Antibody-Drug Conjugates: A Discriminating Approach to Chemotherapy

Insights in Engineering Leadership White Paper

Abstract

Around the world, billions of dollars are spent each year to fight cancer with chemotherapy treatments. Throughout the history of chemotherapy use, one of the biggest challenges has been the side effects of the treatment. Traditional chemotherapy drugs attack not only malignant cells, but other healthy, fast-growing cells in the patient's body. New chemotherapy treatments based upon antibody-drug conjugates (ADCs) are beginning to make their way to market. This new generation of cancer fighting drugs holds the promise of reducing side-effects and improving success rates when compared to traditional chemotherapy drugs. ADC-based drugs will impact the chemotherapy market in the coming years, and the associated technology will likely influence treatment of other diseases as well.

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Section 1: History and Evolution of Chemotherapy

Traditional chemotherapy has its roots in World War II chemical weapons research. During that time, it was observed that naval personnel who had been exposed to Mustard Gas had toxic changes in their bone marrow cells. The U.S. Army was also studying chemical alternatives to mustard gas with the goal of creating more effective weapons and developing better protective measures. That work eventually led to the creation of a compound called “nitrogen mustard”, which was found to be toxic to lymphoma cells. Today, chemotherapy is actually the last choice for cancer treatment. The best option is surgical removal of small, localized tumors. Radiation is then often used to destroy small tumors which were not or could not be removed. The chemotherapy option is used to destroy cancer that can’t be removed by surgery or targeted by radiation. (American Cancer Society, 2012)

Traditional chemotherapy treatments, however, have harsh side effects on most cancer patients. The approach has been referred to as the carpet-bombing strategy for fighting cancer. Traditional chemotherapy does not discriminate between cancer cells and other fast-dividing cells which are common in the body. This is why common side-effects include hair loss, nausea and vomiting, to name a few. (Forbes, 2013)

In recent years a new weapon has been under development in the fight against cancer, the Antibody-Drug Conjugate (ADC). As the name implies, the drug is an antibody with a cytotoxin attached to its structure. The type of antibody used to create the drug is selected based upon unique biomarkers found on the cancer cells to be targeted. (Roche, 2014) ADC-based chemotherapy can be thought of more like a “guided missile” approach to fighting cancer, directly delivering the cytotoxic agents to the malignant cells. This approach benefits the patients by allowing them to stay on the treatment regimen longer, while reducing the toxic side-effects associated with traditional chemotherapy treatments. (The Wall Street Journal, 2013)

Annually, billions of dollars are spent worldwide on chemotherapy treatments. Biotechnology companies and pharmaceutical companies are investing, collaborating and partnering in all areas of ADC-based technology, including antibody production, linker technology, the conjugation process and the identification of biomarkers on malignant cells. As research, development and approval of ADC-based technology moves forward, ADC-based chemotherapy drugs will impact the existing chemotherapy market, improve the quality of life for cancer patients and influence research and development in other pharmaceutical markets.
Section 2: Existing Chemotherapy Landscape

2.1. Chemotherapy Market

At the start of the 21st century, patient costs for typical cancer treatments such as surgery and radiation therapy were $5,700 and $4,500, respectively. On the other hand, chemotherapy and its related services were upwards of $12,800 per patient. (The American Journal of Managed Care, 2012) Oncology drugs were close to a $26 billion business in the US alone in 2012. (New York Magazine, 2013) This is with 40% of Medicare spending going to oncologists using chemotherapy drugs at a cost of $2.3 billion to the Federal Government. (Chemoth, 2011) Clearly, there is big money to be made in treating cancer.

2.2. Chemotherapy Business Model and Industry

Unlike most medical treatments, the sale and administration of chemotherapy drugs are performed directly by oncologists who deal directly with the drug manufacturers in their offices. This is a result of a practice that was started 40 years ago when only oncologists would risk handling the highly toxic substances. What could only be described as an onerous and otherwise unattractive business model for large drug manufacturers, an individual-by-individual small volume market, has blossomed into a multi-billion dollar industry while retaining the short supply chain, and one would think mark-up, thus cost to patient, would be contained. However, as a result of this direct to "mom-and-pop" business practice, oncologists derive almost 50% of their profit from sales of chemotherapy drugs. (The New England Journal of Medicine, 2011)

There are in excess of 100 chemotherapy drug manufacturers in the US alone. However, in terms of market share, Sanofi-Aventis is one of the largest chemotherapy drug companies with 34% in 2008, or $5 billion in sales. Eli Lilly & Company also has close to a 9% market share.

In terms of a patient’s cost, drugs such as Roche’s Avastin, approved in 2004 for the treatment of breast, colon, lung and brain cancer, can be up to $55,000 a year with projected sales of $8 billion by 2013.

2.3. Competing Targeted Therapies

Alternatively, a targeted therapy drug, such as tamoxifen, a cellular receptor for estrogen, can be used to treat a breast cancer patient and cost less than $2,000 annually, compared to chemotherapy costs ranging from $10,000 to +$40,000. (Chemo,) (National Cancer Institute, 2012) “Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules involved in tumor growth and progression” according to the National Cancer Institute. ADCs, or Anti-Drug Conjugates combine the promise of targeted cancer therapies with the effectiveness of the chemotherapy “nuclear option” of destroying specific rapidly producing cells.

Antibody-Drug Conjugates: A discriminating approach to chemotherapy
2.4. The Advantages of ADC’s

“The concept of antibody-drug brings together the targeting advantages of antibodies and the cytotoxic potential of chemotherapy, heralding the promise of targeted accumulation of drug in the tumour cell or tissue” says MA Firer of the Ariel Center for Applied Cancer Research at Ariel University in Israel (OA Cancer, 2013). So they do not attack all rapidly dividing cells, such as esophageal, thus vastly reducing deleterious side effects and having the potential to shorten total treatment cycles by decreasing recovery times between treatments as well as increasing overall patient recovery percentages. Even with only two approved by the Food and Drug Administration (FDA), so far, see Table 1, with 13 more in the approval system and 55 in open clinical trials, these new drugs threaten chemotherapy drug manufacturers’ market share as well as Oncologists long term profitability. (Chemo, 2011) (National Cancer Institute, 2012)

Section 3: ADC Technology

3.1. Anatomy of Antibody Drug Conjugates

ADCs are a new class of highly potent bio-pharmaceutical drugs, and represent an innovative therapeutic application that combines the properties of monoclonal antibodies (mAbs) with the potent small molecule drugs (cytotoxin) that provides the cell-killing efficacy. ADCs consists of an antibody (a whole monoclonal antibody or an antibody fragment) connected, via a stable, chemical linker, to a biological active cytotoxic (anticancer) payload or drug (see Figure 2). (Elvidge, S., 2013) (ADC Review, 2013). In Figure 3, characteristics of ADCs are highlighted. (Zolot, Rachel S., et.al., 2013). The most active area of development for this class of therapeutics has been oncology. (Ritter, Amy, 2012)

3.2. How ADCs Work

“In developing antibody-drug conjugates, an anticancer drug (e.g. a cell toxin or cytotoxin) is coupled to an antibody that specifically targets a certain tumor marker” (e.g. protein/antigen) that “is only to be found in or on tumor cells”. (Wikipedia, 2014). The ADC drug stays inert while circulating through the patient’s system while the “antibodies track down these proteins down in the body and attach themselves to the surface of cancer cells. The biochemical reaction between the antibody and the target protein (antigen) triggers a signal in the tumor cell, which then absorbs or internalizes the antibody together with the cytotoxin. After the ADC is internalized, the cytotoxic drug is released and kills the cancer.” (Wikipedia, 2014)
3.3. Key Considerations When Creating an ADC

The concept of an ADC is not new, but creating a clinically successful therapeutic drug has been challenging. For the therapeutic to work well, careful consideration has to be put in each of the key components — the antibody, the toxin, and the linker that holds them together. (Ritter, Amy, 2012)

3.3.1. Choosing the Right Antibody

“In general, mAbs as therapeutics are selected to have high affinity for the targeted antigen and high selectivity. Other desirable properties in an antibody include long circulation times, immune-effector functions, and tumor suppressing activity.” (Ritter, Amy, 2012)

“When choosing the antigen, it is important that it be expressed at high levels in the tissue of interest to maximize the amount of ADC bound by the tumor, but at low levels elsewhere in the body to minimize off-target toxicity. Moreover, it is thought that internalization of the ADC is important for its effectiveness. Many of the chemical-linking strategies used to construct ADCs rely on conditions found inside a cell, either in the cytoplasm or in the lysosome, to release the active agent. In some instances, developers have been able to leverage experience gained through the development of mAb therapies to create their ADC.” (Ritter, Amy, 2012)

3.3.2. Choosing the Right Linker

Developing the right and stable link between the antibody and cytotoxic (anti-cancer) agent is a critical aspect of an ADC. Linkers “control the distribution and delivery of the cytotoxic agent to the target cell.” (Wikipedia, 2014)

Many areas around the linker process have improved, however, the linker strategy for ADC manufacturing and their application has certainly contributed perhaps the most in moving the field forward. “The creation of linkers that are stable in circulation but labile upon binding of the ADC to its target has resulted in the current generation of ADCs having better stability and lower systemic toxicity” (Lancaster Laboratories, 2013) than earlier ADCs.

Early versions of ADCs suffered from instability while in circulation. The linkage between the mAb and the cytotoxic small molecule were destroyed by endogenous proteases in the blood, and the premature release of the cytotoxin resulted in side-effect profiles similar to that of conventional chemotherapeutic. (Lancaster Laboratories, 2013)

The current generation of linkers is “more resistant to degradation in the blood while still allowing release of the payload at the target.” (Lancaster Laboratories, 2013) “The choice of a linker is influenced by which toxin is used, as each toxin has different chemical constraints.” (Lancaster Laboratories, 2013) “The availability of better and more stable linkers has changed the function of the chemical bond.” (Wikipedia, 2014)
Linkers can be divided into two broad categories: cleavable and non-cleavable.

- **Cleavable Linkers**
  - Rely on processes inside the cell to liberate the toxin and “are catalyzed by enzymes in the cancer cell where it releases the cytotoxic agent.” (Wikipedia, 2014)
  - “The cytotoxic payload delivered via a cleavable linker can escape from the targeted cell” and “attack neighboring cancer cells.” (Wikipedia, 2014)

- **Non-cleavable Linkers**
  - Keep the drug within the cell and “require catabolic degradation of the conjugate for release of the cytotoxic small molecule.” (Ritter, Amy, 2012)
  - “As a result, the entire antibody, linker and cytotoxic agent enter the tumor cell where the antibody is degraded to the level of an amino acid.” (Wikipedia, 2014)
  - “The resulting complex -- amino acid, linker and the cytotoxic agent -- now becomes the active drug.” (Wikipedia, 2014)

Both classes of linkers are designed to release the cytotoxic molecule only after the ADC has reached the interior of the cancer cell. “Cleavable and non-cleavable types of linkers have been proven to be safe in preclinical and clinical trials.” (Wikipedia, 2014)

There is a lot of research ongoing to develop new linker technologies that provide “flexibility without worrying about the changing cleavage kinetics.” (Wikipedia, 2014)

### 3.3.3. Choosing the Right Cytotoxic Agent

The clinical trial results of earliest versions of ADCs that used standalone chemotherapeutics (e.g. doxorubicin, methotrexate, etc.) as the cytotoxic arm of the conjugate were disappointing. “It is thought that part of the problem was the relatively low potency of the toxins used.” (Ritter, Amy, 2012) The newer classes of cytotoxins are more potent than the older molecules. “There are only a few major chemical classes of toxins being explored. They can be divided into two types, those that cause damage to DNA and those that interfere with tubulin polymerization.” (Ritter, Amy, 2012)

### Section 4: Regulatory and Societal Factors

#### 4.1. Food and Drug Administration Approval of ADCs

Surprisingly, the process to take a drug from experimental to mainstream usage can take up to 12 years and cost upwards of $1 billion dollars. (MedicineNet.com, 1999) (Envita Medical Center, 2013) The various stages and average times involved are:

1. Preclinical (lab testing – 3.5 years),
2. Phase I (safety, absorption, dosage – 1 year),
3. Phase II (drug effectiveness – 2 years), and
4. Phase III (clinical trials – 3 years).

After the preclinical stage, a drug manufacturer must apply for an Investigational New Drug (IND) permit. When approved, the three test phases can then proceed, with FDA interaction between each phase. Once the clinical trials are complete, if the drug is determined to be still viable, the manufacturer must submit a New Drug Application (NDA) which encompasses and summarizes all the data. This final report can contain tens of thousands of pages of material, and historically can take up to 2.5 years for the FDA to review and approve.

Regarding FDA approval of the specific drugs required for a cancer patient, it is important that there be little to no delay in approval of new treatments, especially if they are tailored to a specific patient or class of patients. Any unnecessary delays can be very detrimental to cancer patients on limited time and with rapidly advancing symptoms. At this time, only two ADCs are approved for general use, Adcetris and Kadcyla.

The FDA has established various teams to assist in the qualification of critical drugs, such as ADCs. (U.S. Food and Drug Administration, 2012)

These teams are:

- The Center for Drug Evaluation and Research (CDER) which is a division of the FDA that reviews the application data and approves the use of new drugs,
- The Office of Biotechnology Products (OBP) is responsible for quality, safety, efficacy and availability of therapeutic and monoclonal antibody products, and
- The Office of New Drug Quality Assessment (ONQQA) assesses the critical quality attributes and reviews the manufacturing processes of new drugs.

These groups aim to work together to ensure a safe, effective drug is made available for the public in the shortest amount of time.

Additionally, throughout the years, the FDA has enacted various legislation to shorten the approval cycle time. Two such programs may provide a faster path to introduction of cancer fighting therapies, they are the Fast Track Development Program with a goal review time of only 60 days (compared to the average 2.5 year timeframe), and the Breakthrough Therapy Designation (BT) which streamlines the required clinical testing. (U.S. Food and Drug Administration, 2012) These programs were specifically designed to address faster approval of drugs that cope with serious conditions, such as those of cancer patients.

4.2. Clinical Trials and Consortia

Clinical trials (i.e. Phase III) are underway by many different and varied companies, from big pharmaceuticals to start-ups. In fact, over 30 ADCs are currently in the clinical development stage, and more than 50 in the preclinical stage. (Immunomedics, 2013)

There is strong collaboration between companies, and among companies and academia. There are also numerous consortia formed specifically for cancer research and the emerging Antibody-Drug Conjugates: A discriminating approach to chemotherapy
Antibody-Drug Conjugates: A discriminating approach to chemotherapy

treatment technologies. The goal of these consortia is to work together and streamline the development process by involving and funding like-minded companies. What is unclear is what manner of Intellectual Property (IP), patent protection, and possible revenue sharing agreements are in place or destined to happen, and who will ultimately regulate the market. Annual reports of the major companies do contain reference to partnerships, but they are only specific to the year of the report.

Although each cancer-related consortia may focus on a specific cancer type, there are groups identified within them related to specific treatment methods. In most cases, these groups are focusing on the most promising option, both in effectiveness and the well-being of the patient. An example of various Consortia existing in this realm include:

- **International Lung Cancer Consortium (ILCCO)** – recent focus on genetics and DNA repair.
- **Melanoma Genetics Consortium (GenoMEL)** – non-profit consortium with worldwide participation and focused on the genetics of familial melanoma.
- **International Cancer Genome Consortium (ICGC)** – UK – launches and coordinates research projects aimed at understanding the genomic changes in many forms of cancer

### 4.3. Privacy

Much of the revolutionary research being performed these days focuses on genetics of the patient, or treatment group. While no one is expected to oppose anyone from realizing a faster path to healing or remission, DNA testing and associated research is still intrusive or concerning for some, specifically as it applies to security of personal information. In regard to ADCs, although the science is based on treatment at the molecular level, it is independent of a patient’s DNA.

The future of medicine will likely bring us many more developments based on our DNA, though. To that end, The Personal Genome Project (PGP) was recently established which intends to employ 100,000 voluntary participants, who agreed to share their information for the purpose of science, and pool their information into ultimately helping others. (Scientific American, 2013)

### Section 5: Winner and Losers in the ADC Market

Currently there are two FDA approved ADC therapies (Adcetris & Kaycyla) and over 50 ADCs in various phases of clinical development.
5.1. FDA Approved ADC Therapy:

5.1.1 Adcetris

Seattle Genetics entered the ADC market with Adcetris after FDA approval in 2011. Adcetris is the first new drug that the FDA has approved for Hodgkin Lymphoma (HL) since 1977, and the first drug specifically for anaplastic large cell lymphoma (ALCL) treatment. On the average greater than 73% of the patients saw a 6-13 month improvement in response. (Adcetris, 2011) (See Figure 4)

Treatment cost range from $94,500 to $121,500. (Medical News Today, 2011) Annual revenue for the HL and ALCL target ADC increased to 250 million from 2012 revenue of $138 million. Takeda Group equally invested during the development for the rights to market Adcetris in all countries except US and Canada. (Seattle Genetics, 2014) (Seattle Genetics, 2013)

5.1.2 Kadcyla

Developed and marketed by Roche, ADC product Kadcyla received FDA approval in 2013 and targets HER2 positive metastatic breast cancer. Treatment cost is typically $94,000, double the cost of the current chemotherapy Herceptin. (Decision Resources, 2013) Survival rate increased to 31 months over the 25 months for patients taking the traditional Herceptin and taxane chemotherapy, with an increased duration of response of 6 months (See Figure 5) and those experiencing side effects reducing from 58% to 40%. (Roche, 2013) (Genentech, 2014)

Peak sales expected to be in the $2-5 billion range and should make up for some of the market erosion when Herceptin generics come to the market. Kadcyla, which uses T-DM1 technology licensed from ImmunoGen, should open the path for more ADC’s based on ImmunoGen linker technology. Roche pays 3-5% royalties from sales of Kadcyla to ImmunoGen for ADC technology. (Decision Resources, 2013)

5.1.3 Mylotarg

Pfizer developed Mylotarg as the first FDA approved ADC therapy, in 2000, targeting acute myeloid leukemia (ACL), but Mylotarg was subsequently removed from the market in 2010 for toxicity concerns. (U.S. Food and Drug Administration, 2010)

5.2 ADC Pipeline

5.2.1 Seattle Genetics

Seattle Genetics is well positioned within the ADC market with FDA approved Adcetris, a pipeline that includes over 20 ADCs in various phases of clinical development (see Figure 6)
and an additional 15 ADC’s under clinical development in collaboration with companies such as Genentech, Bayer, Pfizer, Celldex and others (see Figure 7). (Seattle Genetics, 2014) Licensing agreements generate $250 million with upward potential of over $4.5 billion in milestone payments. (Seattle Genetics, 2014)

5.2.2 ImmunoGen

In addition to Kadcyla, ImmunoGen has 4 proprietary linker chemistries under development, 3 of which are already in clinical trial and another 7 compounds are under clinical development through collaboration with companies such as Amgen, Bayer, Biotest, Lilly, Novartis, and Sanofi (see Figure . (Immunogen, 2014) (Immunogen, 2013) Licensing agreements brought in $24 million in 2013 and collaboration support of $7.8 million ($5.6 million from Novartis). (Immunogen, 2014)

Section 6: Future of the ADC Market

6.1. ADC Market Expectations

The use of ADCs to fight cancer is still in the design phase of the S-curve in terms of technical capabilities, similar to where the digital camera market was in the late-1980’s. (See Figure 9) There is ongoing innovation in nearly all technical areas of ADC creation. For example, ADC Biotechnology is working to simplify the conjugation processes, with the goal of producing drugs with less side-effect inducing cytotoxic residue. (ADC Biotechnology, 2014)

Biotechnology companies will continue to form partnerships and cross license technology with big pharmaceutical companies, as is evident by the pipeline and partnership information seen for companies like Seattle Genetics and ImmunoGen. This will result in an increasing number of ADCs entering clinical trials. As more and more ADCs are approved by the FDA, the global revenue from ADCs will grow quickly.

6.2. Future Opportunities for ADC Technology

In the near term, there will be opportunities in the area of antibody production in order to meet increasing demand, and in the area of ADC manufacturing to improve drug quality to improve effectiveness and reduce toxic side-effects. (ADC Biotechnology, 2014)

The research and development efforts going into ADCs today will lead to future opportunities in the fight against cancer. Seattle Genetics has licensed technology from Spirogen (recently acquired by AstraZeneca) for linker technology that will enable creation of a single antibody that is conjugated with two cytotoxic drugs.
Biotechnology companies are researching Antibody-Dependent Cellular Cytotoxicity (ADCC) therapies. This approach uses an antibody to connect to an effector cell (i.e., Killer T-cell) from the patient’s own immune system on one side and to the target cancer cell on the other, allowing the effector cell to release cytotoxic granules and cytokines to kill the target cell. (Cerep, 2011)

Research is also being conducted into Antibody-Radionuclide Conjugates (ARCs), an approach which is similar to ADCs in terms of the targeting capabilities, but the antibody is conjugated with a radionuclide instead of a cytotoxin. (Clinical Cancer Research, 2011)

Further out on the horizon, ADC-related technology will likely find its way into the fight against infectious diseases. Pre-clinical studies are currently under way to investigate the use of monoclonal antibodies to inhibit the growth of methicillin-resistant Staphylococcus aureus (MRSA). (Drug Discovery & Development, 2010) Research is also underway to use antibodies or similar proteins to bind with viruses, such as influenza or polio, to keep them from infecting other cells. (UW Medicine, 2012)
Appendix: Tables and Figures

Table 1

<table>
<thead>
<tr>
<th>Status</th>
<th>Total number</th>
<th>Blood cancers</th>
<th>Solid cancers</th>
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There are about 55 open clinical trials with ADCs, as mono- and combination therapy.

(OA Cancer, 2013)

**Figure 2:** Antibody Drug Conjugate and its three key components (Monoclonal Antibody, Linker, Cytotoxic agent).

(Source: http://surfaceearth.com/2012/08/01/cancer-treatment-2/)
Figure 3: Characteristics of ADCs (Zolot, Rachel S., et.al., 2013)

![Characteristics of ADCs](image)

Figure 4: Tables of Adcetris Efficacy (Adcetris, 2011)

### Table 2: Efficacy Results in Patients with Hodgkin Lymphoma

<table>
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<tr>
<th></th>
<th>Percent (95%CI)</th>
<th>Duration of Response, in months</th>
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<tr>
<td></td>
<td></td>
<td>Median (95% CI)</td>
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<tr>
<td>CR</td>
<td>32 (23, 42)</td>
<td>20.5 (12.0, NE(^*))</td>
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<tr>
<td>PR</td>
<td>40 (32, 49)</td>
<td>3.5 (2.2, 4.1)</td>
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<tr>
<td>ORR</td>
<td>73 (65, 83)</td>
<td>6.7 (4.0, 14.8)</td>
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### Table 3: Efficacy Results in Patients with Systemic Anaplastic Large Cell Lymphoma

<table>
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<th>Percent (95%CI)</th>
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<tr>
<td></td>
<td></td>
<td>Median (95% CI)</td>
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<tr>
<td>CR</td>
<td>57 (44, 70)</td>
<td>13.2 (10.8, NE(^*))</td>
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<tr>
<td>PR</td>
<td>29 (18, 41)</td>
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<tr>
<td>ORR</td>
<td>86 (77, 95)</td>
<td>12.6 (5.7, NE(^*))</td>
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Figure 5: Kadcyla Duration of Response (Genentech, 2014)

![Graph showing the duration of response for Kadcyla and lapatinib + capecitabine.](image)

**KADCYLA (n=173)**

- 12.6 months
- 95% CI: 8.4-20.8

**Lapatinib + Capecitabine (n=120)**

- 6.5 months
- 95% CI: 5.5-7.2

**No. at risk:**

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<td>ADCETRIS® (brentuximab vedotin)</td>
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<td>ALCANZA: Relapsed CD30-positive cutaneous T-cell lymphoma</td>
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<td>Frontline HL in patients 60+ (+= dascarbazine)</td>
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<td>Frontline diffuse large B-cell lymphoma (+ RCHOP)</td>
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**Figure 6:** Seattle Genetics ADC Pipeline (Seattle Genetics, 2014)
Figure 7: Seattle Genetics ADC Collaborator Pipeline (Seattle Genetics, 2014)

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**Wholly Owned by ImmunoGen**

We have three wholly owned compounds with our Targeted Antibody Payload (TAP) technology in clinical testing, with fourth on track to enter the clinic this year.

**IMGN901** – Potential new treatment for small-cell lung cancer – an aggressive cancer with a median survival of less than a year – and other CD56-positive cancers.
- Randomized Phase II trial under way.
- Results, next-step decision expected in 2014.

**IMGN853** – Potential new treatment for many ovarian, endometrial and non-small cell lung cancers.
- Encouraging initial data reported.
- First efficacy data in target patient populations expected in 2014.

**IMGN529** – Potential new treatment for non-Hodgkin lymphoma (NHL) and other B-cell malignancies.
- Only agent in development for NHL to contain an active antibody plus the TAP technology used in Kadcyla®.
- Presentation of first clinical data expected in 2014.

**IMGN289** – Potential new treatment for many head and neck and non-small cell lung cancers.
- EGFR-targeting TAP compound that provides both EGFR inhibition and direct cancer killing.
- Investigational New Drug (IND) application active – human clinical testing expected to start by year end.

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**In Development through Partnerships**

Kadcyla – Commercialization off to a great start!
- ImmunoGen now earning growing royalty revenue.
- Lead Phase III trial, EMILIA, showed survival benefit, plus tolerability advantages, compared to standard care.
- FDA approved in late February and launched in US soon after by Genentech, a member of the Roche Group.
- Roche reported US sales of approximately $19 million for Q1 2013 and $68 million for Q2 2013.
- Progress being made outside the US, including regulatory achievements in key international markets.

Roche is developing Kadcyla for multiple uses – for advanced and early stage HER2-positive breast cancer, and for advanced HER2-positive gastric cancer.

Other leading companies – Amgen, Bayer, Biotest, Lilly, Novartis, Sanofi – are developing targeted anticancer compounds under license with ImmunoGen.

- Compounds in development for glioblastoma, mesothelioma, multiple myeloma, NHL, ovarian cancer, renal cell carcinoma, and other cancers.
- Seven compounds are already in the clinic through these collaborations, with submission of INDs for additional TAP compounds expected in 2014.
- Encouraging initial findings reported for three compounds, with clinical data for most if not all of these seven compounds expected by mid-2014.

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**Figure 8: Immunogen Compound Pipeline** (Immunogen, 2013)
Antibody-Drug Conjugates: A discriminating approach to chemotherapy
Bibliography

Section 1


Section 2


Section 3


Section 4


Antibody-Drug Conjugates: A discriminating approach to chemotherapy
Insights in Engineering Leadership White Paper


Section 5


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Antibody-Drug Conjugates: A discriminating approach to chemotherapy
Section 6


Companies Mentioned
Seattle Genetics
Roche
Genentech
Igenica

Useful Websites
United States Food and Drug Administration
World Antibody Drug Conjugate Summit
Fierce Biotech
The Antibody Society

www.seattlegenetics.com
www.roche.com
www.gene.com
http://www.igenica.com

www.fda.gov
www.adc-summit.com
www.fiercebiotech.com
www.antibodysociety.org
National rankings consistently place UC Berkeley’s undergraduate and graduate programs among the world’s best. Berkeley is home to top scholars in every discipline, accomplished writers and musicians, star athletes, and stellar scientists—all drawn to this public university by its rich opportunities for groundbreaking research, innovative thinking and creativity, and service to society.