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CANCER: A NEW GAME

“Cancer didn’t bring me to my knees, it brought me to my feet.”
Michael Douglas, Actor

The medical community is in the midst of a renaissance in the treatment of many types of cancer. A new-yet-old approach known as Immuno-Oncology (IO) is in the vanguard of current research. IO utilizes one’s own immune system to better recognize and attack cancerous cells from within the human body. The breakthroughs that have taken place within the last ten years have been game-changing as concerns the treatment and care of cancer patients. We believe this is an area worth investigating further, not only on the basis of the fascinating research that is being done but also because we feel it will offer attractive investment implications for the foreseeable future. In this quarter’s Investment Strategy Update, we attempt to understand the investment implications of these exciting new technologies.

Cancer Statistics and Finding the Right Game Plan

The World Health Organization states that cancer is the second leading cause of death worldwide, behind only cardiovascular disease. In 2015 cancer claimed almost nine million lives globally. In 2018, there will be an estimated 1,735,350 new cases diagnosed and 609,640 cancer deaths in the United States alone, according to the American Cancer Society.

Lung cancer is the most prevalent form of cancer world-wide and represents the single largest market for cancer treatments using IO drugs. According to the Mayo clinic, a little more than half (56%) of people diagnosed with early-stage lung cancer lived for at least five years after diagnosis. In contrast, the five-year survival rate for people diagnosed with late-stage lung cancer that has spread (metastasized) to other areas of the body is only 5 percent.

Knowing survival rates, along with the stage of cancer, are key factors in understanding a prognosis and developing a treatment plan. Further analysis of statistics can help doctors know how other people with similar cancers at similar stages responded to treatment. Late last year, an analytics firm known as Global Data posited that IO has become the fifth option alongside those currently available to treat cancer: surgery, radiotherapy, chemotherapy, and other targeted therapies. IO is making significant headway as the option of choice, as not only are the treatments more effective, but oftentimes with a better side effect profile.
What’s Old is New, and Effective

Conceptually, IO is not all that new. Over 125 years ago, a surgeon by the name of Dr. William Coley suggested that harnessing the immune system might be useful in the treatment of cancer. What led him to this conclusion was an observation he made while treating a handful of his patients. He noted that some patients experienced cancer remission concurrent with a significant bacterial infection. A natural side effect of the body fighting its bacterial infections was that the immune system recognized cancer cells in the process and destroyed them as well. He later combined common streptococcal (think strep throat) bacteria with other common organisms (specifically, those that cause the orange/red sludge found on shower drains and tile grout) into a cocktail that he used to treat thousands of cancer patients. Many experienced nearly complete remission. Despite this promising start, mixed acceptance by the medical community, combined with the dawn of chemo and radiation therapies, caused Dr. Coley’s immunotherapy treatment to fall out of favor.

Fast forward and several new treatments known as “checkpoint inhibitors” have been approved by the Food and Drug Administration (FDA) and are proving to be extremely effective in the battle against cancer. Two of these drugs currently have sales in excess of $1 billion annually. This approach has spawned a research frenzy, as it is estimated that there are currently over 4,000 clinical trials of over 800 IO compounds being developed for different solid tumors and eight types of blood cancers.

Transformative Technologies in Medicine

An important function of the body's defenses is the ability to differentiate between naturally occurring healthy cells and those recognized as foreign or invasive (for example, cancer cells). Under normal circumstances, the immune system is able to identify and destroy cancer cells in our body, while leaving the healthy cells, as well as vital organs, alone to function as they are meant. However, cancer is a cunning enemy and cancer cells have been able to adapt and mutate, thus disguising themselves from detection by our immune system. This allows them to mix in with healthy cells, making blanket treatments under traditional protocols both more difficult and riddled with toxic side effects. What checkpoint inhibitors do is unmask the hiding cancer cell, allowing the immune system to attack cancer cells that were previously undetected.

While these targeted IO-based approaches to cancer treatment have produced astounding results, doctors, researchers, and lab technicians are constantly exploring new ways to combat cancer. The latest iteration of IO is something known as CAR-T cell therapy. Also called adoptive cell transfer (ACT), CAR-T is a genetically-modified IO treatment. In late 2017, the FDA unanimously approved a CAR-T therapy, with one panel member stating that the novel therapy was “the most exciting thing I’ve seen in my lifetime.” That particular therapy was aimed at treating leukemia in children, with other therapies being developed as this is written. CAR-T works by removing a patient’s cells, re-engineering them in a laboratory to produce a surface molecule called a chimeric antigen receptor (CAR) and then infusing the newly modified cells back into the patient’s blood stream to attack those that are cancerous.
Investment Implications

In 2016, the cancer IO market was estimated to be worth $41 billion, and is expected to reach $120 billion by 2025. To date, small to mid-sized biopharmaceutical companies have played an outsized role in the evolution of Immuno-Oncology. After smaller biotech companies go through the R&D process and then navigate the FDA approvals process, larger pharmaceutical companies often step in to acquire the company with the newest therapy. This pattern of acquisitions has emerged as the cost to develop a single new drug has approached $1 billion. The M&A activity that we have seen in smaller biotech companies is expected to increase, resulting in further consolidation of the industry.

We have taken a diversified approach with this in mind. We have found that owning shares of larger pharmaceutical companies that are actively investing in IO, and that also aim to acquire promising smaller companies, has worked well once we are able to identify those that are better positioned for a specific market. For lung cancer, there has been intense competition between two of the major U.S. drug manufacturers, each aiming to dominate the treatment with a competing immunotherapy using a checkpoint inhibitor. As their results from years of clinical trials are made public, we are seeing that these drugs are able to outperform chemotherapy and radiation therapy.

A second approach is to own a large basket of small- to mid-cap biotech stocks that are active in developing new IO therapies. This tactic is prudent given the volatility inherent in small-cap biotech companies as they navigate the approvals process. There are two catalysts that drive shareholder value for investing in these stocks: one, taking the compound all the way to approval and two, acquisition. These companies become attractive to their larger peers who want access to the smaller company’s pipeline of drugs. They are often bought outright at substantial premiums.

An indirect approach to capitalize on the increase in R&D spending on IO is to invest in companies that provide the cutting-edge tools required for medical research.

As always, it will be important to avoid those companies that are too heavily dependent on older technologies. These might include any of the other treatment forms that paved the way for where we are today and the medical advances we have seen in this space. In other words, it might not be a good career choice to become a cancer surgeon.

Looking Forward

The future of IO treatment is getting brighter. Traditionally, standard treatment utilizes chemo, radiation, or both, along with an IO drug/therapy. Now, these drugs are being studied and approved as stand-alone therapies. We also are seeing combinations of IO drugs in place of radiation and chemo. One downside is that these kinds of treatments are very expensive—often reaching into the hundreds of thousands of dollars per patient per year. Yet their novelty and ability to extend life, and in some cases effectively cure cancer, has thus far outweighed the cost burden associated with using them.
As we move into a new era in the fight against cancer, the chances of success appear to be improving. As technology fuels further research and development, small biotech and large pharmaceutical companies alike should find success in bringing new, leading-edge therapies to market. There will undoubtedly be more failures along the way, but they will be offset by continuing progress in competing cancer treatments. R&D budgets will continue to grow, and with time and further success, cancer could cease to be the death sentence it once was.

**Market Outlook**

Concerns about tariffs and possible trade wars have recently made the news on a daily basis. But for now, the U.S. economy and corporate earnings continue to enjoy strong growth. Meanwhile, the Federal Reserve Board raised short-term interest rates by another quarter percent in June, as expected. Bond market rates rose as well, but not by quite as much as short-term rates, causing some flattening of the so-called yield curve. A flatter yield curve can be a sign that an economic cycle is reaching its late stages.

We do not believe that any negative effects from the current trade spats will be enough to derail our country’s economy, although we are watching for signs that events could spiral out of control. Short of that, stock market corrections should represent buying opportunities. The Fed has stated its intent to continue gradually raising short-term interest rates. It does not want to prematurely end the economic cycle, however, so it is unlikely to accelerate this process until inflation picks up beyond what are still rather modest increases. Shorter maturity, high-quality bonds are still a useful hedge against stock market volatility.