Progress In Hematological Malignancies

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Senior Consultant
Defined Health

23rd Annual Cancer Progress Conference
March 6th – 7th, 2012
23rd ANNUAL CANCER PROGRESS CONFERENCE

“The Premier Cancer Conference for Healthcare Executives”
March 6th - 7th, 2012
The Westin New York at Times Square

2012 Sponsors

- Astellas
- Bristol-Myers Squibb
- Eisai
- Genentech
- Janssen
- Lilly
- TEVA
- BioCentury

For further information concerning Lilly grant funding, visit www.lillygrantoffice.com

NATIONAL FOUNDATION FOR CANCER RESEARCH
Research for a Cure

3/22/2012
Cancer is Now The Largest Global Pharmaceutical Category With WW Sales Exceeding $80B

- Targeted therapies are changing the landscape of cancer treatment and likely will be used in most cancer patients in 5-10 years. Monoclonal antibodies, oral tyrosine kinase inhibitors, and other targeted therapies could exceed $60B in worldwide sales by 2016.

WW Revenue By Major Oncology Drug Category

EvaluatePharma
Cancer Drugs Constitute a Growing Component of Overall Pharma Sales for Leading Oncology Franchises

<table>
<thead>
<tr>
<th>Pharmaceutical Sales of Top 10 Oncology Franchises</th>
<th>Sales $B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche</td>
<td>35</td>
</tr>
<tr>
<td>Novartis</td>
<td>40</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>45</td>
</tr>
<tr>
<td>Sanofi</td>
<td>50</td>
</tr>
<tr>
<td>Celgene</td>
<td>10</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>15</td>
</tr>
<tr>
<td>Pfizer</td>
<td>20</td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>25</td>
</tr>
<tr>
<td>Takeda</td>
<td>30</td>
</tr>
<tr>
<td>GlaxoSmithkline</td>
<td>35</td>
</tr>
</tbody>
</table>

**Sales $B**

- **Oncology sales**
- **Overall Sales**

*EvaluatedPharma*
Heme Oncology is Gaining Prominence in Leading Oncology Portfolios, Mostly Through Acquisitions

EvaluatePharma
Blood Cancers Represent Only 9.5% of 1.6 Million New Cancer Cases Diagnosed in The US Each Year

- Solid Tumors Represent >90% Of Newly Diagnosed Cancer Cases and Deaths Each Year
  - Lung, GI, Prostate, Breast and Ovarian are Deadliest
Yet, Marketed Therapies For Blood Cancers Comprise Half of The Oncology Top 10 Blockbusters

Top ten oncology blockbusters are expected to grow 26% over the next five years - Forecasted to Exceed $20B by 2016

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Class</th>
<th>Patent Expiry</th>
<th>Revenue 2016 ($M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avastin</td>
<td>Roche</td>
<td>VEGF MAbs</td>
<td>2018</td>
<td>$7.8</td>
</tr>
<tr>
<td>Rituxan</td>
<td>Roche</td>
<td>CD20 MAbs</td>
<td>2018</td>
<td>$7.7</td>
</tr>
<tr>
<td>Herceptin</td>
<td>Roche</td>
<td>HER2 MAbs</td>
<td>2019</td>
<td>$6.5</td>
</tr>
<tr>
<td>Revlimid</td>
<td>Celgene</td>
<td>IMID</td>
<td>2026</td>
<td>$5.5</td>
</tr>
<tr>
<td>Alimta</td>
<td>Eli Lilly</td>
<td>Antimetabolites</td>
<td>2017</td>
<td>$3.0</td>
</tr>
<tr>
<td>Erbitux</td>
<td>BMS/ Merck KGaA</td>
<td>EGFR MAbs</td>
<td>2018</td>
<td>$2.8</td>
</tr>
<tr>
<td>Provenge</td>
<td>Dendreon</td>
<td>Immunotherapy</td>
<td>2017</td>
<td>$2.6</td>
</tr>
<tr>
<td>Gleevec/Glevic</td>
<td>Novartis</td>
<td>Abl/c-Kit Inhibitor</td>
<td>2015</td>
<td>$2.3</td>
</tr>
<tr>
<td>Tasigna</td>
<td>Novartis</td>
<td>Abl/c-Kit Inhibitor</td>
<td>2023</td>
<td>$2.3</td>
</tr>
<tr>
<td>Velcade</td>
<td>JNJ/ Takeda</td>
<td>Proteosome Inhibitor</td>
<td>2018</td>
<td>$2.2</td>
</tr>
</tbody>
</table>

EvaluatePharma
Oncology is Not Immune to Generic Substitution – But Blood Cancers Less Effected by Near Term Genericization

- Nearly $17 B of oncology drugs face patent expiry and generic substitution in the next 3 years.
- Total revenue generated by sales of mature oncology products are expected to decrease from $14B in 2009 to less than $8B in 2014.
- Products indicated primarily for solid tumors which a largely small molecule cytotoxics and TKIs are the main source of lost revenues.
- Conventional small molecule drugs are expected to have the largest impact as long as the regulatory route of biosimilars remains stringent.
- Accordingly, revenues from mature products for blood cancers are expected to have a prolonged rate of decline since they are more often biologic therapies and protected by orphan drug laws.

*EvaluatePharma, Defined Health analysis*
Changing Balance of Pharma Market Forces: Drug Developers Now See Greater Commercial Risk in Broad Clinical Programs vs. Scientific Risk in Underserved Niches

- Scientific Risk
  - Underserved Niche Indications
  - Biomarker Stratification
  - Biologics Platforms

- Commercial Risk
  - Regulatory Risk for Broad Indication
  - Market Access
  - Generic SOC Competition
  - Share of Voice in MedOnc
Oncology Pipeline Has Become Less Focused on “Big Five” Tumors

Competition In Common Tumors Has Increased Programs Positioned Niche Cancers
Scientific/Clinical Risk: Drugs in Development For Heme Malignancies Have Lower Attrition Rates

- Higher success rates in heme malignancies may reflect inherent differences in the underlying biology of these cancers versus the highly heterogeneous solid tumors.

Source: Deloitte Recap, [www.recap.com](http://www.recap.com)
Data current as of January 31, 2012, see following slide for details
Deloitte Recap DEVELOPMENT optimizer™
Solid Tumors Dominate The Early Oncology Pipeline; However, Hem/Onc Products are More Evenly Distributed

- Although there are roughly 8 times the number of agents in development for solid tumors than for blood cancers in early stage, relatively few are bridging the Phase II “Valley of Death”.
- Novel agents for blood cancers appear more rationally based and developers use less of a “shots on goal” clinical strategy.
- One trend to note is that the number of programs pursuing “Big 5” tumors has decreased in recent years; more promising programs are using biomarkers to identify likely responder segments.

ADIS R&D Insight, Thomson Pharma Partnering
Biologic Platforms: Blood Cancers Lead the Way Cancer for Novel Antibody Technologies

1908: Paul Ehrlich envisions antitoxins (antibodies) as “magic bullets” that could selectively deliver toxins to pathogens.

1975: Kohler and Milstein describe generation of murine mAbs.

1988: First chimeric (mouse-human) antibodies described.

1995: Panorex (edrecolomab, murine anti-EpCAM) approved for post-operative CRC in Germany (later withdrawn).

1997: Rituxan (rituximab, chimeric anti-CD20) approved for relapsed/refractory NHL in US.

1998: Herceptin (trastuzumab, humanized anti-HER2) approved for HER2+ metastatic breast cancer in US.

2000: Mylotarg (Gemtuzumab ozogamicin, humanized anti-CD33 + calicheamicin) approved for relapsed AML in US.

2003: Bexxar (tositumomab, murine anti-CD20 + 131I) approved for refractory NHL in US.

2006: Vectibix (panitumumab, human anti-EGFR) approved for metastatic CRC in US.

2004: Avastin (bevacizumab, humanized anti-VEGF) approved for metastatic CRC in US

2006: Zevalin (ibritumomab tiuxetan, murine anti-CD20 + 90Y) approved for relapsed/refractory NHL in US.

2009: Arzerra (ofatumumab, human anti-CD20) approved for refractory CLL in US.

2009: SGN-35 (brentuximab vedotin, anti-CD30 + monomethyl auristatin E) awarded fast-track status for refractory HL by FDA.

2010: Genentech submits BLA to FDA for T-DM1 (trastuzumab + emtansine) for refractory HER2+ metastatic breast cancer.
**Products Approved for Blood Cancers are Often Eligible for Orphan Designation**

- During the years 2000 to 2010, 18 of the 38 therapeutic oncology drugs approved by the FDA were first indicated for blood cancers (47%).
- Pivotal trials of these orphan oncology drugs had the following characteristics:
  - Smaller participant numbers (96 vs. 290 patients exposed to drug)
  - Were less likely to be randomized (30% vs. 80%)
  - Orphan trials were less likely to be double-blind (4% vs. 33%).
  - Primary study outcomes with orphan trials more likely to assess disease response (68% vs. 27%) rather than overall survival (8% vs. 27%).
  - However, more treated patients had serious adverse events in such trials (48% vs. 36%).
- All 18 received FDA orphan designation and/or designation as orphan medicinal products by the EMA; while only 5 of 20 solid tumor oncology products received orphan designation.

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Company</th>
<th>1st indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>Mylotarg (gemtuzumab)</td>
<td>Wyeth</td>
<td>CD33 positive AML</td>
</tr>
<tr>
<td>2000</td>
<td>Trisenox (arsenic trioxide)</td>
<td>Cell Thera</td>
<td>APL</td>
</tr>
<tr>
<td>2001</td>
<td>Campath (alemtuzumab)</td>
<td>Berlex Labs</td>
<td>B-cell CLL</td>
</tr>
<tr>
<td>2001</td>
<td>Gleevec; (imatinib)</td>
<td>Novartis</td>
<td>CML</td>
</tr>
<tr>
<td>2002</td>
<td>Zevalin (ibritumomab)</td>
<td>IDEC Pharma</td>
<td>NHL</td>
</tr>
<tr>
<td>2003</td>
<td>Bexxar (tositumomab)</td>
<td>Corixa</td>
<td>CD20 positive, Relapsed follicular NHL</td>
</tr>
<tr>
<td>2003</td>
<td>Velcade (bortezomib)</td>
<td>Millennium Pharma</td>
<td>3rd-line MM</td>
</tr>
<tr>
<td>2004</td>
<td>Clolar (clofarabine)</td>
<td>Genzyme</td>
<td>Relapsed Pediatric ALL</td>
</tr>
<tr>
<td>2004</td>
<td>Vidaza (azacitidine)</td>
<td>Pharmion Corp</td>
<td>MDS subtypes including refractory and CMML</td>
</tr>
<tr>
<td>2005</td>
<td>Revlimid (lenalidomide)</td>
<td>Celgene;</td>
<td>low- and int-1-risk MDS</td>
</tr>
<tr>
<td>2005</td>
<td>Arranon (nelarabine)</td>
<td>GlaxoSmithKline</td>
<td>T-cell ALL and T-cell lymphoblastic lymphoma</td>
</tr>
<tr>
<td>2006</td>
<td>Zolinza (vorozostat)</td>
<td>Merck &amp; Co</td>
<td>CTCL</td>
</tr>
<tr>
<td>2006</td>
<td>Sprycel (dasatinib);</td>
<td>BMS</td>
<td>imatinib-resistant CML</td>
</tr>
<tr>
<td>2006</td>
<td>Dacogen (decitabine)</td>
<td>MGI Pharma</td>
<td>Int-2 and high risk MDS</td>
</tr>
<tr>
<td>2007</td>
<td>Tasigna (nilotinib)</td>
<td>Novartis</td>
<td>imatinib-resistant CML</td>
</tr>
<tr>
<td>2008</td>
<td>Treanda (bendamustine)</td>
<td>Cephalon</td>
<td>Relapsed CLL</td>
</tr>
<tr>
<td>2009</td>
<td>Arzerra (ofatumumab)</td>
<td>GlaxoSmithKline</td>
<td>Campath refractory CLL</td>
</tr>
<tr>
<td>2009</td>
<td>Istodax (romidepsin)</td>
<td>Gloucester Pharma</td>
<td>CTCL</td>
</tr>
<tr>
<td>2009</td>
<td>Folotyn (pralatrexate)</td>
<td>Allos Therapeutics</td>
<td>PTCL</td>
</tr>
</tbody>
</table>

_FDA.gov, Leukemia & Lymphoma Society, Defined Health analysis_
Biomarkers: Although Understanding of Neoplastic Pathways Has Outpaced Translation – Heme Has Been The Poster Child for Biomarker Driven Drug Development
Therapies for Blood Cancers Appear to Demand Higher Pricing

- Recently approved drugs for blood cancers were priced at >2 times the price per treatment for the solid tumor agents introduced during the same period.
  - For oncology drugs launched in the last 3 years, the average annual treatment costs for blood cancers was $61K vs. $21K for solid tumors
  - Treatment cost of the solid tumor agents was in a narrow band of $19K to $30K whereas the blood cancers ranged much more widely: $37k to $98K.

Leukemia & Lymphoma Society, Compass Strategic Consulting, DH analysis
Hematological Malignancies Represent a Broad Spectrum of Diseases, Each with Diverse Outcomes

Comparison of Diseases by Survival Rate, Age of Onset & Incidence

SEER database; scientific literature. Incidence is indicated by the size of the sphere.
Outcomes in Blood Cancers Have Been Transformed Through Both Trial and Error and Rationally Designed Transformative Therapies

*Improvement in patient outcomes can be rapid with rationally designed transformative therapies, or incremental advances in treatment standards*

Then and Now: Age of Onset Compared to Overall Survival

**SEER database; scientific literature**
¼ Heme Pipeline In Development For NHL (*the most prevalent*) – Significant Portion For Rare Blood Cancers

**Number of Agents In Clinical Development (P1-reg) For Hematological Malignancies**

- **NHL** 26%
- **MM** 19%
- **CLL** 13%
- **AML** 18%
- **OTHER MYELOID** 10%
- **ALL** 6%
- **CML** 5%
- **HL** 3%

*(Total= 400)*
Heme Pipeline Closely Tracks Unmet Needs in Terms of Mortality

Comparison of Development Stage Agents Compared to a Composite Factor of Incidence and Outcomes (Incidence/5-year Survival)

SEER, ADIS R&D Insight, Thomson Pharma Partnering
Non-profits are Proactively Investing in Pipeline Agents Aligned With the Unmet Needs of Blood Cancers

- Founded in 1949, The Leukemia & Lymphoma Society (LLS) has been providing grant funding to leading academic investigators and providing CORE grants in the pursuit of curing leukemia, lymphoma and myeloma.
- Today, LLS is taking a more proactive role in advancing promising therapies by supporting translational research towards clinical results.
- The Therapy Acceleration Program (TAP) is a strategic initiative to speed the development of blood cancer treatments and supportive diagnostics.
- TAP looks to fund projects related to therapies that have the potential to change the standard of care for patients with blood cancer, especially in areas of high unmet medical need.
- The goal is to enable critical proof of concept data necessary to draw further resources to partner to complete the testing, registration and marketing of new treatments.

*Personal communication, J. DeGennaro, PhD | Executive Vice President, Chief Mission Officer*
Non-profits are Proactively Investing in Pipeline Agents Aligned With the Unmet Needs of Blood Cancers

- Found in 1998, Multiple Myeloma Research Foundation (MMRF) pledges to pursue innovative means to accelerate the development of next-generation multiple myeloma treatments.

- MMRF provides end-to-end solution to accelerate drug development which works by bridging drug discovery gaps and by developing business solutions that inject speed and efficiency into drug development.

- MMRF partners with leading cancer centers, researchers, and the biopharma industry to deliver much-needed new treatments to patients.

- Industry partners, including Novartis, Celgene, Merck, and Onyx

- MMRF collaborations led to FDA approval of 4 treatments for myeloma have been approved: Velcade, Thalomid, Revlimid and Doxil

- MMRF’s portfolio includes investments in discovery, translation and phase I and II clinical trials.

DH secondary research; MMRF website
2011 Marked Record Oncology Deal Activity

Number of Deals By Oncology Deals By Therapy Area

Oncology Deals, Total Potential Value

EvaluatePharma; PharmaVentures
## 2011-2012 Highlighted Deal Activity for Hematological Products

<table>
<thead>
<tr>
<th>Alliance</th>
<th>License / Acq</th>
<th>Asset / Class</th>
<th>Indication (Phase)</th>
<th>Upfront (Mlns)</th>
<th>Total (Mlns)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celgene/ Avila</td>
<td>Acquisition</td>
<td>AVL-292, selective Btk inhibitor</td>
<td>B-Cell Maligs [Phase I]</td>
<td>$350.0</td>
<td>$925.0</td>
<td>Cash plus milestones contingent upon the development and regulatory approval of AVL-292. Potential milestone payments contingent upon the development and approval of candidates generated from the Avilomics platform.</td>
</tr>
<tr>
<td>Janssen / Pharmacyclics</td>
<td>WW License</td>
<td>PCI-32765</td>
<td>NHL, CLL, Myeloma [Phase II]</td>
<td>$150.0</td>
<td>$975.0</td>
<td>WW 50/50 profit share rights to J&amp;J. Collaboration to focus on development of product for oncology excluding inflammation &amp; immune mediated conditions; development costs to be shared.</td>
</tr>
<tr>
<td>Ono Pharma / Onyx Pharma</td>
<td>Japan License</td>
<td>Carfilzomib</td>
<td>Myeloma [Phase III]</td>
<td>$59.0</td>
<td>$349.0</td>
<td>Carfilzomib and ONX 0912 for oncology in Japan</td>
</tr>
<tr>
<td>Mundi Pharma/ Allos</td>
<td>Ex-US and CA License</td>
<td>Folotyn (pralatrexate)</td>
<td>PTCL (Marketed)</td>
<td>$50.0</td>
<td>$311M</td>
<td>Milestones for regulatory &amp; commercial progress-and sales-dependent payments+ tiered double-digit royalties. Joint funding of development costs.</td>
</tr>
<tr>
<td>BMS / Innate Pharma</td>
<td>WW License</td>
<td>IPH 2102</td>
<td>AML, [Phase I]</td>
<td>$35.0</td>
<td>$465.0</td>
<td>WW rights to develop, manufacture &amp; commercialize IPH2102 &amp; related compounds blocking KIR. BMS to fund development of IPH2102 and tiered double-digit royalties.</td>
</tr>
<tr>
<td>Spectrum / TopoTarget</td>
<td>NAFTA and India License</td>
<td>Belinostat</td>
<td>PTCL [Phase III]</td>
<td>$30.0</td>
<td>$354.5</td>
<td>Belinostat histone deacetylase inhibitor for Peripheral T-Cell Lymphoma in NAFTA &amp; India</td>
</tr>
<tr>
<td>Celgene/ Acetylon</td>
<td>Equity Investment</td>
<td>ACY-1215™</td>
<td>Myeloma [Phase I]</td>
<td>$15.0</td>
<td>-</td>
<td>Purchase of Series B-2 Preferred Stock. Celgene does not receive rights or options to Acetylon technology under the agreement terms.</td>
</tr>
<tr>
<td>Epizyme / Eisai</td>
<td>WW License</td>
<td>EZH2</td>
<td>Preclinical</td>
<td>$6.0</td>
<td>$206.0</td>
<td>Cancer therapeutics targeting EZH2 epigenetic enzyme, option to US profit split and co-promotion</td>
</tr>
<tr>
<td>BI / Micromet</td>
<td>WW License</td>
<td>BiTE bispecific antibody</td>
<td>Myeloma [Discovery]</td>
<td>$6.6</td>
<td>$72.6</td>
<td>BiTE bispecific antibody for the treatment of multiple myeloma</td>
</tr>
</tbody>
</table>
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