Zacks Small-Cap Research

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Diffusion Pharmaceuticals Inc. (DFFN-OTC)

DFFN: Initiating Coverage of Diffusion Pharmaceuticals: Lead Compound Entering Phase 3 Clinical Trial in Brain Cancer…

Based on our probability adjusted DCF model that takes into account potential future revenues from TSC in GBM, pancreatic cancer, and brain metastases, DFFN is valued at $4/share. This model is highly dependent upon the continued clinical success of TSC and will be adjusted accordingly based upon future clinical results.

Current Price (05/31/16)	$0.90
Valuation	**$4.00**

OUTLOOK

Diffusion Pharmaceuticals, Inc. (DFFN) is a clinical stage biopharmaceutical company focused on the development of the company's Phase 3 ready asset, trans sodium crocetinate (TSC).

TSC is a small molecule that alters the rate of diffusion of oxygen through the blood, resulting in increased oxygen in hypoxic tissues. Since tumors are known to be hypoxic, Diffusion is targeting TSC for the treatment of brain cancer, pancreatic cancer, and brain metastases. TSC works as an adjunct to standard of care radiation and chemotherapy, rendering those treatments more effective. Phase 2 results for TSC in brain cancer showed increased survival compared to a historical control group, with limited side effects. If successful, TSC would be added to first line treatment for brain cancer.

SUMMARY DATA

52-Week High	**$2.60**
52-Week Low	**$0.40**
One-Year Return (%)	**-61.54**
Beta	**-0.12**
Average Daily Volume (sh)	**7,236**
Shares Outstanding (mil)	**102**
Market Capitalization ($mil)	**$92**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**0**
Insider Ownership (%)	**30**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2016 Estimate	**N/A**
P/E using 2017 Estimate	**N/A**

Risk Level	**High,**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue

(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2015	0 A	0 A	0 A	0 A	0 A
2016	0 A	0 E	0 E	0 E	0 E
2017					0 E
2018					0 E

Earnings per Share

(EPS is operating earnings before non-recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2015	-$0.19 A	-$0.35 A	-$0.18 A	-$0.24 A	-$1.00 A
2016	-$0.06 A	-$0.03 E	-$0.03 E	-$0.03 E	-$0.15 E
2017					-$0.09 E
2018					-$0.12 E

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WHAT'S NEW

Initiating Coverage

We are initiating coverage of Diffusion Pharmaceuticals, Inc. with a $4.00 valuation. Diffusion is a clinical stage biopharmaceutical company developing treatments to improve the current standard-of-care (SOC) therapy for various oncology indications. The company's lead asset, trans sodium crocetinate (TSC), is a small molecule that alters the diffusion of oxygen through the bloodstream in order to increase the tissue oxygenation.

Many types of tumor cells are known to be hypoxic (lacking oxygen), which makes SOC radiation and chemotherapy less effective. By increasing the amount of oxygen that gets into the tumor cells, TSC can increase the effectiveness of the SOC treatments, potentially leading to improved clinical outcomes. Getting oxygen from the lungs to the tissues is a multi-step process that involves diffusion (oxygen to the tissues, carbon dioxide away from the tissues), which is the movement of molecules from an area of high concentration to an area of low concentration. Each of the steps in gas diffusion in the body involves some form of resistance, with movement through plasma accounting for the majority of the resistance. Lowering this resistance could lead to an increase in the amount of oxygen that could diffuse through the plasma, leading to an increase in tissue oxygenation.

Diffusion's Chief Scientific Officer studied diffusion for most of his career as a Professor at the University of Virginia. It was through this work that he developed TSC, which has been studied in a number of different animal models and shown to improve outcomes in a variety of conditions where tissue oxygenation is important, such as hemorrhagic shock and ischemia. His focus turned to the treatment of cancer due to the fact that many solid tumors are hypoxic and increasing the level of oxygen in those cells could improve the effectiveness of SOC treatments.

When combined with radiation and chemotherapy, TSC was shown to have a number of positive effects in a rat model of glioma, such as an increase in median survival times, decreasing tumor growth, and increasing tissue oxygenation in tumors.

Diffusion performed a Phase 1/2 clinical trial in patients with glioblastoma multiforme (GBM) to assess the effect of adding TSC to SOC radiation therapy. The results from the trial compared quite favorably to a historical group, as overall survival at two years was 37% in the TSC group compared to 27% in the historical control group. Importantly, no additional adverse events were reported and TSC was well-tolerated throughout the study.

The company is currently developing TSC for use in GBM, pancreatic cancer, and brain metastases. All of these tumors have a high degree of hypoxia and each of them presents with a very poor prognosis for the patient, indicative of the need for better treatment options. Diffusion will be initiating a Phase 3 clinical study in GBM in 2016. A Phase 2 clinical trial in pancreatic cancer will be initiating within the next 12 months, while a clinical trial in brain metastases will get underway in 2018.

As of March 31, 2016, Diffusion had approximately $5.9 million in cash and cash equivalents. We believe this will be enough to fund operations into the third quarter of 2016, however the company will need to raise money in order to fully fund the Phase 3 clinical trial in GBM, which we anticipate will cost approximately $45 million to complete.

Our valuation for Diffusion is derived from a probability adjusted discounted cash flow model that takes into account potential future revenues from the sale of TSC in GBM, pancreatic cancer, and brain metastases. Using a 15% discount rate, we arrive at a current valuation of $4/share. The stock is currently trading at a steep discount to this valuation, which represents an attractive opportunity for investors to initiate a position in a company with a truly novel anti-cancer therapeutic.

INVESTMENT THESIS

Tumor Hypoxia

Tumor hypoxia refers to a condition that is common to a number of different types of solid tumors where rapid growth leads to an immature and defective vasculature and poor circulation within the tumor, ultimately resulting in the interior portions of the tumor receiving insufficient quantities of oxygen. Hypoxic tumors typically have a number of negative characteristics associated with them, including an increased likelihood of metastasis and invasiveness (Graham *et al*., 1999), decreased radiosensitivity (Harrison *et al*., 2002), and worse disease-free and overall survival probabilities (Hockel *et al*., 1996).

Focusing specifically on treatment resistance, there appear to be a number of mechanisms through which hypoxia operates:

- Chronic hypoxia prevents the activation of the G1/S cell cycle control checkpoint, which allows the accumulation of DNA replication errors (Bristow *et al*., 2008). DNA damage is corrected during the cell cycle checkpoint, thus by allowing the errors in the genome to accumulate, hypoxia contributes both to genomic instability that can lead to alterations in tumor growth but also to resistance to treatments that target the cell cycle.

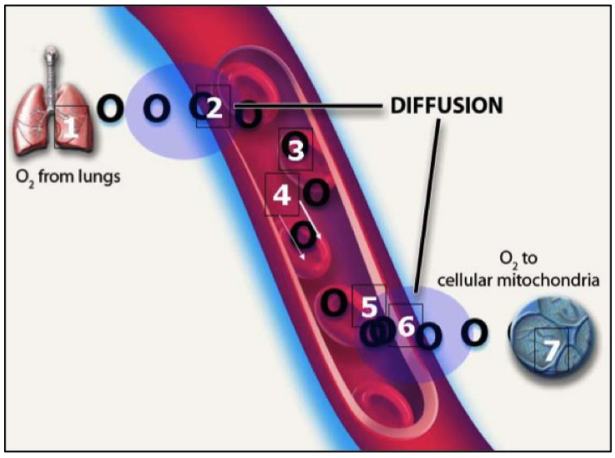
- The presence of molecular oxygen appears to be required for the effective use of radiation treatment (Yoshimura *et al*., 2013). Ionizing radiation results in DNA single- and double-strand breaks. These ionized breaks then react with molecular oxygen to become unrepairable. In the absence of oxygen, these strand breaks are more easily repaired.

- The absence of oxygen appears to trigger the increased expression of DNA repair proteins leading to less severe DNA damage (Ren *et al*., 2013).

The preceding indicates that tumor hypoxia is a serious impediment to effectively treat cancer, and a compound that decreases tumor hypoxia (or increases tumor oxygenation) could theoretically have a strong impact on cancer treatment.

Tissue Oxygenation

Getting an adequate supply of oxygen to the tissues in our body begins in the lungs, where gas exchange occurs and oxygen enters the bloodstream while carbon dioxide exits the bloodstream to be exhaled. The process of gas exchange occurs via diffusion, which is the movement of molecules from an area of high concentration to an area of low concentration. The following figure depicts the steps necessary to move oxygen from the lungs to the tissues. 1) Once the oxygen enters into the bloodstream it must 2) diffuse through the plasma and then 3) enter red blood cells where it binds to hemoglobin. The oxygen is then 4) transported through the bloodstream, and as it enters areas of the body with low oxygen concentration, the oxygen is 5) off-loaded by the red blood cells so that it can again 6) diffuse through the blood plasma and capillary walls to enter tissues. The oxygen then 7) enters the mitochondria where it is utilized for metabolic purposes.



Source: Diffusion Pharmaceuticals, Inc.

Each of the steps described above for the movement of oxygen through the body results in some form of resistance, with diffusion through the plasma being a de facto "rate-limiting" step in the movement of oxygen through the body, accounting for 70-90% of the overall resistance (Yamaguchi *et al*., 1985). Thus, if the movement of oxygen through plasma could be increased, it would be possible to increase the amount of oxygen that can make its way through the pathway at any given time and into the various tissues in the body, including hypoxic tissues such as tumors.

Trans Sodium Crocetinate

Diffusion's Chief Scientific Officer, Dr. John Gainer, began his career studying diffusion-limited processes and quickly realized the applicability to the physiological process of hypoxia. Dr. Gainer was the first to attempt to alter the diffusion of oxygen through the plasma with the use of small molecules. He originally identified crocetin, a natural carotenoid compound related to vitamin A, as a molecule that could effectively increase oxygen diffusion through the plasma. Crocetin was originally shown to be an effective treatment in a rat model of atherosclerosis (Gainer *et al*., 1974). This work continued into the mid-1990s with various animal models, including hemorrhagic shock (Gainer *et al*., 1993).

Since crocetin is an isomeric mixture, the suspicion that the *trans*-isomer elicits the therapeutic benefit led to the development of a pure *trans*-isomer salt compound, which was named trans sodium crocetinate (TSC). TSC was shown to be more effective than crocetin in a severe model of hemorrhagic shock in both rats (Roy *et al*., 1998) and pigs (Stern *et al*., 2002). Additional data obtained using TSC shows that the compound:

- Restores blood pressure, heart rate, and plasma lactate after hemorrhagic shock (Giassi *et al*., 2002)
- Increases the blood arterial oxygen tensions in respiratory-compromised rats (Gainer *et al*., 2005)
- Increases survival in rats breathing 10% oxygen (Singer *et al*., 2000)

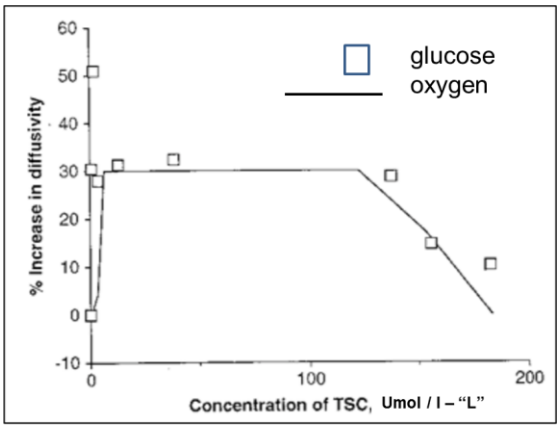
All of the aforementioned data appears to be a direct result of increasing the amount of oxygen that reaches tissues. This effect is believed to be due to a novel mechanism of action attributable to TSC, whereby the molecule is able to directly affect the diffusion of oxygen through the plasma in order to increase its availability to hypoxic tissues.

As mentioned above, there are a number of steps involved in getting oxygen from the lungs to tissues, with the diffusion of oxygen through the plasma resulting in the greatest "resistance". The process of diffusion follows Fick's law, which states that the rate of oxygen diffusion through plasma is dependent upon 1) the plasma thickness; 2) the concentration gradient of oxygen; and 3) a proportionality constant known as the diffusion coefficient (also known as diffusivity). Thus, those are the three factors that could potentially be altered in order to increase the diffusion of oxygen.

The plasma thickness is set by arterial anatomy, and thus is not readily altered. The concentration gradient of oxygen can be altered by increasing the percentage of oxygen that a patient breathes (air is 21% oxygen) or through the addition of hemoglobin-like molecules into the bloodstream. Dr. Gainer was the first to try to alter the diffusivity of oxygen through the use of small-molecules that would alter the intermolecular forces in plasma.

It is believed that TSC alters the molecular arrangement of water molecules in the plasma (which is composed of 90% water), with the altered structure being less dense than untreated plasma. Water is composed of two hydrogen atoms and one oxygen atom, with a net positive charge found on the hydrogen atoms and a net negative charge found on the oxygen atom. This results in the formation of hydrogen bonds, which are simply an attraction between the net-negatively charged oxygen of one water molecule and the net-positively charged hydrogen atoms of another water molecule. Theoretically, one water molecule can form four hydrogen bonds with neighboring water molecules. However, the literature indicates that a water molecule actually forms, on average, 2 to 3.6 hydrogen bonds (Gainer, 2008).

Increasing the number of hydrogen bonds that a water molecule forms would increase the structure of the water molecules. For water, an increase in structure results in a decrease in density (for example, ice is less dense than liquid water). Applying this to plasma, since it is composed of approximately 90% water, increasing the structure of water molecules in plasma would result in a decrease in plasma density and an increased ability for oxygen molecules to diffuse through it. Both computer simulations (Laidig *et al*., 1998) and physical experimentations (Stennett *et al*., 2007) have shown that TSC increases water structure and results in additional hydrogen bonds being formed per water molecule, which leads to an increase in the diffusivity. The results apply not just to oxygen, but to the diffusivity of any small molecule in plasma, as shown in the following figure where the addition of TSC results in the same percentage increase in diffusivity through water or plasma for oxygen and glucose.



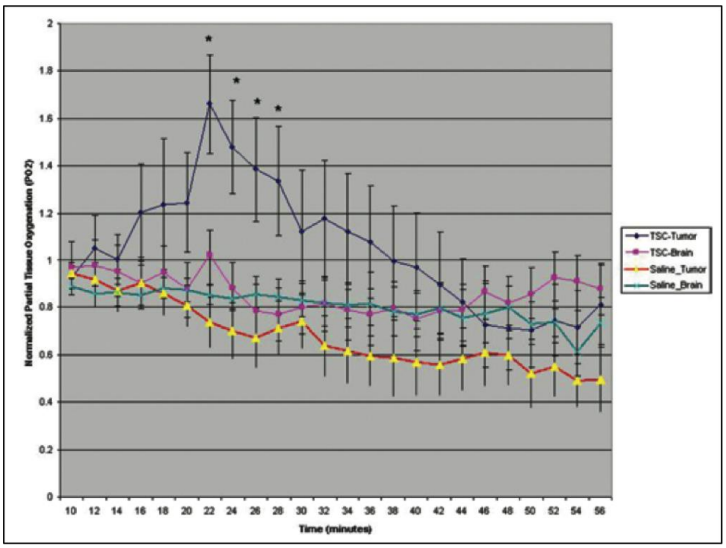
Source: Gainer *et al*., 2008

Trans Sodium Crocetinate Increases Oxygenation of Hypoxic Tumors

While first studied for the treatment of hemorrhagic shock, ischemia, and traumatic brain injury, the use of TSC as an agent to increase the oxygenation of tumors quickly become a central area of research. As described above, tumor hypoxia is a leading cause of resistance to both radiation and chemotherapy in a number of solid tumors, thus an agent that could increase the oxygenation of tumors could prove effective in resistant cancers. Examples of TSC's effect in various tumor models are as follows:

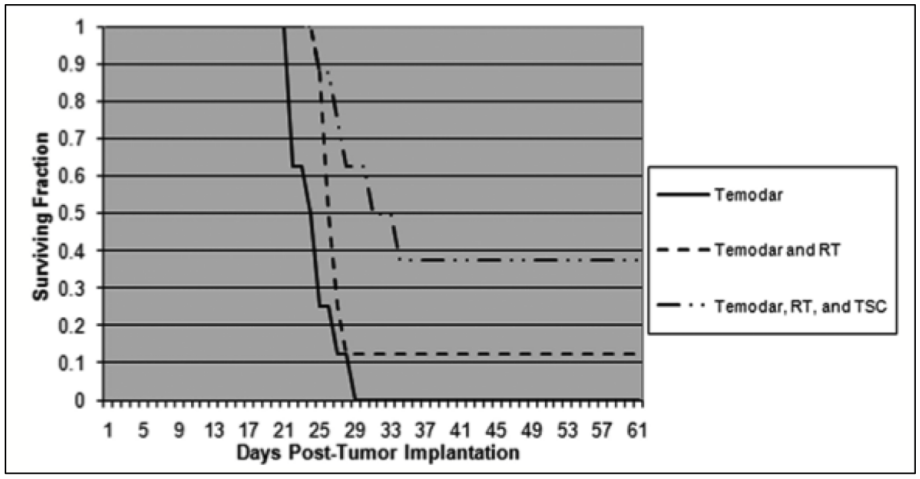
Sheehan *et al*., 2008: A rat C6 glioma model was used, whereby C6 glioma cells were injected into the brain to form a tumor. Following confirmation for the presence of a tumor, the animals were then divided into four groups: 1) TSC alone, 2) radiation alone, 3) radiation plus low-dose TSC, and 4) radiation plus moderate-dose TSC. The animals were observed for 60 days following tumor implantation or until death. By magnetic resonance imaging (MRI), there was a statistically significant reduction in tumor size seen in the group receiving moderate-dose TSC plus radiation compared to the group receiving only radiation. Median survival times for the groups receiving TSC only and radiation only were 15 and 30 days, respectively, while approximately 70% of the animals in the low- or moderate-dose TSC plus radiation groups lived the full 60 days.

Sheehan *et al*., 2009: A rat C6 glioma model was used, whereby C6 glioma cells were injected into the brain to form a tumor. Following confirmation for the presence of a tumor, the animals were then injected with either TSC or saline and tissue oxygenation measurements were recorded before and after the infusion. Results showed that the brain tumors had hypoxic regions compared to contralateral cerebral tissue. Two to eight minutes after infusion of TSC, tissue oxygenation measurements increased above baseline by as much as 60% (shown in the following figure). After the temporary elevation, tumor oxygenation measurements returned to baseline. No significant elevation in tissue oxygenation was seen in the contralateral cerebral tissue.



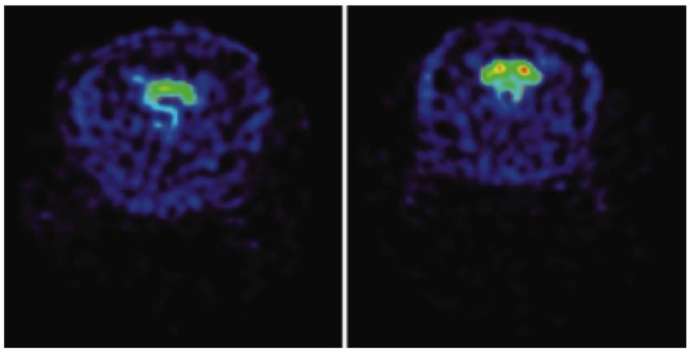
Source: Sheehan *et al*., 2009

Sheehan *et al*., 2010: A rat C6 glioma model was used, whereby C6 glioma cells were injected into the brain to form a tumor. Following confirmation for the presence of a tumor, the animals were divided into three groups: 1) temozolomide (TMZ; a standard chemotherapeutic agent used in treating brain cancer, discussed below) only, 2) TMZ plus radiation, and 3) TMZ plus radiation plus TSC. The animals were observed for 60 days following tumor implantation or until death. Results showed that mean survival of the TMZ and TMZ plus radiation groups was 23 and 29 days, respectively. Mean survival of the TMZ plus radiation plus TSC group was 39 days, a statistically significant increase. There was also a statistically significant reduction in the MRI-documented mean tumor size 30 days following tumor implantation. Lastly, close to 40% of the TMZ/radiation/TSC animals survived to 60 days (10% in the TMZ/radiation group and 0% in the TMZ only group), and all of those animals demonstrated the complete disappearance of tumors.



Source: Sheehan *et al*., 2010

Sheehan *et al*., 2011: A rat C6 glioma model was used, whereby C6 glioma cells were injected into the brain to form a tumor. Following confirmation for the presence of a tumor, the animals were then injected with Copper(II) diacetyl-di(N4-methylthiosemicarbazone) (Cu-ATSM), an imaging agent that is preferentially taken up by hypoxic tissues. In addition, tumor hypoxia was monitored following infusion with either TSC or saline. Results showed that all tumors preferentially took up Cu-ATSM compared with contralateral cerebral tissue. Infusion of TSC resulted in a 31% decrease in hypoxic tumor volume. The following image shows hypoxic regions in representative tumors 45 minutes after injection with TSC (left) or saline (right). Red and yellow indicate high levels of oxygen deprivation.

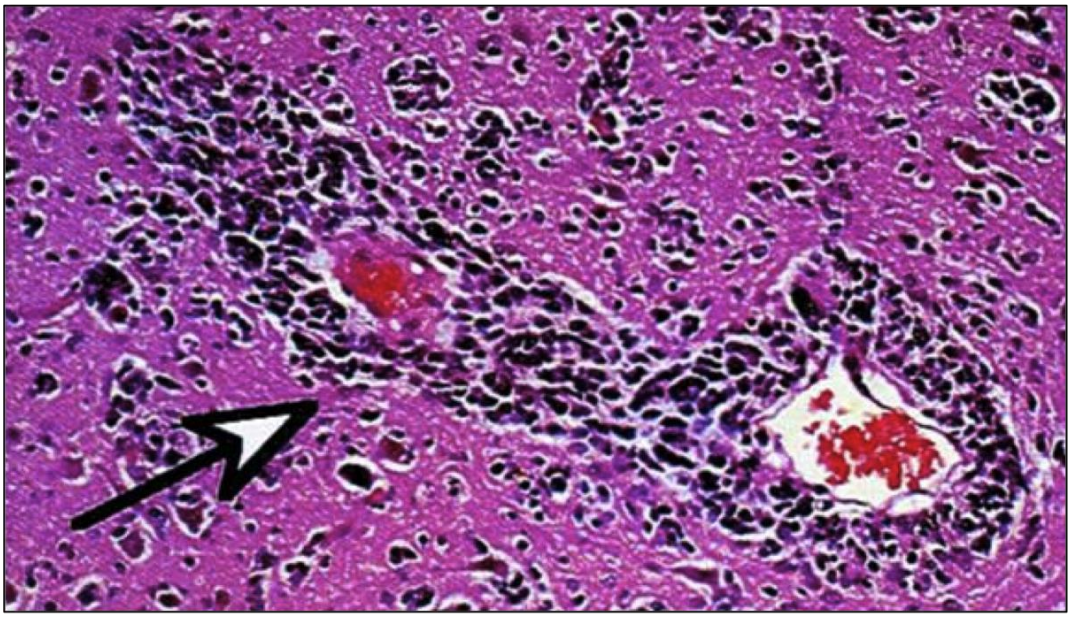


Source: Sheehan *et al*., 2011

TSC Indication I: Glioblastoma Multiforme

Glioblastoma multiforme (GBM) is the most aggressive of the category of tumors known as gliomas, which all arise from glia cells within the central nervous system. There are four grades of gliomas, with the highest grade, Grade 4 or GBM, being the most aggressive and the most common form in humans. Unfortunately, most patients with GBM don't live much longer than one or two years, and this has not changed appreciably over the years. The reason these tumors are so difficult to treat is multi-dimensional and has to do with the both the genetic make-up of the tumor (most GBM cells have multiple activating mutations and other genetic anomalies) as well as the way the tumors grow (they are highly infiltrative and arise in many different regions of the brain).

Current standard-of-care (SOC) treatment for GBM consists of surgery to resect as much of the tumor as possible followed by radiation and chemotherapy to kill any tumor cells that were not removed through surgery. While some types of solid tumors can be cured surgically, this is very rare in GBM due to the diffuse nature of the tumor. The following figure shows GBM cells (dark circles) surrounding blood vessels (bright red) in the brain, indicative of the growth typically seen with GBM tumors that make it so difficult to achieve complete resection.



Source: Holland *et al*., 2000

Gliomas are the most common type of intracranial cancer, accounting for 81% of all malignant brain cancers, and GBM accounts for 45% of all gliomas (Ostrom *et al*., 2014). There are approximately 25,000 people diagnosed with malignant brain cancer each year in the U.S. Since GBM is mostly diagnosed in older individuals (median age = 65 years), the aging demographics of the Western world has resulted in the incidence of GBM increasing from 5.1 per 100,000 in the 1970's to 10.6 per 100,000 in the 1990's (Chakrabarti *et al*., 2005). Those diagnosed with the disease have a very grim prognosis, with the median survival time of untreated patients being only 4.5 months. Current standard of care treatment only provides a 12-14 month median overall survival after diagnosis (Johnson *et al*., 2012).

Treatment of GBM

SOC treatment for GBM tumors always begins with surgical resection of as much of the tumor as can safely be done. This is done both to remove as much tumor mass as possible as well as alleviate any effects the tumor may be having on the patient. As mentioned above, due to the invasive nature of GBM tumors, complete tumor removal with "clean margins" (no visual presence of tumor) is almost never possible. Unfortunately, this leads to recurrence of the tumor in almost all GBM patients, with 90% occurring at the primary site (Wen *et al*., 2008).

Surgical resection is always followed by radiotherapy coupled with the use of chemotherapeutic agents. Radiotherapy involves the administration of irradiation to the whole brain (Grossman *et al*., 2004). While nitrosoureas were the most common chemotherapeutic agents used for a number of decades, in 1999 temozolomide (TMZ) became available and is now a part of the standard of care. This is due to a clinical trial that showed the addition of TMZ to surgery and radiation increased median survival in newly diagnosed GBM patients to 14.6 months compared to 12.1 months for the surgery and radiation only group (Stupp *et al*., 2005).

Bevacizumab (Avastin®) is a highly successful drug for Roche, with worldwide sales of close to $7 billion in 2015 (EvaluatePharma) based on its ability to successfully treat patients with colorectal, non-small cell lung, renal cell, and ovarian cancer. Two separate clinical trials of bevacizumab in newly diagnosed GBM patients showed no difference in overall survival in patients treated with radiation, TMZ, and bevacizumab compared to patients treated with only radiation and TMZ (Gilbert *et al*., 2014; Chinot *et al*., 2014). However, bevacizumab was shown to increase six-month progression free survival in patients with recurrent GBM from a historical 9-15% to 25% with overall six-month survival of 54% (Raizer *et al*., 2010). Another trial showed that recurrent GBM patients treated with bevacizumab at a lower dose but a higher frequency had even higher six-month progression-free survival of 42.6% (Friedman *et al*. 2009).

Resistance Mechanisms to Treatment

Clearly, development of effective GBM therapeutics has been quite challenging. This is in part due to a number of mechanisms intrinsic to GBM tumors that make them very difficult to treat:

- Highly infiltrative: As discussed above, GBM tumors infiltrate into the surrounding healthy tissue of the brain, making complete surgical resection virtually impossible. The aggressive nature of GBM cells means that a small number of cells left behind after surgery are capable of continued growth, leading to the poor prognosis for GBM patients.

- Hypoxia: A majority of the GBM tumor environment is hypoxic, or lacking in adequate oxygen supply. As mentioned previously, this lack of oxygen limits the effectiveness of radiation as the amount of DNA-damaging free radicals generated by radiation treatment is decreased.

- Hydrostatic pressure: The vasculature of GBM tumors is highly irregular and leaky, resulting in very high hydrostatic pressure. This makes drug delivery to the tumor difficult, as the therapeutic agents are not able to infiltrate deep into the tumor.

- DNA damage repair: Resistance to TMZ is mediated by the DNA repair protein methyl guanine methyl transferase (MGMT). High levels of MGMT activity in GBM cells blunt the therapeutic effect of alkylating agents (such as TMZ). Conversely, methylation of the promoter of the *MGMT* gene results in loss of MGMT expression and decreased DNA repair activity (Qian *et al*., 1997). Methylation status is highly predictive of survival in newly diagnosed GBM patients, with a 2004 study showing 18-month survival of 62% for patients with a methylated MGMT promoter compared to just 8% for patients without a methylated MGMT promoter (Hegi *et al*., 2004).

Based on the aforementioned difficulties in therapeutic development, the limited treatment options, the grim prognosis for GBM patients, and the intrinsic resistance mechanisms, it is clear that a significant unmet medical need for more efficacious GBM therapies currently exists.

GBM Therapies Under Development

There are a number of companies developing GBM therapies, as shown by a search on clinicaltrials.gov that yields over 300 results for “glioblastoma multiforme” and “open trials”. In addition to the therapeutics previously mentioned, current trials are examining the following:

- DCVax®-L: This product uses a patient’s dendritic cells as a vaccine. After surgery, a portion of the tumor that is removed from the patient is combined with the patient’s dendritic cells to “educate” the dendritic cells to respond to tumor antigens. The “educated” dendritic cells are then reintroduced into the patient, at which point the dendritic cells stimulate B- and T-cell responses to the tumor. The treatment is currently being tested in a Phase 3 clinical trial in conjunction with standard of care (NCT00045968). The trial’s sponsor is Northwest Biotherapeutics.

- Nivolumab/Ipilimumab: These are monoclonal antibodies directed against immune regulatory proteins. Nivolumab is directed against programmed death-1 (PD-1) while ipilimumab targets cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4). Both agents have activity in treating metastatic melanoma, with ipilimumab (Yervoy®) approved for that indication. While there is currently no clinical data for either molecule in GBM patients, preclinical data shows that both agents are active in orthotopic murine models of glioblastoma (Fecci *et al*., 2007; Zeng *et al*., 2013). Nivolumab is being compared to bevacizumab in a Phase 3 trial involving recurrent GBM patients while simultaneously being tested in combination with ipilimumab (NCT02017717). The trial’s sponsor is Bristol-Myers Squibb.

- Veliparib: This is a small molecule inhibitor of poly ADP ribose polymerase (PARP), an enzyme involved in DNA single-strand break repair. Preclinical data showed that veliparib enhanced killing of four GBM cell lines when used in conjunction with radiotherapy and TMZ (Barazzuol *et al*., 2013). The compound is currently being tested in a Phase 2/3 study in patients with newly diagnosed GBM (NCT02152982). The trial’s sponsor is AbbVie.

GBM is an Orphan Disease

Malignant brain cancers are diagnosed in approximately 25,000 individuals every year, making it an “orphan disease”. The Orphan Drug Act of 1983 was designed to provide financial incentives for and to reduce the costs

associated with developing drugs for rare diseases and disorders. A “rare disease or disorder” is defined by the Act as affecting fewer than 200,000 Americans at the time of designation or one for which “there is no reasonable expectation that the cost of developing and making available in the United States…will be recovered from sales in the United States.” A sponsor must request that the FDA designate a drug currently under development for a “rare disease or condition” as an orphan drug, and if the FDA agrees that the drug and indication meet the criteria set forth in the Act, certain incentives become available including:

- ✓ The FDA must provide the sponsor with “written recommendations for the non-clinical and clinical investigations (based on the information available at the time of the request)… that would be necessary for approval of such drug for such disease or condition…”

- ✓ For a period of seven years post-approval, the FDA may not approve an application from a different sponsor for the “same drug” for the same disease or condition. For biological treatments, the FDA defines same drug to mean one that contains the “same principle molecular features.” The 7-year exclusivity period conferred by orphan drug status is important because patent protection and Hatch-Waxman data exclusivity have limited effectiveness in excluding competitors from introducing equivalent drugs with slightly different structures. An exception is provided by any change that leads to improved safety or efficacy.

- ✓ Grants and contracts are available to defray the costs of development. For 2013-17, the amount appropriated is $30 million per year, which is a fairly modest sum but could make a significant difference for a small company such as Diffusion.

- ✓ A tax credit in the amount of 50% of qualified clinical testing expenses is established by related legislation (Title 26 Part 1-28). The tax credits can be rolled forward by up to 15 years for companies that have no tax liability in the year in which expenses are occurred (e.g., pre-revenue biotech companies).

- ✓ Waiver of PDUFA fees. For FY 2016, these are $2.37 million for full NDAs, a huge benefit for a company with limited financial resources.

Similar laws have been passed in other major markets such as Europe and Japan. In Europe, orphan drug status is not associated with tax breaks or subsidies at the European Union level, but the exclusivity period is longer at 10 years. In Japan, the exclusivity period is also 10 years, and takes special significance, as the approval times are so long that many drugs are reaching the end of their patent life when finally approved.

In July 2011, Diffusion announced that TSC was granted Orphan Drug Designation by the FDA for the treatment of GBM. This entails Diffusion to all the incentives listed above. However, TSC is not the only compound in development for treating GBM that has been granted Orphan Drug Designation, as DCVax®-L and veliparib have all also been granted Orphan Drug Designation for treating GBM.

GBM Market Analysis

It is predicted there will be approximately 25,000 malignant brain tumors diagnosed in the U.S. in 2016 (CBTRUS). Gliomas make up approximately 81% of all malignant brain tumors, with GBM comprising approximately 45% of all gliomas (Ostrom *et al*., 2014). Thus, we estimate that there will be approximately 9,000 cases of GBM diagnosed in the U.S. in 2016. Worldwide, there were an estimated 250,000 malignant brain tumors diagnosed in 2012 (GLOBOCAN 2012). There were a similar percentage of gliomas and GBM worldwide, thus we estimate that 90,000 individuals were diagnosed with GBM in 2012.

The FDA originally approved TMZ in 1999 for the treatment of GBM. Schering-Plough marketed the drug until their 2009 merger with Merck. At the time of the merger, TMZ (sold as Temodar®) was a blockbuster medication, with 2008 revenues of just over $1 billion. Patent exclusivity for Temodar® (marketed as Temodal® outside the US) ended in 2009 in the EU and in 2014 in the US. However, based upon an agreement between Merck and Teva Pharmaceuticals, a generic version of Temodar® was launched in the US in August 2013. Thus, sales have declined from a high of $1.065 billion in 2010 to $312 million in 2015 (EvaluatePharma).

Avastin® is one of the world’s top-selling medications, with annual sales close to $7 billion (EvaluatePharma). However, given the small patient population associated with GBM, we estimate sales for Avastin® in this indication of only approximately $170 million per year.

Trans Sodium Crocetinate Phase 1/2 Clinical Trial in GBM

Thus far, TSC has been evaluated in 148 human subjects in Phase 1 and Phase 2 clinical trials, with no serious adverse events reported thus far. Below we highlight the recently completed Phase 1/2 clinical trial of TSC in patients with GBM, an indication for which TSC will be tested in a Phase 3 clinical trial set to begin later in 2016.

The Phase 1/2 clinical trial in GBM enrolled 59 patients with newly diagnosed disease that received TSC in conjunction with radiation and TMZ (Gainer *et al*., 2016). In the Phase I portion of the trial, TSC was initially administered three times per week at half-dose to three patients prior to radiation. Six additional patients received full dose TSC for six weeks in combination with radiation. No dose-limiting toxicities were identified in the nine patients during the Phase I portion of the trial. Fifty additional patients were enrolled in the Phase II trial at full dose TSC in combination with TMZ and RT. Four weeks after completion of RT, all patients resumed TMZ for five days every four weeks, but no further TSC was administered.

Initial results from trial were presented at the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting, which discussed data from 18 trial sites covering the first 21 months. Preliminary results were then announced in July 2015, with a number of important findings disclosed at that time. The results presented by Diffusion were in relation to a historical control group, which is from a 2005 study that showed the addition of TMZ to standard of care (surgery plus radiation) increased overall survival from 12.1 months to 14.6 months (Stupp *et al*., 2005). Diffusion reported that:

- TSC plus radiation and TMZ increased the patients' chance of survival at two years by 37% compared to the historical control group. The overall survival at two years was 37% in the TSC group compared to 27% in the historical control group.

- In the subgroup of patients considered inoperable, the chance of survival at two years for those who received TSC was increased by over 100 percent, as 40 percent in the TSC group were alive at two years compared to less than 20 percent in the control.

- 71 percent of people treated with TSC were alive at one year compared to 61 percent of people in the historical control group.

- No serious negative safety findings attributed to TSC were observed in the TSC study and adverse events were consistent with those seen in previous trials of GBM featuring radiation and TMZ.

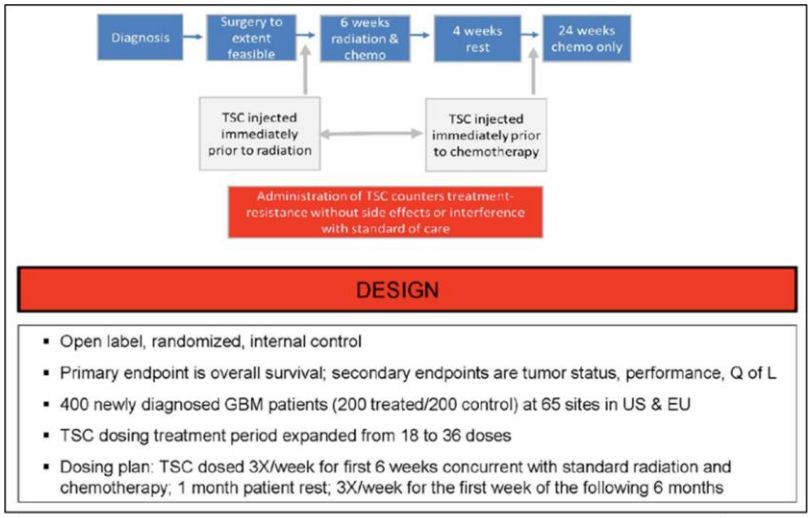
Since the study lacked a control arm it is difficult to draw definitive conclusions regarding the activity of TSC, however these data are still very encouraging, particularly since a clinical benefit was observed with little to no additional toxicity.

Plans for TSC Phase 3 Clinical Trial in GBM

Following the announcement of the results from the Phase 1/2 clinical trial in GBM, Diffusion held an end of Phase 2 meeting with the FDA to discuss plans for the company's upcoming Phase 3 clinical trial. At the meeting, an agreement was reached on the trial design for the Phase 3 study, which includes:

- ✓ A single, successful trial that will serve as the basis for an application for approval.
- ✓ The trial will consist of 400 newly diagnosed GBM patients with half given TSC in conjunction with standard of care radiation and TMZ
- ✓ There is significant leeway to increase TSC dosing exposure based on the Phase 1/2 safety results and supporting toxicology, which means that TSC can be used for both the radiation + chemotherapy and subsequent chemotherapy-only phase of GBM treatment

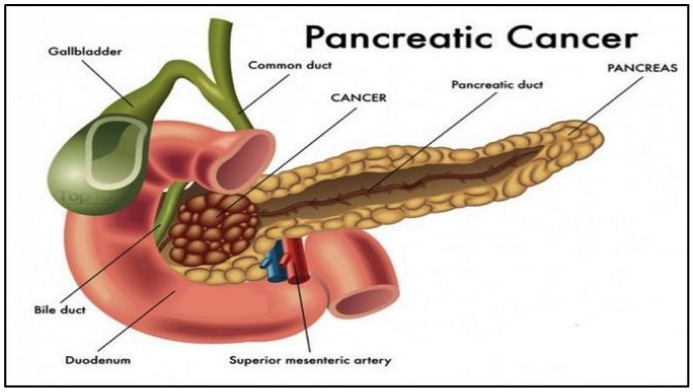
One of the major differences between the Phase 3 trial and the Phase 1/2 trial is the addition of TSC doses during chemotherapy. In the Phase 1/2 trial, TSC was only given prior to radiation (18 doses total), however in the Phase 3 study, the company is planning to give the patients 36 total doses of TSC, 18 in conjunction with radiation and 18 in conjunction with chemotherapy. The following figure gives a graphical representation of the Phase 3 trial.



Source: Diffusion Pharmaceuticals Inc.

Since the company is increasing the planned number of doses of TSC from 18 to 36, an expanded toxicology study will be performed and the results submitted to the FDA prior to initiation of the study. In addition, a Chemistry, Manufacturing, and Controls (CMC) amendment will be submitted describing the cGMP production of TSC. We are confident that both of these issues will be taken care of by the company in a timely manner such that the first patient can be dosed in the Phase 3 trial in the second half of 2016. The primary endpoint of the study is overall survival, and we expect topline results to be available in the second half of 2019.

TSC Indication II: Pancreatic Cancer



Source: jbanews.com

Pancreatic cancer is responsible for 7% of all cancer deaths in both men and women, making it the fourth leading cause of cancer death in the U.S. (American Cancer Society). The disease is notoriously difficult to diagnose in early stages due to initial symptoms (anorexia, malaise, nausea, fatigue, and back pain) quite often being nonspecific and subtle in nature.

Surgical resection is the only potential curative therapy for pancreatic cancer. Due to differences in locations of the tumors and their proximity to nearby blood vessels, only 20% of cases are eligible for surgery. Of the tumors that are surgically resected, 80% of those patients will still develop metastatic disease within two to three years following surgery (Daniel *et al*., 2008). For those with pancreatic cancer that cannot be surgically removed, the median overall survival is 10 to 14 months. For those with Stage IV disease (meaning the cancer has metastasized), the 5-year survival rate is just 1%.

Pancreatic cancers are known to be highly hypoxic. A study reporting the direct measurement of oxygenation in human pancreatic tumors prior to surgery showed dramatic differences between tumors and normal tissue (Koong *et al*., 2000). The partial pressure of oxygen (pO_2) ranged between 0-5.3 mmHg in tumors but in adjacent normal tissue it ranged from 9.3-92.7 mmHg. This same effect holds true in mouse models of pancreatic cancer, which typically also have high degrees of hypoxia (Chang *et al*., 2011; Guillaumound *et al*., 2013).

Treatment of Pancreatic Cancer

Treatment of pancreatic cancer is highly dependent upon the stage of the cancer, which indicates how far it has spread in the body. For cancers that are confined to the pancreas and have not grown into nearby blood vessels, surgery is the preferred treatment option as it offers the only realistic chance for a cure. Surgical resection is often combined with chemotherapy and/or radiation after surgery (adjuvant treatment) to prevent recurrence. For tumors that are "borderline resectable" (meaning that most, but usually not all of the tumor could be removed by surgery), treatment usually consists of neoadjuvant chemotherapy in an attempt to shrink the tumor as much as possible prior to surgery. Metastatic pancreatic cancer is not amenable to surgery and is typically treated with chemotherapy.

Gemcitabine is the SOC chemotherapy agent for metastatic pancreatic cancer. The FDA has approved its use in combination with two other chemotherapeutic agents: erlotinib (Tarceva®) and nab-paclitaxel (Abraxane®). In patients with metastatic disease, the use of erlotinib with gemcitabine led to a significantly higher 1-year survival rate than with the use of gemcitabine alone (23% vs. 17%, $P = 0.023$) as well as an increased median overall survival (6.24 months vs. 5.91 months, $P = 0.038$) (Moore *et al*., 2007). A more recent study showed that the addition of nanoparticle albumin-bound (nab)-paclitaxel to gemcitabine significantly improved overall survival in treatment naïve patients with metastatic cancer, as overall survival was approximately two months longer in patients treated with combination therapy (8.5 vs. 6.7 months) (von Hoff *et al*., 2013).

FOLFIRINOX (leucovorin + 5-fluorouracil + oxaliplatin + irinotecan) is a combination regimen that significantly improved overall survival compared to treatment with gemcitabine (11.1 months vs. 6.8 months) (Conroy *et al*., 2011). However, treatment with FOLFIRINOX is accompanied by serious adverse events, and for that reason is only recommended for the healthiest patients.

Onivyde® (irinotecan liposome injection) was approved by the FDA in 2015 in combination with fluorouracil and leucovorin to treat patients with metastatic pancreatic cancer who failed treatment with gemcitabine-based chemotherapy. In the pivotal clinical trial, patients treated with Onivyde® plus fluorouracil/leucovorin lived an average of 6.1 months, compared to 4.2 months for those treated with only fluorouracil/leucovorin.

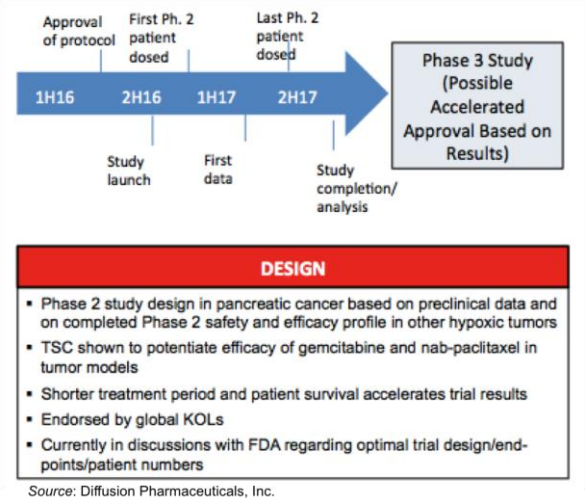
Pancreatic Cancer Market Analysis

In 2016, approximately 49,000 people will be diagnosed with pancreatic cancer in the U.S. More than half of these patients will be diagnosed with metastatic disease. As previously noted, the 5-year survival rates for patients with pancreatic cancer are dismal (<14%) and are particularly bad for those with metastatic disease (~1%), thus indicating the need for more effective treatment options for these patients.

Gemzar® (gemcitabine) is now available as a generic, however prior to losing patent protection the drug generated peak revenues of approximately $700 million in the U.S. for Eli Lilly. Tarceva® (erlotinib), which is approved for the treatment of metastatic non-small cell lung cancer and metastatic pancreatic cancer, generated revenues of $1.2 billion in 2015 for Roche and Astellas (EvaluatePharma). Abraxane® (nab-paclitaxel) is approved for the treatment of breast cancer, non-small cell lung cancer, and metastatic pancreatic cancer and generated revenues of $1.1 billion worldwide in 2015 (EvaluatePharma).

Proposed Plan for TSC Phase 2 Clinical Trial in Pancreatic Cancer

The Phase 2 clinical trial for TSC in pancreatic cancer is based on the successful Phase 1/2 clinical trial in GBM as well as the fact that pancreatic tumors are usually highly hypoxic. Global experts in the field of pancreatic cancer agree that pancreatic cancer is the most appropriate target for expansion of the use of TSC, and a clinical advisory board of these key opinion leaders has been assembled to facilitate the pancreatic cancer clinical trial. The company is currently continuing discussions with the FDA regarding trial design/end-points/patient numbers. The figure below gives an overview of the proposed study.



Source: Diffusion Pharmaceuticals, Inc.

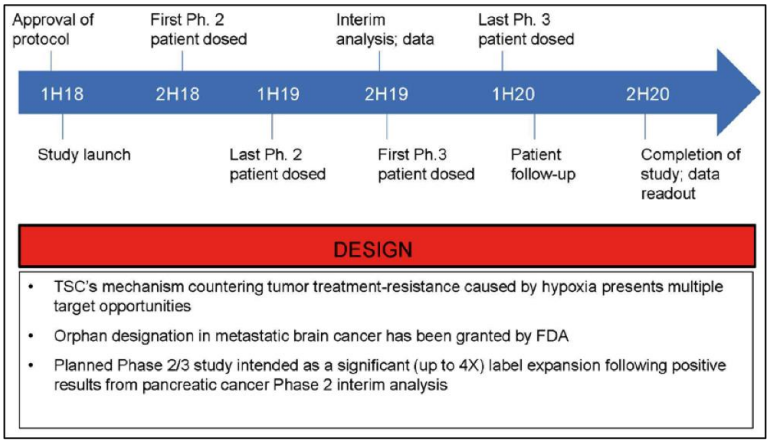
Indication III: Metastatic Brain Cancer

Metastatic brain cancer occurs when a primary tumor spreads to the brain. Primary brain cancers, such as GBM, are relatively rare, however metastatic brain tumors are much more common and represent a life-threatening complication for many different types of cancer. Up to 30% of adult cancer patients will suffer from brain metastases (Norden *et al*., 2005). While an exact figure is difficult to determine, it is estimated that 170,000 cases of metastatic brain cancer occur every year in the U.S. Lung cancer is the type of cancer most likely to metastasize to the brain, followed by kidney and skin cancer (Schouten *et al*., 2002). Just as with primary brain cancers, the prognosis for patients with brain metastases is very grim. Median overall survival for those with brain metastases is less than one year (Sundström *et al*., 1998).

The most pressing issue for patients with brain metastases is getting symptoms under control, which are typically brought on by the presence of a tumor putting pressure on the surrounding region of the brain. Symptoms can include headaches, speech difficulties, seizures, and visual disturbances. Corticosteroids are often used to control swelling and anti-epileptic medications are given to prevent the recurrence of seizures. Surgery can be performed if the tumor is located in a portion of the brain that allows it. Whole brain radiation therapy is utilized for most patients, however it is most effective for those with primary tumors that are more sensitive to it, such as lung and breast cancer. Chemotherapy is used sparingly due to the inability for the vast majority of those drugs to cross the blood-brain barrier in sufficient quantities to be effective. There are currently no FDA-approved medications for the treatment of brain metastases.

Plans for TSC Phase 2/3 Clinical Trial in Metastatic Brain Cancer

Diffusion is planning to utilize a Phase 2/3 clinical trial in metastatic brain cancer as a means of expanding the label significantly (4X). We anticipate the first patient being dosed in the Phase 2/3 metastatic brain cancer trial in the second half of 2018, an interim analysis to take place in 2019, and the data to be available in the second half of 2020. A timeline of expected events is shown below.



Source: Diffusion Pharmaceuticals, Inc.

Financials and Capital Structure

As of March 31, 2016, Diffusion had approximately $5.9 million in cash and cash equivalents, which we estimate is enough to fund operations into the third quarter of 2016. However, in order to run the Phase 3 trial of TSC in GBM, the company is going to need to raise additional capital. We estimate it will cost approximately $45 million to fully fund the Phase 3 GBM trial.

As of May 16, 2016, the company had approximately 102.4 million shares outstanding. In addition, there are approximately 17.9 million stock options, 2.1 million shares from convertible debt, and 4.8 million warrants for a fully diluted share count of approximately 127 million.

Intellectual Property

Diffusion is the exclusive owner of 11 patents in the U.S. and 26 patents abroad. Key patent life extends to 2026 with expected extensions until 2031. TSC has been granted Orphan Drug Designation for the treatment of both GBM and metastatic brain cancer. A formulation patent provides protection for the TSC oral drug product until 2031 with extensions possible.

Risks to Consider

Future clinical trial results may not be positive: Diffusion reported clinical trial results from a Phase 1/2 clinical trial of TSC in GBM patients that were compared to a historical control group. While the results were positive in comparison to the control group, there is no guarantee that the company would attain positive results in a future clinical trial where a patient cohort treated with TSC is directly compared to a control group not treated with TSC.

Diffusion will need to raise additional capital to fully fund the upcoming Phase 3 trial in GBM: As of March 31, 2016, the company had approximately $5.9 million in cash and cash equivalents. The company will need to raise additional capital in order to fully fund the upcoming GBM Phase 3 clinical trial, which could result in significant dilution to current shareholders.

Changes to standard of care treatments could decrease necessity for TSC: TSC is not an anti-cancer agent on its own, but instead works with standard of care radiation and chemotherapy to enhance their anti-cancer abilities. If new therapies are developed that supplant the use of radiation and chemotherapy as first line agents, then TSC's potential market share could decrease substantially.

Diffusion is highly dependent on TSC, as the company's other assets are all pre-clinical: Through the merger with RestorGenex, Diffusion acquired RES-529, an inhibitor of the mTORC1 and mTORC2 complexes that is being developed for the treatment of cancer. However, this compound is still in pre-clinical development, thus we do not include it in the company's valuation. In addition, even if successful in clinical testing, the earliest we project TSC could reach the market is 2020, thus the company will have a number of years of operating losses in the near term.

MANAGEMENT PROFILES

David G. Kalergis – Chief Executive Officer and Chairman of the Board

Mr. Kalergis, along with Professor John Gainer, is co-founder of Diffusion Pharmaceuticals Inc., and, since 2004, has served as the company's Chief Executive Officer. Before attending graduate school, Mr. Kalergis worked as an intelligence analyst for the U.S. Government. In 1982, after receiving MBA and JD degrees from the University of Virginia, he was associated with the New York City law firm of Dewey, Ballantine, Bushby, Palmer & Wood, practicing in the areas of corporate finance, public offerings and mergers and acquisitions. In 1991, Mr. Kalergis became the first private investor in Pharmaceutical Research Associates, Inc. (PRA), a contract research organization providing clinical trials services to international pharmaceutical and biotechnology companies. PRA went public in 2004 and is now among the world's largest CROs. He served on PRA's Board of Directors, and, from 1991 to 1994, as head of Business Development before being named General Counsel. Mr. Kalergis graduated from the University of Virginia College of Arts and Sciences with a B.A. in Psychology. In 1982 he graduated from the Combined Program of the Colgate Darden Graduate School of Business Administration and the University of Virginia School of Law, receiving both J.D. and M.B.A. degrees. Mr. Kalergis is also a graduate of the Harvard Business School's Leadership and Strategy in the Pharmaceutical and Biotechnology Industry program.

John L. Gainer, PhD – Chief Scientific Officer

Dr. Gainer was Professor of Chemical Engineering at the University of Virginia, serving as a member of the faculty from 1966-2005. As co-founder and Chief Scientific Advisor of the Company, and the inventor of the trans bipolar carotenoid family of molecules, he plays a critical role in charting the path of their further development and commercialization. He has authored more than 100 scientific journal articles, including more than 30 published in medical journals. He has spent four decades investigating the transport properties of small molecules in solvents and biological systems. His more recent research, funded by the Office of Naval Research, focused on the use of trans bipolar carotenoid molecules to treat hemorrhagic shock, which is the major cause of death in combat, and to treat Acute Respiratory Distress Syndrome (ARDS). Dr. Gainer has spent two sabbaticals investigating drug actions and related research, one at Karolinska Institute in Stockholm, Sweden, and one in the laboratories of a major pharmaceutical company. He has been a member of the International Society for Oxygen Transport in Tissues since its inception in 1973. He has received several teaching awards, including the University of Virginia Alumni Association's Distinguished Professor Award and the Outstanding Teacher Award from the Southeastern Section of the American Society for Engineering Education. Dr. Gainer received his PhD in Chemical Engineering from the University of Delaware in 1964.

David R. Jones, MD – Chief Medical Officer

Dr. Jones has served as Diffusion's Chief Medical Officer since September 2012. In addition to serving as Diffusion's Chief Medical Officer, Dr. Jones is also the Fiona and Stanley Druckenmiller Endowed Professor for Lung Cancer Research and Chief of Thoracic Surgery at Memorial Sloan-Kettering Cancer Center in New York, NY, a position he has held since 2013. From 2007 to 2013, Dr. Jones was Professor of Surgery and Division Chief for Thoracic & Cardiovascular Surgery at the University of Virginia. In addition to his clinical practice, Dr. Jones has published more than 220 scientific articles, authored or co-authored over 35 book chapters, and served as Principal Investigator or Co-Investigator of over 30 clinical trials. Dr. Jones received his undergraduate degree in Chemistry and M.D. from West Virginia University. He then completed his thoracic surgery residency and a postdoctoral research fellowship in molecular oncology at the University of North Carolina – Chapel Hill.

Ben Shealy – Senior Vice President, Finance & Treasurer

Mr. Shealy has over twenty five-years of experience in financial management and private and public corporate financings. As SVP-F of the company, Mr. Shealy has responsibility for implementing the company's overall financial strategy and managing the performance of day-to-day operational finance and accounting matters. Prior to joining Diffusion Pharmaceuticals Inc., he was Vice President of REBAR where he directed M&A activities that involved the firm's $100M+ investment in start-up companies. Mr. Shealy's Wall Street background encompasses both the sell-side (Donaldson, Lufkin & Jenrette and Prudential-Bache Capital Funding) and the buy-side (John Hancock Derivatives Group). Mr. Shealy earned a BS in Accounting from San Jose State University, an MBA in Finance from Columbia University in New York City and is a CFA Charter holder. Mr. Shealy resides in central Virginia with his wife and five children.

VALUATION

Diffusion is a clinical stage biopharmaceutical company developing treatments to improve the current standard-of-care (SOC) therapy for various oncology indications. We believe the company's lead asset, trans sodium crocetinate (TSC), offers a unique solution to the issue of tumor hypoxia that could prove to be quite beneficial to patients suffering from very difficult to treat cancers such as glioblastoma multiforme (GBM), pancreatic cancer, and brain metastases.

Trans Sodium Crocetinate

Trans sodium crocetinate (TSC) is the *trans*-isomer of crocetin, a natural carotenoid compound related to vitamin A. Crocetin was originally identified as a compound that could be used to facilitate the movement of oxygen through the plasma. Early work showed that crocetin was an effective treatment in a rat model of atherosclerosis and hemorrhagic shock (Gainer *et al*., 1993). Crocetin is an isomeric mixture, and it was later shown that TSC was more effective than crocetin in various model systems.

TSC's unique mechanism of action is related to its ability to increase the amount of oxygen that reaches tissues. This occurs because TSC alters the molecular arrangement of water molecules in the plasma, thereby altering the diffusivity of oxygen (or other small molecules) through the plasma. An increase in tissue oxygenation, particularly in hypoxic tissues that are typically found in solid tumors, enables radiation and chemotherapy treatments to be more effective.

To date, TSC has been evaluated in 148 human subjects in Phase 1 and Phase 2 clinical trials, with no serious adverse events reported thus far. A Phase 1/2 clinical trial of TSC in GBM patients showed that treatment with TSC in addition to radiation and temozolomide (TMZ) resulted in a 37% increase in the chance of survival at two years compared to a historical control group. In addition, 71% of patients treated with TSC were alive at one year compared to 61% in the historical control group. These results were seen with no additional negative safety findings and a rate of adverse events that was similar to previous trials of GBM patients using radiation and TMZ.

The company is currently planning to initiate a Phase 3 clinical trial of TSC in GBM patients in 2016. The trial will feature 400 patients and the FDA has indicated that only one Phase 3 trial will be necessary for a regulatory filing. Topline results from this study are likely in the second half of 2019.

Diffusion is planning on pursuing additional indications for TSC in the treatment of pancreatic cancer and brain metastases. Both of these conditions have very poor prognoses for patients and are known to be hypoxic, thus making them potentially amenable to adjunct treatment with TSC. The company will need to meet with the FDA to discuss trial design, end points, and patient numbers for each of those indications. The trial in pancreatic cancer will likely begin in late 2016 or the first half of 2017, while a trial in brain metastases would most likely not begin before 2018.

Valuation

Diffusion's valuation is derived from a risk-adjusted discounted cash flow model that takes into account potential future revenues from the sale of TSC in GBM, pancreatic cancer, and brain metastases. For all indications we assume that the company will partner and receive 15% royalties on net sales.

For GBM, we model for the Phase 3 trial to initiate in late 2016, a new drug application (NDA) to be filed in 2020, and approval in 2021. If successful, we believe TSC would quickly be incorporated into standard of care for newly diagnosed patients. Using these assumptions the company would likely attain a sizeable share of the market (perhaps up to 75-80% peak market share), which would lead to worldwide sales of approximately $900 million. Applying a 15% discount rate and a 60% probability of approval leads to a net present value for TSC in GBM of $127 million.

For pancreatic cancer, we model for the Phase 2 trial to initiate in 2017, an NDA filing in 2020, and approval in 2021. Just as with GBM, if TSC proves to be successful when added to the standard of care for pancreatic cancer, we believe the company could attain peak market share of up to 50%. We model for this to translate into peak sales

of approximately $1.5 billion worldwide. Applying a 15% discount rate and a 33% probability of success leads to a net present value for TSC in pancreatic cancer of $193 million.

For brain metastases, we model for a Phase 2/3 trial to initiate in 2018, an NDA filing in 2021 and approval in 2022. The brain metastases market is much larger than for primary brain cancer like GBM, thus even a 20% market share would lead to peak worldwide revenues of approximately $4 billion. Applying a 15% discount rate and a 33% probability of success leads to a net present value for TSC in brain metastases of $239 million.

Combing the net present value for each of the company's development programs along with current cash total and expected burn of $60 million leads to a net present value for the company of approximately $505 million. Dividing that by the current fully diluted share count of 127.4 million shares leads to a valuation of approximately $4.00 per share. The stock is currently trading at a significant discount to this valuation, and as more investors become aware of the potential for TSC, we believe the share price will increase to be more in alignment with our valuation.

PROJECTED FINANCIALS

Diffusion Pharmaceuticals, Inc.
Income Statement

Diffusion Pharmaceuticals, Inc.	2015 A	Q1 A	Q2 E	Q3 E	Q4 E	2016 E	2017 E	2018 E
TSC (GBM)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
TSC (Pancreatic Cancer)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
Grants & Collaborative Revenue	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-
Cost of Sales	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-	-
Research & Development	$3.9	$2.4	$2.5	$2.7	$2.8	$10.4	$7.0	$10.0
General & Administrative	$2.5	$3.9	$1.0	$1.0	$1.0	$6.9	$4.0	$6.0
Other Expenses	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Operating Income	($6.4)	($6.2)	($3.5)	($3.7)	($3.8)	($17.2)	($11.0)	($16.0)
Operating Margin	-	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	($0.3)	($0.0)	($0.0)	($0.0)	($0.0)	($0.1)	($0.2)	($0.2)
Pre-Tax Income	($6.7)	($6.2)	($3.5)	($3.7)	($3.8)	($17.3)	($11.2)	($16.2)
Income Taxes Paid	$0.0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($6.7)**	**($6.2)**	**($3.5)**	**($3.7)**	**($3.8)**	**($17.3)**	**($11.2)**	**($16.2)**
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**-**	**($0.06)**	**($0.03)**	**($0.03)**	**($0.03)**	**($0.15)**	**($0.09)**	**($0.12)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	-	100.0	110.0	120.0	122.0	113.0	130.0	140.0

Source: Zacks Investment Research, Inc. *David Bautz, PhD*

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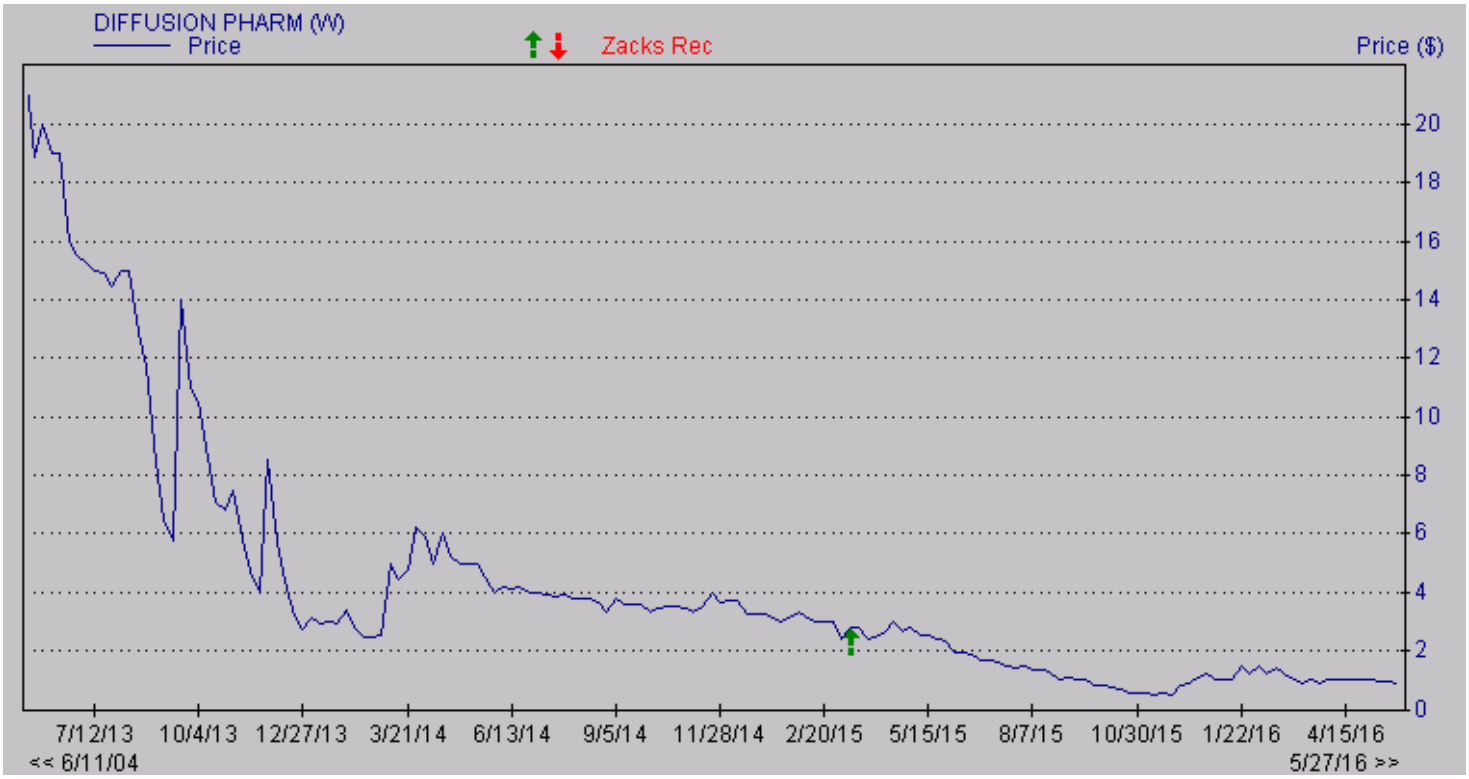
HISTORICAL STOCK PRICE



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