

Seeking Alpha

ImmunoCellular Therapeutics: A Small But Interesting Player In Dendritic Cancer Vaccines

by: Smith On Stocks August 24, 2011

Investment Overview

ImmunoCellular Therapeutics' ([IMUC.OB](#)) lead product ICT-107 is a dendritic cell vaccine for treating glioblastoma multiforme (GBM). Its technology is a next generation version of that used by Dendreon to develop Provenge for prostate cancer. GBM is a relatively rare, but deadly primary tumor of the brain. While it only affects about 11,000 Americans each year, it is the fourth leading cause of cancer deaths. Obviously, current therapy is not that effective and there is an urgent need for new therapeutic approaches.

The investment interest in ImmunoCellular is based on results from a phase I trial of ICT-107 in 16 newly diagnosed glioblastoma multiforme patients. This was a small open label trial done at a single center so that results have to be viewed with great caution. That said, the results were extremely promising as judged by survival data. After one year of therapy, 100% of the 16 patients on a treatment regimen of ICT-107 that was added to standard of care (SOC) were alive. Historical data indicates that for patients treated with SOC, only 61% of patients remain alive at one year. The results were also durable so that at two years, 80% of patients on ICT-107 plus SOC were alive versus 27% expected for SOC.

ImmunoCellular is now enrolling a 102 patient, double blind randomized trial that will compare ICT-107 plus SOC to SOC. If phase I results are replicated, this phase II trial could be the basis for filing a BLA and set the stage for ICT-107 to become a major advance in the treatment of GBM and potentially a commercial blockbuster. Success would further validate its technology of dendritic cell vaccines and raise hopes that this technology can be used against a broad number of other cancer targets. Potentially, this could attract keen interest from large pharma for partnering with or possibly outright acquisition of the company. My best judgment is that would have to await successful results in the phase II trial.

The phase I data and the appeal of the technology platform motivated me to do some initial research which is presented in this report. Although the phase I data are intriguing, the reader should carefully consider the following points:

1. ICT-107 is just beginning a randomized phase II trial. Final results are expected in 2H, 2013 and could be the basis for a conditional approval that could lead to a commercial launch in 2014.
2. The company is a small bulletin board company and has limited resources. It is a virtual company that has three fulltime employees and an additional two senior consultants who

devote all their time to the company. The chief scientific officer and chief financial officer spend about 40% of their time with the company. In addition, ImmunoCellular supports 7 FTEs working in projects at academic centers. However, management emphasizes that this group of people has been involved in taking 30 different products through phase I-III and some into commercial launches. Specifically, in cell/gene therapy alone, they have experience with trials, involving 15 products.

3. IMUC has a small market capitalization of about \$50 million based on shares outstanding. There are an additional 15 million warrants outstanding. Financial resources are limited as the company only has about 10 million of cash. The burn rate of the company is about \$7 million per year and the company might have to raise an additional \$10 to \$20 million prior to obtaining important phase II data on ICT-107 in 2H, 2013 that would allow partnering or possibly an outright acquisition of the company.

4. The phase I data has provided a very encouraging signal of efficacy. However, it is often the case that phase II data is not as good as phase I. The small number of patients treated in phase I is a concern as is the fact that the study was done at a single research center. On the other hand, the phase II trial is designed to be successful if it demonstrates just six months of improvement in survival as compared to the 24+ months that was seen in phase I.

5. The phase II trial is small and may not provide sufficient data for regulatory approval in which case a phase III trial might be required that would add further years to the development schedule. It could also fail as there is no certainty in the outcomes of clinical trials.

6. There is considerable work going on from other companies in developing vaccines and drugs for GBM. There is another dendritic vaccine called DC-Vax being developed by Northwest Biosciences ([NWBO.OB](#)) and other dendritic vaccines for GBM are being worked on in academic settings. NWBO uses a tumor sample to make a vaccine while IMUC uses synthetic antigens. There is some data that suggests the IMUC approach may be more effective, but the sample size is small. GBM is known to be driven by the angiogenic factor VEGF so that Avastin and other anti-VEGF drugs appear to have a role to play. Avastin has been approved for recurrent GBM and is now in a phase III trial for front line treatment of GBM that will report out in 2012. Celldex ([CLDX](#)) is developing rindopepimut as a vaccine against EGFRvIII, a transforming oncogene that is a functional variant of the epidermal growth factor EGFR. However, EGFRvIII is expressed in only 20-30% of GBM tumors. I have not done enough research to have a firm view on the timing of development or how these and other drugs will compete against or work in concert with ICT-107.

7. Management believes that ICT-107 may have advantages in comparison to other dendritic cell vaccines under development in that it is specifically designed to attack cancer stem cells (CSCs) as well as the daughter cells that arise as a result of the differentiation of the CSCs. This would be of great importance because CSCs play a major role in metastases and recurrences of cancers.

8. ICT 107 is addressing a small patient population and will have to be priced at a significant price level. The reimbursement issue recently experienced with Provenge has raised investor awareness and concern about reimbursement. The phase II trial design could result in eight doses in the first year, four in the second, three in the third and one in the fourth. I am speculating that if the phase II trial is successful in showing a median survival increase of six months that each dose will be priced at \$15,000. This would result in first year drug costs of \$120,000, second year \$60,000, third year \$45,000 and fourth year \$15,000. The four year total would be \$240,000. The actual price will be driven by the clinical benefit that is determined in the clinical trials.

9. The addressable market for ICT-107 is about 8,000 patients or \$1.9 billion at price of \$240,000 per patient.

My interest in, and reason for writing on the company is based on my view that the dendritic cell vaccine approach is a dramatically different and potentially much better approach to treating GBM, and other cancers that can potentially have a very meaningful impact on survival of GBM patients. However, I am not issuing an investment opinion at this time. This is due to three primary factors. As a general principal, I don't like to issue opinions on companies on which I am just beginning coverage and for which I lack the perspective that can only come with time. Secondly, I generally (not always) want to see phase II data before making conclusions on the efficacy of a product. Lastly, I am still wrestling with how to properly meld and balance the nine issues that I just raised into a balanced investment thesis.

An Overview of Glioblastoma Multiforme

There are two types of brain tumors: (1) primary tumors such as GBM that arise in the brain and (2) secondary tumors that are caused by metastases of tumors that originate elsewhere in the body. Primary brain tumors affect glial cells which are non-nerve cells that provide support and protection for the neurons in the brain. Glial cells surround neurons and hold them in place, supply nutrients and oxygen to them and insulate one neuron from another. They were once thought of as the glue of the nervous system, but this view has changed. They are now seen to play an additional role in neurotransmission and are now thought of as partners to the neuronal cells.

Secondary tumors of the brain occur in the terminal phases of a metastasized cancer that has occurred outside the brain. Metastases leak into the lymphatic system and blood vessels, circulate through the bloodstream, and some are deposited in the brain. The most common types of cancers that result in secondary tumors of the brain in order of frequency are lung cancer, breast cancer, malignant melanoma, kidney cancer and colon cancer. ICT-107 is not targeted at these secondary cancers.

Astrocytomas are a type of primary tumor of the brain. They originate in star-shaped glial cells in the cerebrum called astrocytes. These tumors don't usually spread outside the brain and spinal cord to affect other organs. People can develop astrocytomas at any age. The less aggressive types are more often found in children or young adults, while the

aggressive types are more prevalent in adults. As is conventional with all tumor types, astrocytomas are categorized into four grades according to how aggressively they grow.

1. Grade I are slow growing and are generally benign; they don't spread readily into surrounding tissue. Surgeons can often remove most of the tumor and either this alone or in combination with radiation can provide long term survival and in some cases total remission.
2. Grade II are slow growing astrocytomas that can evolve into more malignant, higher grade tumors. Median survival for these patients is about four years.
3. Grade III are anaplastic astrocytomas that grow more rapidly than lower grade tumors and are more likely to invade healthy tissue and crowd normal cells in the brain. This can lead to symptoms such as seizures, neurologic deficits, headaches, or changes in mental status. Anaplastic astrocytomas recur more frequently after surgery than lower grade tumors, because their greater tendency to spread into surrounding tissue makes them difficult to completely remove surgically. Individuals with grade III astrocytomas have a median survival time of about 24 months with surgery followed by radiation and chemotherapy.
4. Grade IV is glioblastoma multiforme which is the most common and malignant primary brain tumor. These grow rapidly and can become large before producing symptoms as described for anaplastic astrocytomas. About 10% of glioblastoma multiforme results from progression from low grade or anaplastic astrocytomas with the remaining 90% arising spontaneously. Surgery is the start of treatment unless resection would result in unacceptable damage to the brain. This is followed by radiation and chemotherapy. Median survival is about 15 months with surgical removal of the tumor followed by radiation and chemotherapy. This is the immediate target of ICT-107.

Incidence of Glioblastoma Multiforme

It is estimated that there are about 13,000 diagnoses of glioblastoma multiforme each year in the US, of which 85% or 11,000 patients undergo surgical resection. Of the 11,000 newly diagnosed patients, issued related to immunohistochemistry limit ICT's usefulness to about 80% of this population. Hence, the addressable market for ICT-107 is about 8,000 patients or \$1.9 billion at price of \$240,000 per patient.

Current Treatment of Glioblastoma Multiforme

Current treatment of GBM starts with the surgical removal of as much of the tumor mass as possible. However, GBM grows tentacle like extensions into surrounding tissue making it difficult to remove distant parts of the tumor without damaging surrounding tissue. Tumor cells are invariably present and remain in areas of the brain that are away from the site of initial diagnosis and inevitably this leads to a recurrence. Following surgery, treatment is aimed at eradicating as much of the remaining tumor mass as possible. The standard of care is generally as follows:

1. Surgical resection tries to remove as much tumor mass as possible.

2. Corticosteroids are added to reduce the inflammation caused by the surgery and to control swelling. Because corticosteroids depress the immune response, ICT-107's ability to create an immune response would be affected if it is used in conjunction with corticosteroids. However, in the phase II trial ICT-107 is added at day 70 by which time patients will have been tapered off steroids.
3. An MRI scan is made a few days after surgery to identify residual elements of the tumor
4. Radiation, gamma knife surgery or their combination are used to try to eradicate whatever remains of the tumor.
5. Radiation and the chemotherapy drug temozolomide are added to further reduce remaining tumor mass. These can be used in sequence or together.

Effectiveness of ICT-107 in Comparison to Standard of Care

Investor interest in ImmunoCellular is based on a phase I trial involving 16 newly diagnosed patients that began in May of 2007 and was performed at Cedars-Sinai. Two primary objectives were to determine safety and if an immune response could be generated against the cancer, but progression free survival and overall survival were obviously looked at. In this trial, post-surgical patients underwent six weeks of SOC, radiation combined with temozolomide. After a washout period, patients were given three doses of ImT-107 spaced two weeks apart. This was an open label, single arm study which means that there was not a comparison of results to another arm of the study in which patients were given SOC. Hence, to judge the results of this phase I trial it is necessary to look at how SOC performed in another study.

The best published report evaluating SOC was a major trial conducted by a cancer cooperative group, which was published in *The New England Journal of Medicine* in the March 10, 2005 edition. It compared radiation therapy alone to radiation combined with temozolomide. The study was called "Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma". The patients in the trial were 18 to 70 years of age with newly diagnosed glioblastoma multiforme that was confirmed by pathologists examining tissue samples of the tumor. The study was intended to focus on glioblastoma multiforme (grade IV) and to exclude patients with anaplastic astrocytoma (grade III), who have a better prognosis. The primary end point was overall survival; secondary end points were progression-free survival, safety, and the quality of life.

Both the ICT-107 trial and the standard of care trial looked at progression free survival and overall survival. The following table compares these two parameters for each trial at several points of time post-surgery.

The striking improvement in survival and progression free survival is what has impressed most people. If these results can be duplicated in the phase II trial, it would be a therapeutic and commercial homerun. However, there are some significant caveats. The phase I trial of ICT-107 + SOC was quite small and was done at one center. Both of these factors can sometimes inadvertently introduce positive bias in patient selection with the

result that the results can't be reproduced in larger trials involving several centers. There is an axiom in cancer drug development that phase II results seldom are as good as phase I.

How Dendritic Cell Therapeutic Vaccines Work

Dendritic cell vaccines represent a radical new approach to treating GBM. They take advantage of the adaptive immunity component of the human immune system in which diverse populations of white blood cells are trained to work together to eliminate cancer cells. The cell type that orchestrates the response is the dendritic cell. Its natural role is as a scavenger cell that detects and then digests cancer cells (and other pathogens) separating them into fragments, which are then displayed on its surface.

Dendritic cells then activate another class of white blood cell called T-cells which are broadly divided into killer T-cells and helper T-cells. A naïve T-cell circulates in the blood stream and lymphatic system until it encounters a dendritic cell displaying the cancer cell antigens. Upon contact, the killer T-cell is programmed to recognize, seek out and destroy the cancer cells that display the same antigens as those expressed on dendritic cells. The helper T-cells enable killer T-cells to proliferate. The killer T-cells attach to cancer cells and release proteins called chemokines that destroy the targeted cell.

The T-cell is one key component of the adaptive immune system and another is the B-cell. The B-cells produce antigen specific antibodies that bind to antigens found on cancer cells and initiate a distinct process that also destroys cancer cells. Helper T-cells also enhance B-cell production of antigen-specific antibodies. To the extent that all three of these elements- killer T-cells, helper T-cells and B-cells are activated the more powerful the response.

The adaptive immune system response to cancer can be generally characterized by the following sequence:

1. Dendritic cells ingest cancer antigens, break them into small fragments and display them on their outer cell surfaces.
2. Dendritic cells bearing these cancer antigen fragments attract and activate naïve T-cells, which become antigen-specific helper T-cells and killer T-cells.
3. The killer T-cells seek out and attach themselves to cancer cell antigens that they have been trained to recognize. Upon attachment to cancer cells they release chemokines which attack and try to destroy the cancer cells.
4. The activated helper T-cells produce factors that greatly enhance the cell division of killer T-cells and mature their cancer-killing properties.
5. The activated helper T-cells also produce factors that greatly enhance antibody production by B-cells that in turn are specific for the cancer-associated antigens.
6. The killer T-cells and antibodies, acting alone or in combination, destroy cancer cells.

The Target Antigens for Dendritic Cell Vaccines May Be the Key

In the opinion of IMUC management, the antigens targeted by dendritic vaccines may result in significant differences in their efficacy. This hypothesis is based on the fact that a tumor is a hierarchical organization. At the top of the pyramid are cancer stem cells (CSCs) which differentiate into daughter cells that form the base of the pyramid and make up most of the tumor mass. Tumor invasion to a new site and the resultant metastases is believed to come from CSCs, not from daughter cells. ImmunoCellular believes that it has selected a cocktail of tumor antigens, some of which are widely expressed on cancer stem cells. They feel that ICT-107 is targeting the CSC roots of the tumor more so than other dendritic cell vaccines and that the reason for dramatic improvement in disease free survival and overall survival seen in the phase I trial was in large part due to this mechanism of action.

In January 2010, IMUC issued a press release summarizing the results of a study which investigated the expression of antigens on cancer stem cells. CSCs were isolated from the tumors of five GBM patients and were found to have significantly higher expressions of the antigens Her-2/neu, AIM2, and TRP-2 than the daughter cells that make up the bulk of the tumor. ICT-107 is targeted against these three antigens as well as three additional antigens- gp-100, MAGE-1 and IL13Ra2. This supports the hypothesis that ICT may target stem cells as well as daughter cells that make up the tumor mass.

The Phase II Trial Planned for ICT-107

The phase II trial design plans to enroll 102 patients at 20 centers in the US and Canada. It will be randomized into two arms with 2/3 of patients receiving ICT-107 and 1/3 receiving a placebo which will be an unloaded dendritic cell. The primary endpoints will be overall survival and progression free survival. If successful, this trial could be the basis for filing a BLA. It is scheduled for completion in 2013.

Patients in the trial will be newly diagnosed GBM patients. Patients will first be surgically resected. Approximately six weeks later, they will be given radiation plus temozolamide for six weeks and on week 10-12 they will be given four doses of ICT-107 at one week intervals. During the remainder of the first year, they will receive temozolamide and four more doses of the vaccine at various and different times. Assuming survival, they will receive eight doses in the first year, four doses in the second year, two in the third and two in the fourth.

Manufacturing Dendritic Vaccines

A number of companies are working on personalized dendritic cell vaccines. Each uses a manufacturing process that starts with drawing blood from a patient which is separated to obtain a type of white blood cell called a monocyte that can differentiate into a dendritic cell. The monocytes are isolated from the blood sample and then given growth factors that cause them to change into dendritic cells. These dendritic cells are then exposed (pulsed) to antigens that are characteristic of the tumor. These antigens can be obtained from the tumor by gathering tumor tissue and then lysing the cells or they can be obtained as off the shelf reagents. These dendritic cells with antigens now expressed on their surface are re-

infused into the body to initiate the killer T-cell, helper T-cell, B-cell cascade that attacks tumor cells. The step wise process as follows:

1. *Collection.* A sample of a patient's blood is drawn and white blood cells are collected in an outpatient procedure called leukapheresis.
2. *Isolation of precursors.* Cells called monocytes are separated from the collection and sent to a manufacturing facility.
3. *Differentiation by Growth Factors.* The monocytes are transformed to immature dendritic cells in a culture through the application of specific growth factors in a several day process.
4. *Antigen Display.* Fragments of cancer-associated antigens or deactivated whole cancer cells are added to the culture where they are ingested, and processed by the maturing dendritic cells which then display fragments of cancer-associated antigens on their outer cell surfaces
5. *Harvest.* These dendritic cells are then harvested and separated into administration vials.
6. *Quality Control and Shipment.* The final product lot undergoes quality control testing to assure sterility and potency before shipment to administration or storage sites.

Comparing ImmunoCellular's Manufacturing Process to the One Used for Dendreon's Provenge

ICT-107 differs from Provenge, even though both drugs are dendritic cell vaccines. Most importantly, Provenge is targeted at prostate cancer and ICT-107 against GBM. Provenge loads the dendritic cell with only one antigen, prostatic acid phosphatase (PAP) that is linked to GM-CSF, while ICT-107 loads six synthetically produced antigens. The reason is that GBM displays different antigens which occur in different amounts from patient to patient whereas PAP occurs on most prostate cancer cells.

The administration of Provenge requires three treatments given at two week intervals. This requires the patient each time to have blood drawn, shipped to the manufacturing facility and then shipped to an infusion center for infusion. ICT-107 requires only one blood draw and manufacturing run. From this, 20 doses can usually be created in which the drug is aliquoted, frozen and shipped back to the infusion center. Cryopreservation may be able to allow doses to last for years. The ICT-107 manufacturing process is more efficient and cheaper than that for Provenge.

Management believes that cost of goods sold for ICT-107 may be 5% versus the 50% expectation for Provenge. The total cost of a production run to produce about 20 doses that have a commercial value of \$200,000 to \$300,000 at the current scale is about \$16,000. The company believes that it can reduce this to \$8,000 at full scale.

Disclosure: I am long [DNDN](#).