in the growth of the market. The year of impact and the extent of impact are quantified in the forecasting model to provide close-to-accurate data sets.

**Diseased Population**

The diseased population for any indication is the prevalence. The prevalence rates are usually obtained from various journals, online publications, sources such as the World Health Organization (WHO) or associations and foundation websites for that particular disease.

**Diagnosis Population**

Out of the patients who undergo diagnostic tests to confirm a disease, only a few people get diagnosed with the disease. This number as a % of the treatment-seeking population is the diagnosis rate. The diagnosis population is primarily driven by the sensitivity of the diagnostic tests, state-of-the-art technology, patient access to these diagnostic tests, and cost of the diagnostic tests.

**Prescription Population**

For any disease, multiple treatment options exist. For example, in cancer treatment various treatment options such as surgery, radiation therapy and drug therapy are available. The prescription population is defined as the number of patients who are prescribed drug therapy. This is calculated as a % of the diagnosis population. The prescription population is primarily driven by the age at which the disease is diagnosed, the disease stage, patient health and the cost of drug treatment.

### 9.5.2 Market Size by Geography

The treatment usage pattern and annual cost of treatment in each country has been factored in while deriving the individual country market size.

**Forecasting Model for Therapeutic Areas**
The above figure represents a typical forecasting model constructed by GBI Research. As discussed previously, the model is built on the treatment flow patterns. The model starts with the general population, then diseased population as a % of general population, and then follows the treatment-seeking population as a % of the diseased population, and the diagnosed population as a % of the treatment-seeking population. Finally, the total volume of units sold is calculated by multiplying the treated population by the average dosage per year per patient.

### 9.6 Geographical Landscape

GBI Research analyzes seven major geographies, namely the US, the top five countries in Europe (the UK, Germany, France, Spain and Italy), and Japan. The total market size for each country is provided, which is the summarized value of the market sizes of all the indications for that particular country.

### 9.7 Pipeline Analysis

This section provides a list of molecules at different stages in the pipeline for various indications. The list is sourced from internal databases and validated for the accuracy of phase and mechanism of action at clinicaltrials.gov and company websites. The section also includes a list of promising molecules, which is narrowed down based on the results of the clinical trials at various stages and the novelty of the mechanism of action.
9.8 Competitive Landscape

Profiles of leading players are provided, along with an overview of key products marketed by the companies for various indications. An analysis of strengths, weaknesses, opportunities and threats of each company with respect to various indications is also listed.

GBI Research aims to cover all major M&A, licensing deals and co-development deals related to the market. This section is sourced from the companies' websites and internal databases.

9.8.1 Expert Panel Validation

GBI Research uses a panel of experts to cross-verify its databases and forecasts.

GBI Research’s expert panel comprises marketing managers, product specialists, international sales managers from medical device companies, academics from research universities, and key opinion leaders from hospitals.

Historic data and forecasts are relayed to GBI Research’s expert panel for feedback and adjusted in accordance with their feedback.

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