



New Cancer Treatments

Investing in the Next Generation

By Paul Woods

In spite of advances in the treatment of cancer, it remains a deadly disease. As our population ages, cancer rates are increasing. Many types of cancer are curable in their early stages, and many treatments can hold cancer at bay for a period of time. However, cancer cells have the annoying habit of mutating and eventually overcoming treatments designed to control them. A cure remains elusive and cancer will probably pass heart disease in the next few years and become the leading cause of death in America.

Cancer is a disease characterized by a breakdown of cell growth regulators. The resulting loss of cellular growth control allows cancer cells to proliferate rapidly. For this to occur, tumor suppressor genes also have to fail to function. These are genes that normally inhibit the division of cells if they detect DNA damage or defects in the cell. Unfortunately, cancer cells have the ability to overcome both these genetic systems and overwhelm healthy tissues.

The First Generation

First generation cancer chemotherapy is composed of compounds that target and kill rapidly growing cells. Unfortunately, hair cells, cells in the stomach lining, and bone marrow cells also grow faster than others. The result is that most first generation chemotherapy leaves a patient bald, sick, and with a severely damaged immune system.

What many patients aren't told about first generation cancer chemotherapy is that 20-30% of them will die from the side effects of the drugs, not the disease. Another 25% of cancer patients are too sick to be given these drugs. In spite of this, the current market is believed to be in excess of \$10 billion and growing rapidly.

The Second Generation

The approach used by early chemotherapy is the equivalent of flooding a building to put out a fire in a wastebasket. In contrast, second generation drugs are designed to specifically target cancer cells and leave surrounding tissues undamaged. The goal of these treatments is to make cancer a treatable disease by stopping tumor growth and preventing cancer from metastasizing.

By eliminating the poisonous side effects, cancer patients that are too sick to be given first generation drugs can now be treated. In addition, keeping patients alive longer will also expand what is already a \$10 billion market. The result is that some of these new drugs have enormous potential.

The Fly in the Ointment

Before getting specific, we need to add one caveat. New drugs require approval by the Food and Drug Administration. In the last few decades, the amount of time required to obtain approvals has doubled. There is new leadership at the FDA saying all the right things about speeding up the drug approval process. However, predicting drug approvals remains extraordinarily difficult and the FDA almost always seems to find a reason to delay the first drug from a new class of drugs. For this reason, investing in companies with drugs awaiting approval by the FDA is very difficult and we recommend that investors focus on companies with drugs already on the market.

Following is an overview of some of the most promising new treatments and the companies that currently appear to have the strongest positions.

Monoclonal Antibodies

The body's immune system is programmed to produce antibodies when foreign substances like viruses, bacteria, and tumors are recognized as invaders. These invaders produce antigens and the body's immune system in turn produces proteins that seek out these antigens and destroy them. Monoclonal antibodies are specialized antibodies engineered to target specific antigens produced by tumors and attack them without harming healthy cells.

One of the first drugs to show the potential of second generation cancer treatments was Rituxin, marketed by Genentech (DNA) and Biogen Idec (BIIB) for the treatment of lymphoma. It has been on the market for about 6 years and is at least as effective as first generation cancer drugs without the poisonous side effects. This drug now produces sales of well over \$1 billion and is still growing rapidly.

Anti-Angiogenesis

Angiogenesis involves the formation of blood vessels to support new tissue growth. Cancer cells grow faster than others and have a constant need for new blood supplies to supply nutrients and support this growth. Anti-angiogenesis is designed to starve tumors of the blood necessary to support them by arresting the growth of new blood vessels.

In May 1998, the New York Times created a furor by running an article on this technology and announcing that a cure for cancer was finally on the horizon. EntreMed (ENMD) was featured and its stock rose 75 points the day the article appeared, even though the company had yet to begin human trials. Once human trials began, results were mostly disappointing. Scientists discovered that it's very difficult to target blood vessel growth on tumors only, and most investors dismissed this technology.

Genentech continued to press ahead and it's fair to say that the investment community was stunned when the company announced in May 2003 that their anti-angiogenesis drug, Avastin, showed very positive results in treating colorectal cancer. Just as surprising was having the FDA approve the drug in near record time in February 2004.

Avastin sales are now growing rapidly, but may just be scratching the surface. Most solid tumors including those associated with breast cancer, lung cancer, and prostate cancer are likely to have at least some susceptibility to this drug, and it appears to have blockbuster potential.

EGF Receptor Blockers

Epidermal growth factors are proteins secreted by various types of cells to promote cell growth. They bind to receptors on the membrane of cells and this process eventually leads to the cell receiving a signal to divide. Epidermal growth factor receptors are found on most solid tumors, and the goal of this technology is to essentially put gum in the lock to prevent the key from being inserted. If these receptors can be blocked, it makes it very difficult for many types of solid tumors to grow.

Erbix, the drug produced by ImClone Systems (IMCL), is the most notorious drug in this group. It was granted fast track status by the FDA for the treatment of colorectal cancer, only to have the New Drug Application rejected in December 2001. While the company's founder and his girlfriend ended up in jail for acting on this news before it was public, the real scandal was the unnecessary delay by the FDA.

The FDA finally got around to approving Erbix in February 2004. While they were dithering, over 300,000 people died of colon cancer. Erbix would probably have helped a significant percentage of these, but no coherent explanation was ever provided for this delay. Although Erbix is priced at a premium and is currently being used as a second line treatment for colon cancer after Avastin, it also has the potential to be used in multiple types of cancer.

Meantime, AstraZeneca (AZN) had already received approval in May 2003 to market Iressa in the U.S. for the treatment of lung cancer. This is a very large potential market, but AZN is already a huge pharmaceutical company, so even a blockbuster drug will have a fairly modest overall impact. However, being first to the market and pricing the drug more reasonably than Erbix gives Iressa a big competitive advantage for the time being.

In the meantime, there's another very impressive EGFR blocker waiting in the wings to treat lung cancer. OSI Pharmaceuticals (OSIP) has partnered with Genentech (DNA) on a drug named Tarceva. This recently demonstrated a remarkable survival benefit in advanced human trials. In patients with lung cancer that failed to respond to initial or secondary treatments, Tarceva increased survival rates by over 42%. FDA approval is possible in early 2005. AstraZeneca is also conducting broad scale human trials on Iressa, but if they can't match Tarceva's impressive survival statistics, OSI's drug may end up becoming the front line treatment in this market.

Tarceva became an even more interesting drug in September with the announcement that it also appears effective in the treatment of pancreatic cancer. In a broad scale human trial with patients suffering from advanced pancreatic cancer, Tarceva increased the survival rate by 23.5%. This is noteworthy as there are few treatment options at present, and pancreatic cancer is the fourth leading cause of cancer deaths.

Cancer Vaccines

Cancer vaccines are an old idea that may finally be showing some promise. The idea behind this treatment is to stimulate the body's immune system to recognize a tumor as a foreign body. Once recognized as such, the body's immune system produces cytotoxic T-lymphocytes (CTLs) that bind specifically to cells with antigens they recognize and kill the targeted cells. When done, the CTLs go to more cells with these antigens and repeat the process until no more of these can be found.

For cancer vaccines to be effective, several conditions have to be met. First, tumor cells must have tumor-specific antigens on their surface. Second, CTLs must be able to find these antigens. Third, CTLs must recognize these antigens as foreign. Finally, the immune system must be able to summon the cavalry and attack and kill the cancer cells. A vaccine that can overcome all these obstacles can, in theory, cure cancer.

The problem is that different vaccines overcome each problem with varying degrees of success. Some stumble on one hurdle, others have a problem with the next. Until further advances are made, it's likely that this therapy will eventually be used in conjunction with surgery or with treatments already discussed to try to clear the last traces of the disease or prevent cancer from recurring.

Because these vaccines target specific tumors and may not be a first line treatment, the potential market is not as large as treatments targeting multiple types of cancer. However, the companies developing these vaccines have relatively small amounts of outstanding shares, so even a drug that eventually generates \$100-500 million in revenues can have a significant impact upon earnings.

Dendreon (DNDN) appears to be closest to the market with a vaccine named Provenge for treating prostate cancer. A clinical trial now underway will be used by the FDA to evaluate the drug and determine whether or not the drug is approved. If the trial is successful, this drug may be on the market in 2006. Cell Genesis (CEGE) also appears to have promising cancer vaccine technology that appears to be a bit behind Dendreon.

Gene Therapy

Genes and the proteins they produce control every stage of life, including disease. As we already discussed, cancer is the product of a breakdown in the genetic systems designed to control it. It's the result of defects in either cancer promoting or cancer inhibiting genes. The successful completion of the Human Genome Project and the broader understanding of DNA opened the door to the enormous potential of gene therapy.

Gene therapy is a technique for the treatment of disease that entails the manipulation or inhibition of defective genes, the replacement of missing genes, or the direction of therapy based upon gene detection. The goal of gene therapy is to repair the root cause of all disease, including cancer. However, like the college football coach said, "potential means you ain't done it yet."

The most promising technology in this area is antisense, which focuses on overcoming diseases by preventing the proteins that cause disease from being formed. Antisense is essentially a jamming signal that targets the RNA that carries instructions from DNA to the cells. Antisense creates a mirror image of the RNA messenger that spreads disease. When injected into the body, it's supposed to bond with the RNA and prevent it from delivering its message to the protein building machinery. According to one scientist, "it's like cutting the wires from central command to the troops. All I have to know is what gene I have to screw up."

Unfortunately, this isn't nearly as easy as it sounds. It turns out the dummy genetic material often does more than just snip communication between bad genes and their deadly proteins. Many antisense drugs have been found to negatively affect other genes and proteins not implicated in disease. Still others have proven ineffective in snipping the wires. Enormous potential and drugs that have yet to demonstrate it have characterized this therapy to date.

Genta, Inc. (GNTA) and its partner Aventis (AVE) are in advanced human trials with Genasense, a drug that continues to show mixed results in treating a number of cancers. It has a number of trials underway for multiple myeloma, leukemia, melanoma, kidney cancer, pancreatic cancer, and lymphoma. So far, the drug has shown some benefits but has not significantly increased survival rates. Until this changes, it's hard to get too excited about Genta.

Isis Pharmaceuticals (ISIS) is the other dominant company in gene therapy. It has a number of drugs in research and has partnered with several high profile pharmaceutical and biotech companies. However, it has also not yet found a drug that demonstrates effectiveness in advanced human trials. If it does, it has already partnered away a big chunk of any potential profits.

Engineered Oncolytic Viruses

Engineered oncolytic virus technology is still in its early stages. It's not as advanced as the treatments already discussed, and is still too early to evaluate. However, it's based upon a very intriguing idea. Engineered oncolytic viruses are viruses that cannot survive in healthy cells. They are designed to be able to only survive and reproduce in cancer cells. In cancer cells, the theory goes, they reproduce very rapidly and cause the cell to burst. Once free, they find more cancer cells and repeat the process until all cancer cells have been wiped out.

There are a handful of companies involved in this area. The leading company appears to be Cell Genesis (CEGE). It's in early human trials, and progress appears to be worth monitoring.

Conclusion

Many of the different types of treatment discussed so far are complementary. Because they have limited side effects and target different aspects of cancer, it's realistic to expect some of these to be used together once they reach the market. The cancer cocktail of the future may very well include monoclonal antibodies, anti-angiogenesis, EGFR blockers, cancer vaccines, and gene therapy.

The eventual goal is to make cancer a treatable disease by stabilizing or shrinking tumors. In the meantime, however, cancer patients can expect to live longer with a better quality of life, and cancer patients too sick for first generation drugs will now have treatments available. This will allow what is already a market in excess of \$ 10 billion to expand significantly. With impressive drugs in several of these areas including 1 ½ potential blockbusters, Genentech (DNA) appears to be the best-positioned company in this group.

For disclosure purposes, it should be noted that Odyssey Advisors, LLC has investments in Genentech, ImClone Systems, and OSI Pharmaceuticals.

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