Equity markets

Major advances in cancer therapeutics 18 August 2015

CIO WM Research
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- Our cancer therapeutics investment theme recommends companies that we believe are potential winners in the rapidly expanding USD 100bn cancer treatment market.
- New cancer therapies, such as various forms of immuno-oncology, are improving patient survival rates, often with reduced side effects compared to conventional therapies.
- In our view, immuno-oncology and other exciting new cancer treatments have the potential to open up more than a USD 25 billion opportunity for the pharmaceutical and biotechnology industry.
- We believe our selection of oncology-related stocks will outperform the broader healthcare sector, initially due to new clinical data that demonstrate the potential for success, and ultimately by cancer companies sharply beating earnings growth expectations.

Investment Guidance

Cancer is a leading cause of death and generates among the highest costs to healthcare systems around the globe. According to the World Cancer Report 2014, published by the World Health Organization (WHO), over 14 million new cases of cancer (excluding non-melanoma skin cancers) and over eight million cancer deaths occurred globally in 2012. The WHO further estimated the annual global financial cost of cancer at USD 1.16 trillion in 2010, with the cost and occurrence expected to rise steadily given the ever aging population worldwide.

Much is changing in cancer treatment and, in our view, there will be many more breakthroughs still this decade. A better understanding of cancer cell biology and the immune system has led to the advances in immuno-oncology, a therapeutic approach that uses the body's immune system to fight cancer. In some cancers, such as melanoma and lung cancer, immuno-oncology has already proven to improve patient survival rates, with more durable responses and reduced side effects in comparison to conventional chemotherapy.

A version of this report is available with specific security recommendations for US onshore investors. For a copy, please consult your UBS Financial Advisor.

Our previous reports on this theme include:
- Major advances in cancer therapeutics, published 14 April 2015
- Major advances in cancer therapeutics - update, published 15 September 2014
- Major advances in cancer therapeutics-update 2, published 23 February 2015
- Major advances in cancer therapeutics-update 3, published 8 March 2015

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Combined sales of two new immuno-oncology drugs launched within the past year are already annualizing at over USD 1 billion. While these new treatments are not a “cure,” they represent a material improvement in length and quality of life for many patients. Importantly, these are still early days for immuno-oncology: there is much more progress on the horizon, such as the high probability that science can create designer T-cells (e.g., CAR-Ts) to personalized cancer treatment.

Cancer therapeutics is a growth-oriented theme, with little economic sensitivity. Pharmaceutical companies with exposure to oncology tend to offer above-GDP earnings growth and high returns on capital. Many new cancer therapeutics are also being developed by smaller biotechnology companies with no earnings history: returns for these companies heavily depend on successful clinical development or commercial partnerships for their respective drugs; hence, we emphasize a long-term investment horizon and diversification when investing in the cancer therapeutics theme.

Cancer - a broad spectrum of opportunity

In its simplest terms, cancer is uncontrolled cell growth. It starts when cells, for genetic, environmental (e.g., sun exposure), lifestyle (smoking, diet) or even unknown factors, become abnormal and grow out of control. Some cancers, like leukemias and lymphomas, affect the blood stream and blood-forming organs, while other cancers invade normal tissues and can spread throughout the body.

The most common types of cancer in men are lung, prostate, colorectal and stomach cancer, and in women breast, colorectal, lung and cervical, although less severe forms of skin cancer would dominate if also taken into account. These cancers, along with blood-borne cancers like leukemia and lymphoma, are among the largest therapeutic markets for pharmaceutical and biotechnology companies today.

There are over 100 forms of cancer, each with its own biological and life-altering characteristics. Treatment often requires multiple rounds of various combination therapies — surgery, chemotherapy, immunotherapy, targeted drug therapy, etc. — to modify disease progression, sometimes increasing life expectancy by only a matter of months.

Given the complexity of the disease, it is unlikely that we will ever find a “golden bullet” that cures cancer; however, scientific progress in both diagnosis and treatment has led to a better outlook for cancer patients over the past few decades. According to the American Cancer Society, the 5-year survival rate for all cancers diagnosed between 2004 to 2010 increased to 68%, up from 49% in 1975 to 1977. While there are some notable success stories, such as prostate and breast cancer, survival rates for some hard-to-treat cancers remain low. Five-year relative survival rates for lung cancer are 18%, compared to 12% 40 years ago, while pancreatic cancer five-year survival is just 7% for patients diagnosed between 2004-10, as compared to 3% for patients diagnosed between 1975-1977. Clearly, the need for new and better treatments for these cancer types is as great as ever.
New cancer treatments

Many conventional cancer treatments — surgery, radiation, hormone therapy and chemotherapy — have evolved significantly over the past century, but much more effective treatments, with better survival outcomes and improved quality of life, have recently come to the fore. Much of the current excitement in cancer treatment stems from advances in the field of immuno-oncology — using the body’s immune system to attack cancer cells.

Initially, immuno-oncology included biotechnology development of substances like interferons, interleukins, and other cytokines aimed at boosting a patient’s immune system. This approach was followed by B-cell therapies that aimed recombinant monoclonal antibodies at tumors. Now research has moved into T-cell mediated immunotherapies. Two rapidly evolving and high sales potential areas of immuno-oncology include the development of checkpoint inhibitors (e.g., PD-1 inhibitors, PD-L1 inhibitors, CTLA-4 inhibitors) and CAR-Ts, which we explore in more detail below.

Checkpoint inhibitors - the current wave of immuno-oncology

The first T-cell mediated immuno-oncology drugs to reach the market are known as checkpoint inhibitors. These drugs are designed to block the cancer’s ability to defend itself from the immune system. The first therapeutic checkpoint was a CTLA-4 inhibitor (Yervoy), approved for malignant melanoma in 2011. Three years later, two PD-1 inhibitors (Opdivo, Keytruda) were approved for use in melanoma and this year for lung cancer.

PD-1 inhibitors are already establishing themselves as the new standard of care in melanoma, and with recent regulatory approval, will almost undoubtedly become the standard of care in lung cancer, a large underserved therapeutic marketplace. The enthusiasm for checkpoint inhibitors are manifold, namely:

- **Improved patient survival rates**
- **Improved safety profile compared to chemotherapy**
- **Improved quality of life while under treatment**

Beyond melanoma and lung cancer, checkpoint inhibitors are being tested in over 30 different types of cancer and, in early stages of human testing, have shown effect in a number of other cancers, including bladder, ovarian, stomach, head and neck, kidney, and liver cancer.

It is important to note that these drugs still only represent the first wave of T-cell mediated immuno-oncology products. There is still an alphabet soup of new approaches in earlier stages of development, including IDO inhibitors, OX-40, CD137, anti-GITR, anti-KIR and other novel mechanisms. These new approaches will undoubtedly be explored in combination with the checkpoint inhibitors and other cancer drugs in hope of improving patient outcome beyond any therapies known today.
**CAR-Ts - the next wave of immuno-oncology**

New developments in T-cell engineering technology hold promise in personalized cellular immunotherapy — using a patient’s immune cells to attack cancer. One such approach, chimeric antigen receptor T-cells (CAR-T cells), has shown remarkable but early evidence of efficacy in leukemia and lymphoma and may have applications in solid tumors.

CAR-T treatment combines the cytotoxic (cell-killing) ability of T-cells (an immune system cell responsible for fighting infections) with the targeted nature of monoclonal antibodies. T cells are first collected from the patient’s own blood, then genetically engineered with special receptors on their surface called chimeric antigen receptors (CARs). These CARs allow the T cells to recognize a specific antigen found on tumor cells. The engineered CAR-T cells are grown in the laboratory and then infused into the patient, where they recognize and kill cancer cells.

CAR-Ts have already shown highly promising results in early studies in certain leukemias and lymphomas, and have now entered more advanced human testing. If these studies prove successful, the first CAR-Ts could be commercialized within the next few years.

While highly promising, CAR-T therapy is still in early stages of development and a number of issues need to be resolved before this therapy becomes a commercial reality. Safety could prove to be a key challenge, particularly in solid tumors. Additionally, the nature of CAR-T treatment also introduces technical hurdles in manufacturing, especially because each treatment is unique to each patient. Nevertheless, if these challenges can be overcome, the commercial potential for personalized immunotherapies is great, in our view.

Other similar approaches include:

- **Universal chimeric antigen receptors** (UCAR-T’s) are derived from a healthy donor’s T-cells and engineered in such a way that they can be used to treat any patient.
- **Bispecific T-cell engagers** (BiTE) are antibodies that bind to both a specific tumor cell and a T-cell, to direct the patient’s immune system to the cancer.
- **Engineered T-cell receptors** (TCR’s) are capable of targeting antigens inside, as well as on the surface of, tumor cells; potentially more useful in treating solid tumors.
- **Antibody-coupled T-cell receptors** (ACTR’s) are re-engineered T-cells designed to be used alongside monoclonal antibodies.

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**Fig. 4: CAR-T cells**

Redesigning T-cells to attack cancer cells

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**CAR-T process:** 1) T-cells are removed from the body; 2) the T-cells are engineered to recognize the relevant cancer target; 3) engineered T-cells (CAR-T’s) are reintroduced to the patient where they multiply and attack the targeted cancer cells.

Source: Nature Biotechnology, v31, n11, 20 October 2015
Investment recommendations

We remain highly enthusiastic about the prospects in cancer therapeutics. It is our opinion that several breakthrough cancer therapies are likely to be introduced over the next few years, applying immune-oncology and other novel therapies, some with multi-billion dollars sales potential. From the current clinical data available, we are convinced that cancer treatment will take major steps forward in improved outcomes and quality of life over the remainder of this decade, opening more than a USD 25 billion opportunity for the pharmaceutical and biotechnology industry.

We believe our selection of oncology-related stocks will outperform the broader healthcare sector, initially due to new clinical data that demonstrate the potential for success, and ultimately by cancer companies sharply beating earnings growth expectations.

We have chosen specific stocks which we believe, as a group, will outperform the S&P 500 over the next year. In our opinion, this select group of companies share common themes: all have a fairly high probability of clinical success with new drugs in development and these new drugs are not yet fully reflected in the valuations of the respective stocks.

We fully acknowledge the risks involved in biotechnology and pharmaceutical investments, especially the risk of clinical failure. A new drug or biologic can fail at any point in clinical development or encounter regulatory issues (e.g., FDA), as well as experience post-approval commercial failure. For these reasons, we highly emphasize the merits of a diverse basket of stocks to invest in this theme.

Concerns over drug pricing are also valid given that many of these new agents will likely be introduced at extremely high prices. However, short of meaningful competition, we believe there is unlikely to be serious price pressure on truly novel therapeutics for life-threatening diseases.

Also, given the price appreciation of our thematic stock basket since April 2014, the valuation of many individual stocks in this group are appreciably higher since that time. However, we have taken valuation into consideration in our stock selection process and, with further clinical and commercial successes; we believe our select group of stocks have a high probability to outperform the S&P 500 over the next year. This list will be constantly monitored, with adjustments made when necessary. This report will be updated at least every six months, as long as it remains in our thematic universe.
Appendix

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<th>Term / Abbreviation</th>
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<tr>
<td>A</td>
<td>actual i.e. 2010A</td>
<td>E</td>
<td>expected i.e. 2011E</td>
</tr>
<tr>
<td>GDP</td>
<td>Gross domestic product</td>
<td>Shares o/s</td>
<td>Shares outstanding</td>
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<td>UP</td>
<td>Underperform: The stock is expected to underperform the sector benchmark</td>
<td>CIO</td>
<td>UBS Chief Investment Office</td>
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