

*Seeking Alpha*

# **Pharma Leaders Emerging In Immunotherapy Approach To Fighting Glioblastoma**

January 16, 2012

By Chemistfrog

One of the least understood areas of the body and of the most difficult to treat for disease, the human brain and its functions has dazzled and baffled scientists and physicians across the ages. Attempts to understand how it functions both physiologically and psychologically typically lead to one conclusion, the more we learn about it the more we realize we don't know about it. Diseases of the brain are difficult to diagnose and treat and are at the center of many areas of study and clinical trials. A primary brain cancer diagnosis strikes fear in its victims as the final outcome and quality of life up to that outcome is often seen as pre-determined with a poor prognosis.

Glioblastoma multiforme (GBM) is one of the most aggressive primary cancer tumors. It accounts for approximately 50% of all functional tissue brain tumor cases and about 20% of all intracranial tumors. Affecting 4-5 new cases per 100,000 persons a year in the United States and worldwide, GBM is not one of the more common or well-known cancers. However, with a current median overall survival of approximately 12 months with the standard of care and only 3 months with no treatment, the diagnosis is devastating for its victims. Only modest gains have been made in the last 30 years, with median survival increases of only about 9 months in that time frame and current prognosis of only 25% of patients surviving 2 years and fewer than 10% reaching 5 years.

## **Chronology of Treatments**

### **Resection and Radiation – 1970's to 1990's as Standard of Care**

Like many cancers, earlier treatments often involved resection (surgical removal) of the tumor and healthy surrounding marginal tissue. The obvious problem posed with Glioblastoma is the potential degradation of brain function as the brain tissue is removed. However, successful resection of Glioblastoma is possible and did increase median survival by about 6 months, giving the patient about 9 months average median overall survival. Still part of the standard of care protocol today, surgical removal has been more fully perfected with median survival times increasing to about a year now with the most success in younger patients treated in the earliest stages of the disease. Often used in conjunction with surgery, radiation treatment was also implemented along the same time period. Like resection, it increased survival to about 9 months median overall survival and is the preferred method of treatment for inoperable tumors and for those over 70

years of age. The side effects of the radiotherapy are typical with this kind of treatment with the most prevalent ones being hair loss, fatigue and nausea.

### **Chemotherapy – One approval 2003 via an implant and another approval 2005**

In 2003 the first [drug was approved](#) for GBM via an implanted device. Containing controlled release carmustine, the Gliadel Wafer (now marketed by Eisai Inc. (PINK: [ESALY.PK](#))) was approved for use in conjunction with radiation and surgery as an adjuvant. After the tumor is surgically removed, the wafer is placed into the remaining cavity where it will reside and slowly release its active ingredient. Meanwhile, radiotherapy could be used to further fight any remaining cancer cells or newly formed ones. This multi-faceted approach yielded trial data in which survival was prolonged in the Gliadel Wafer group with median survival increasing to 13.9 months from 11.6 months,  $p < 0.05$ .

In March of 2005 the [FDA approved TEMODAR](#), produced by Schering-Plough (it merged with Merck in 2009 to form Merck & Co. (NYSE: [MRK](#))), in conjunction with radiotherapy for the treatment of newly diagnosed GBM. The approval of TEMODAR with the active ingredient temozolomide was based on a 573 patient phase 3 study in which the group of patients treated with TEMODAR and radiation yielded the following: 27.2% alive at two years, 16% at three years, 12.1% at four years, and 9.8% at five years. For comparison to those treated with radiation alone, 10.9% were alive at two years, 4.4% at three years, 3.0% at four years, and 1.9% at five years. Median overall survival for the patient set was 14.6 months as opposed to 12.1 months for the patient set receiving radiotherapy only. The results were markedly better, but there is obviously much room for improvement for efficacy and additionally for [safety](#). Forty-nine percent of those treated with TEMODAR reported one or more severe or life-threatening events, most notably fatigue (13%), convulsions (6%), headaches (5%) and low blood platelet levels (5%).

Chemotherapy trials for GBM are still underway for many drugs, however the toxic nature of these agents has proven to be a formidable foe in the battle of the elevated levels required to have potent efficacy versus reduced levels necessary to keep the safety aspect of the treatments in check. This trade-off is even worse for primary cancers of the brain because of the blood-brain barrier that many drugs cannot efficiently penetrate. Additionally, many cancer stem cells (CSC's) survive both radiotherapy and chemotherapy treatments and live to create another generation of cancer tumor cells to proliferate. These new cells and tumors are often more immune to the chemical agent that attacked their predecessors. Damage occurring to surrounding healthy cells is also a bigger concern in the brain due to reduced functionality of the brain along with the fact that the brain is more limited in its ability to repair itself than other parts of the body. It appears that a more targeted approach to GBM is necessary that doesn't fully rely on the "poison the biologic system and hope the healthy cells survive and the fast-growing cancer cells are killed" logic of old.

### **Immunotherapy – A Targeted Treatment Approach for GBM**

## **VEGF Inhibition**

In their earliest stages of development, cancer tumors rely on surrounding blood vessels to supply the necessary nutrients via diffusion. However, as their growth advances they require higher volumes of blood supplied via their own vessels. To do such, they rely on their own angiogenesis (blood vessel formation) promoters. The most common promoter implicated is vascular endothelial growth factor (VEGF). Its inhibition or elimination is proven to be a key mechanism in a new generation of cancer drugs termed VEGF inhibitors. In May of 2009 the [FDA approved](#) the first VEGF inhibitor for recurrent GBM in the form of Genentech's (Pink: [RHHBY.PK](#)) Avastin. At the time of the approval, trial data supporting the approval did not indicate an improvement of survival of the patients, only that there was a significant tumor response in 20-26% of the patients that lasted for about 4 months. Genentech is conducting two phase III trials using Avastin in newly diagnosed GBM and will likely apply for regulatory approval in the U.S. in 2013.

## **Heat Shock Protein and T-Cell Mediated Immunotherapy Approach**

Agenus, Inc. (NASDAQ: [AGEN](#)) Prophage Series vaccines are autologous (patient specific and manufactured from the patient's own cells). They contain the [heat shock protein, gp96](#), and associated peptides that are purified from the patient's tumor tissue. Agenus' [G-200 phase II trial data](#) for patients with recurrent GBM were promising with 93% of the patients alive at 26 weeks after surgery with a median overall survival of 47.6 weeks. Measures of immune response after treatment indicated a significant localized tumor-specific CD8+ T cell response as well as innate immune responses as marked by a significant increase in levels of circulating NK (natural killer) cells. These NK cells play a major role in the destruction of tumor cells and virus-infected cells and kill by releasing cytoplasmic granules of proteins called perforin and granzyme that cause the target cell to die. Updates on G-200 should be forthcoming with a substantial update likely at ASCO in June 2012. Like other immunotherapy vaccines, G-200 is designed to target only cancerous cells, not healthy cells. This targeted approach should limit the toxicities associated with traditional broad acting chemotherapy or radiotherapy. A Phase 2 trial testing G-100 in patients with newly diagnosed glioblastoma is currently enrolling with approximately 24 patients treated per Agenus' November 16th [press release](#). If the G-100 has similar efficacy in new-diagnosed GBM as the G-200's phase II trail for recurrent GBM, this will mark a huge step in moving the median overall survival beyond three and perhaps even four years for these patients.

## **Another Novel Dendritic Cell Immunotherapy Approach**

Northwest Biotherapeutics (OTC: [NWBO.OB](#)) is in a phase II study of its autologous cellular therapy [DCVax-L](#) for newly diagnosed GBM. Phase I results were impressive with a median survival of 33.8 months. Most of the original 19 patients have no evidence of tumor recurrence and four have survival times without progression or recurrence of their cancer that now extends beyond 45 months. Touting their "crossover treatment" policy in which members of the placebo group are allowed to crossover and start receiving the DCVax-L vaccine after certain clinical endpoints are met, Northwest last

[updated](#) its phase II trial in August and should be due to give an enrollment update soon with perhaps an interim data analysis. Northwest is hoping that its crossover policy will attract additional physicians/clinics that may not otherwise be interested in having its patients possibly permanently assigned to the placebo group in which their prognoses would likely be poor. The next enrollment update will help determine if that policy is helping in that regard.

## **ICT-107 and CDX-110: Leaders Emerging?**

### **EGFR and EGFRvIII Growth Regulator Inhibition**

Celldex Therapeutics (NASDAQ: [CLDX](#)) CDX-110 is an off-the-shelf (not autologous) vaccine consisting of 13 amino acids unique to EGFRvIII, a functional variant of the epidermal growth factor receptor (EGFR). The targeting of EGFR is of proven benefit with approvals for similar vaccines such as YM Biosciences nimotuzumab, RHBBY's Tarceva, AstraZeneca's gefitinib and Bristol Meyer's cetuximab. CDX-110's benefit will be limited to those GBM patients with over-expression of EGFRvIII (roughly 25-30% of those EGFR-positive GBM patients). Meanwhile, the aforementioned approved drugs targeting EGFR (EGFR inhibitors) have the benefit of targeting the over expressed EGFR (in 40-50% of GBM patients). However, CDX-110 should not be overlooked as a possible treatment as its treatment in the correctly targeted group is showing tremendous promise.

Trial data, generated by three phase II trials on CDX-110 by Celldex and its former partner Pfizer (NYSE: [PFE](#)) targeting the EGFRvIII+ GBM patient set have been impressive. The 18-patient ACTIVATE trial yielded data with a median progression free survival (PFS) of 14.2 months, median overall survival of 24.6 months and 50% OS at 24 months. The 22-patient ACT II trial data yielded data with a median PFS of 15.3 months, median OS of 24.4 months and 50% OS at 24 months. In the largest trial, ACT III with 65 patients, the data set is still being accumulated with median PFS of 12.3 months, median OS of an estimated 24.3 months and estimated 50% OS at 24 months. As with many off-the-shelf immunotherapy vaccines, the most reported side effects were local injection-site reactions. In the ACT III trial, reversible hypersensitivity reactions occurred in 5% of patients with one reaction being reported as serious and requiring discontinuation of treatment.

### **Dendritic and Targeted Cancer Stem Cell Approach**

ImmunoCellular Therapeutics' (OTC: [IMUC.OB](#)) ICT-107, like DCVax-L, is an autologous vaccine. The vaccine is produced by removing some of the patient's white blood cells (WBC) and culturing them in a laboratory with purified antigens, similar to those on GBM cells. The patient's WBC/DC (dendritic cells) that have been exposed to the tumor antigens will then be reintroduced to the patient as a vaccine over the course of the treatment. The hope is that the ICT-107 vaccine will stimulate the patient's immune response by helping to "teach" the body that the GBM cells and stem cells are foreign causing it to target the residual GBM tumor cancer stem cells (CSC). This will be done

after a combination of surgery, chemotherapy and radiotherapy to increase progression free survival or even induce total remission. The targeted cancer stem cells, and their resistance to standard chemotherapy agents, are thought to be the culprits behind the recurring nature of GBM and many other cancers. More information on these cells can be found in [this article](#) and this excellent National Institute of Health (NIS) [report](#).

Phase I [results](#) were impressive on a 16-patient set of newly diagnosed GBM that received three injections of the vaccine after the standard of care treatment with surgery, radiation and/or chemotherapy. Median OS for the patient set was 38.4 months with a median PFS of 17 months. The three-year OS for the patient set was 55% with 6 patients having no recurrence of the tumor after three years. 19% were still disease-free after four years with one patient now approaching 5 years of PFS. Safety data for ICT-107 compared favorably to current treatments with no serious events while minor side effects were reported such as fatigue, skin rash and itching. With a favorable median OS of 38.4 months versus CDX-110's 22.4 months, ICT-107 phase I data are currently superior with a larger patient population target set without the limitations of treating only the GBM patient population that is EGFRvIII over expressed. ICT-107 [major inclusion criteria](#) are that the patients enrolled are HLA-A1 or HLA-A2 positive. [Published data](#) indicate this includes over 75% of the human population (depending on ethnicity) while CDX-110 has a smaller target group of 10-15% of the total GBM population set.

ImmunoCellular [initiated a Phase II trial](#) on ICT-107 in January 2011 on patients with newly diagnosed GBM. The double-blind, placebo-controlled randomized trial will enroll about 150 patients at more than 20 sites throughout the U.S. Patients will receive at least four vaccinations of ICT-107 on top of the current standard of care with enrollment completion by Q2 2012 and interim data analysis release during Q4, 2012. The phase I trial utilized three injections of ICT-107 over the course of the treatment. With the additional one or more injections in the phase II trial the efficacy may yet be additionally enhanced with a likely acceptable safety profile given the margin of increase allowed as indicated by the phase I trial. With hopes high due to the stellar phase I data behind it, this \$42.4 million biotech will start capturing attention as 2012 catalysts approach. Analysts are already taking note as a December 1st announcement that Global Hunter Securities analysts has given the common stock a [\\$5.00 price target](#) with a "buy" rating. This is only the beginning as ImmunoCellular is on the forefront of immunotherapy vaccines for GBM and other cancers with a wide range of applications. Will ImmunoCellular experience the same type of run that another immunotherapy company, Dendreon (NASDAQ: [DNDN](#)), saw in 2009 with its Provenge cancer vaccine for prostate cancer? GBM is certainly not as common as prostate cancer and has a smaller market, but positive data for phase II ICT-107 will help further legitimize ImmunoCellular's pipeline and its possible indications for other cancers and could vault the company into the spotlight and world of Big Pharma.

**Disclosure:** I have no positions in any stocks mentioned, and no plans to initiate any positions within the next 72 hours.