NEW THERAPIES FOR CANCER

The National Cancer Institute (NCI) estimates that approximately 39% of all Americans will develop cancer in their lifetime. However, due to early detection and new therapies, a cancer diagnosis need not be viewed as a terminal diagnosis. In fact, survival rates for most common types of cancers have been improving. In their simplest form, cancer cells are normal cells that grow without control. Cancer cells then compete with normal cells for nutrition and eventually starve these cells. On a cellular level, cancer cells also differ from normal cells in that they express different proteins on their surface. Chemotherapy has been the standard first line therapy for all cancers. Chemotherapy is not very selective and therefore not very effective, especially for advanced cancers. Also, chemotherapy has significant side effects ranging from hair loss and nausea to immune system suppression. Over the past decade, scientists have been researching new selective ways to fight cancer. Drug companies are beginning to develop therapies using this research.

The Science of Immuno-oncology

The human immune system can detect and eliminate foreign cells and help maintain a healthy body. It uses various checkpoints molecules/proteins to activate an immune response against foreign cells and to remain inactivate in presence of a normal cell. However, cancer cells can sometimes avoid detection by inactivating some of these checkpoints. Cancer cells can express proteins on their surface which can bind to checkpoint molecules on immune cells and prevent their activation. Checkpoint molecules that are the focus of various therapies include PD1. PD1 is a checkpoint protein on immune cells called T cells. Normally, PD1 helps keep the T cell inactive and thus prevents it from attacking normal cells. It does this by binding to its receptor, PDL-1, which is present on the surface of a normal cell. Some cancer cells have evolved to express large quantities of the PDL-1 receptor on their surface. When a T cell comes into contact with such a cancer cell, its PD1 binds to the PDL-1 on the cancer cell and continues to remain inactive. This enables the cancer cell to evade an immune response.

New cancer therapies are targeting the PD1 protein on T cells. Antibodies to PD1 bind to PD1 on the T cells and prevent them from binding to the PDL-1 receptor on the cancer cells. This allows the T cell to become activated against the cancer cell.

The benefits of immuno-oncology therapies are:

1. **Improved outcomes:** On average, overall survival rates (OSU) and progression free survival (PFS) are significantly higher with immuno-oncology therapy compared to conventional chemotherapy. For example, for advanced melanoma (skin cancer), PFS for chemotherapy is several weeks compared to the 6.9 months PFS for immuno-oncology therapy.

2. **Fewer side effects:** Chemotherapy is not very specific for cancer cells and affects normal cells. This causes a wide variety of side effects from nausea to immune system suppression. Immuno-oncology treatments also have side effects but these are much milder and manageable.

The Investment Case

PD1 therapy is fast becoming the backbone of immuno-oncology. In 2015, PD1 treatments were approved as second line therapy, for patients who had failed the initial chemotherapy, for various cancers including metastasized melanoma, and for non-small cell lung cancer (NSCLC). Lung cancer is the second most prevalent cancer in the U.S. with 225,000 newly diagnosed cases per year. In 2016, PD1 treatments were approved for PD1 positive patients as first line therapy, instead of chemotherapy, for NSCLC. In 2017, PD1 + chemotherapy combination treatment was approved a first line therapy for NSCLC for all patients. This treatment is already being used to treat over 30% of newly diagnosed NSCLC patients.

PD1 market was estimated to be $4.96B in 2016 and is expected to grow at a CAGR of 25% over the 2017-2025 time frame. Currently, there are four major pharmaceutical companies, Merck (MRK), Bristol Meyers Squibb (BMY), Roche(RHHBY) and Astra Zeneca(AZN) at the forefront. Of these, MRK’s immuno-oncology drug, Keytruda, in combination with chemotherapy, is the only drug that has been approved (U.S), as first line therapy for treatment of NSCLC. This approval was based on phase II trials. MRK
recently halted its Phase III trial due to positive results. It will file for approval as first line therapy for NSCLC in the European Union (EU) in 2018. Roche also announced positive results for its immuno-oncology drug, Tecentric + chemotherapy for treatment of NSCLC and expects regulatory approvals in 2018. Tecentric has been approved for treatment of advanced NSCLC as second line therapy. It is also approved for advanced bladder cancer. BMY’s drug, Opdivo, has been approved as second line therapy for NSCLC in the U.S. BMY is currently doing phase III studies with Opdivo and chemotherapy combo for NSCLC. Results are expected in the 2018-2019 time frame. In 2017, AZN’s phase III trial did not show significant improvement in progression free survival. The trial is continuing to assess if there is a significant overall survival benefit.

As cancer cells can mutate rapidly, most experts believe that current immuno-oncology treatments will evolve to be combination therapies of two or more check point inhibitors. Results from several Phase II clinical trials have shown that the combination of certain checkpoint inhibitors was even more effective than PD1. Phase III data from these combo trials should become available in 2018. PD1 protein is expressed in only 25% of patients. There are over 245 ongoing clinical trials assessing various checkpoint inhibitors and combinations. Over the next 3-4 years, new checkpoint inhibitors will play a major role in cancer therapy.

While PD1 therapy is being developed for solid tumors, chimeric antigen receptor T cell therapy or CAR-T, is being developed for lymphomas or cancers of the immune system. CAR-T therapy is a highly personalized gene therapy which involves modifying the patient’s own T cells so that they can detect and eliminate cancer cells. This is done by separating T cells from a patient’s blood. These cells are then genetically engineered by inserting specific genes in the DNA. The inserted gene is typically for a surface protein that is expressed by the cancer cells. The modified T cells are then grown in sufficient quantities in a laboratory and injected back in the patient. Inside the patient’s body, these cells can identify and eliminate all the relevant cancer cells. In fact, clinical trials have shown complete remission for some types of lymphomas.

Recently, two CAR-T therapies were approved in the U.S. In August 2017, Novartis’s (NVS) Kymriah, was approved for relapsing B cell acute lymphoblastic leukemia (ALL) in children and young adults, who account for about 60% of cases. In October 2017, the FDA also approved Gilead Sciences’ (GILD) Yescarta, for aggressive B cell non-Hodgkin’s lymphoma.

Unlike PD1 therapy, CAR-T therapy takes longer time and has some serious side effects due to overstimulation of the immune system. Several patient deaths occurred in the Yescarta clinical trials. Despite these draw backs, CAR-T therapy is seen by some as the next step in cancer therapy. Some estimate the CAR-T therapy market to be $8.5B by 2028. This has led to several recent acquisition deals. In August 2017, GILD acquired Kite Pharmaceuticals, which was developing Yescarta. In January 2018, Celgene (CELG) announced a deal to acquire Juno Therapeutics (JUNO) for its CAR-T therapy pipeline. Some biotech companies are already working on next generation CAR-T therapy to improve efficiency and safety.

**Conclusion**

With the aging of the global population, the incidence of cancer is expected to rise. New therapies in cancer treatment, including immuno-oncology, offer a more targeted elimination of cancer resulting in better outcomes and fewer side effects. To date, only 9 immuno-oncology drugs have been approved. There are over 500 ongoing clinical trials using immuno-oncology drugs. As a result, the market for immuno-oncology is expected to grow from approximately $6B in 2016 to over $34B by 2024 making it one of the fastest growing category in healthcare. This is good news for patients as well as investors.

**References:**

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