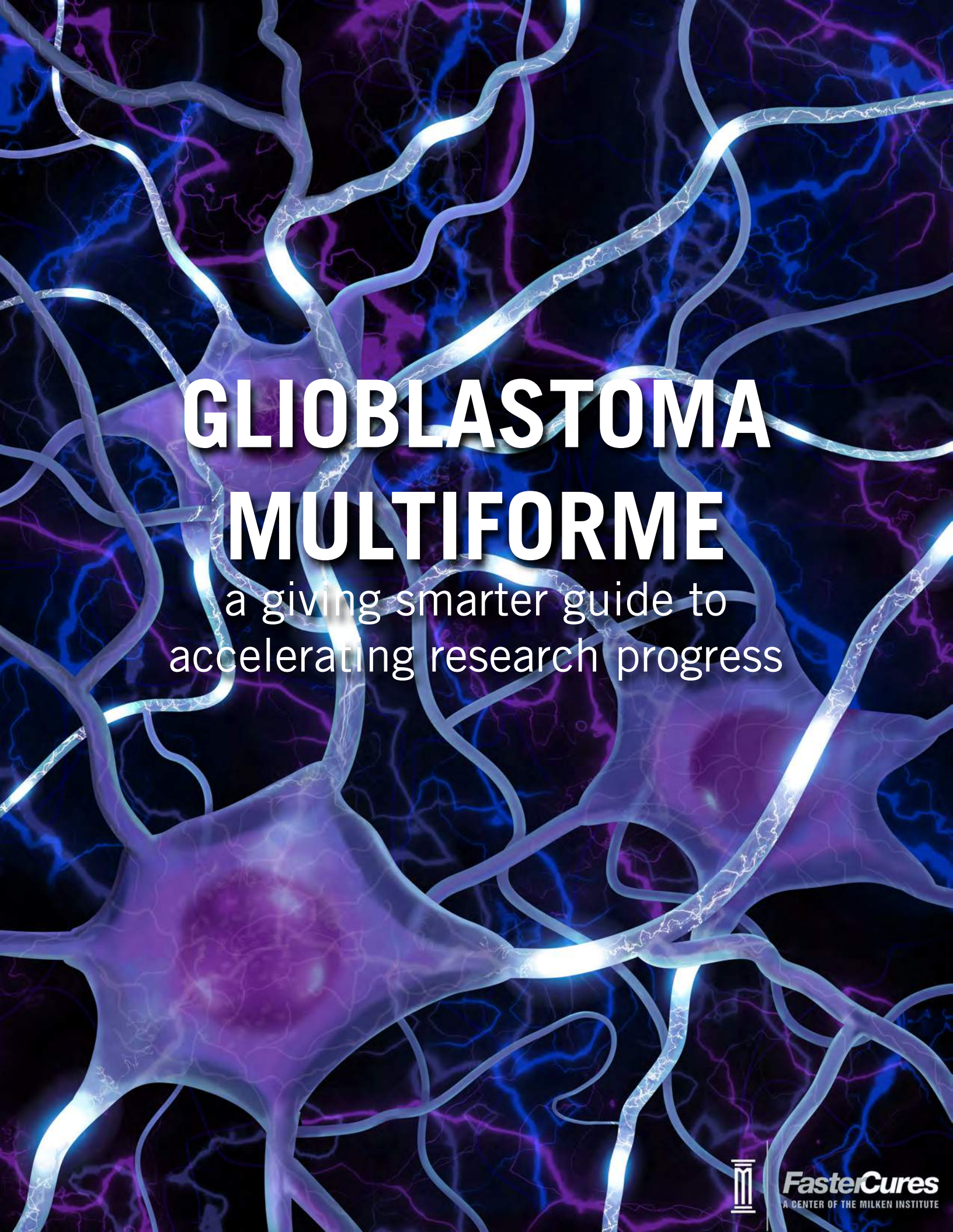

GLIOBLASTOMA MULTIFORME

a giving smarter guide to accelerating research progress

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CONTENTS

EXECUTIVE SUMMARY

Glioblastoma multiforme (GBM) is an aggressive malignant brain tumor involving glial cells of the brain. Glial cells – the most abundant cells within the central nervous system – provide support and protection for neurons throughout the central nervous system, including the brain. Glial tumors (also referred to as gliomas or astrocytomas) arise when glial cells become malignant and grow rampantly. These tumors are categorized using a scale of I to IV to describe the degree of abnormality of glial cells within the tumor, and a high to low grade system to describe growth rate of the tumor. GBM is classified by the World Health Organization (WHO) as a grade IV astrocytoma – the highest grade and most malignant form of all gliomas.

According to the American Brain Tumor Association, GBM accounts for nearly 50 percent of all gliomas and approximately 15 percent of all brain tumors. Throughout the United States and Europe, the incidence of GBM is approximately two to three new cases per 100,000 people per year, giving rise to nearly 14,000 new cases of GBM each year. GBM preferentially affects adults ages 45-65, and is more common in men than women.

The prognosis for GBM patients is very poor, with a median survival time of approximately 14.6 months. Less than 30 percent of patients survive two years after diagnosis, and less than 10 percent survive beyond five years after diagnosis.

GBM is generally treated by first surgically removing the tumor then treating with chemotherapy (Merck's Temodar) and radiation. While this treatment plan is the currently accepted standard of care, it does not effectively prevent tumor recurrence, which ultimately causes death in GBM patients.

Additional treatments are in clinical development for GBM. Most recently, Genentech's Avastin was approved for the treatment of recurrent GBM patients. This agent has been shown to be effective in delaying tumor progression, but recent data show that it does not increase overall survival in GBM patients. This recent finding highlights the need for the development of effective treatment options that not only increase overall survival in GBM patients, but also ultimately provides these patients with the opportunity for a cure.

There are quite a few areas of promising clinical research that could serve as the tipping point toward extending survival in GBM patients and potentially pave the way to a cure. These areas include but are not limited to translational research studies aiming to identify and inhibit aberrant molecular pathways that drive tumor resistance, recurrence, and invasion. In addition, clinical research evaluating the use of oncolytic virotherapy, immunotherapy, and combinations of these treatments with chemo- and targeted therapies are also of tremendous value. While these research areas are indeed poised to have a high impact on GBM treatment options in the near future, severe funding gaps threaten to delay acceleration of progress. As a result, medical philanthropy plays an increasingly important role in accelerating the translation of high-impact research into accessible medical solutions.

DISEASE BIOLOGY

Cancer cells are characterized by uncontrollable growth and invasion of nearby tissues. Abnormal cell division and growth is caused by genetic mutations that either turn on oncogenes (genes that speed up cell division) or silence tumor suppressor genes (genes that slow down cell growth and control cell death). The accumulation of this type of genetic damage over time can lead to the progressive transformation and survival of abnormal cell populations that can form tumors.

Glioblastoma multiforme originates from aberrant growth of astrocytes (a type of glial cell). Survival and expansion of abnormal astrocytes can lead to the development of astrocytomas, which can eventually give rise to glioblastoma. In order to classify and accurately diagnose astrocytomas, the WHO established a four-tiered histologic grading guideline that assigns a grade from one (I) to four (IV), with one being the least aggressive and four being the most aggressive. GBM is the most aggressive malignant brain tumor in humans and is therefore classified as a grade IV astrocytoma.

GBM tumors are further categorized based on the rate of progression. De novo (also referred to as primary) GBM tumors arise quickly and progress rapidly, whereas secondary tumors typically start as low-grade astrocytomas that eventually transform into malignant, rapidly growing glioblastoma. De novo tumors are more common in patients over age 55, and secondary tumors are most often found in patients ages 45 or younger.

Research has shown that there are distinct genetic differences between de novo and secondary tumors. For cases of de novo GBM, key genetic alterations appear to occur simultaneously during a shorter period of genomic instability relative to secondary tumors. This is thought to partially explain the rapid progression of de novo GBM. For secondary GBM, there is a distinct succession of genetic events that occur over a longer period of time that are not necessarily identical to the genetic events that drive de novo tumor formation. This difference in genetic programming highlights the complexity of GBM and the importance of using genomics-based research to unravel this complex biology.

MOLECULAR PATHWAYS AND TARGETS

Within the last three decades, genomic research has identified key mutational targets in the human genome that are associated with GBM. Many of these targets are involved in the PI3K/Akt/mTOR signaling pathway, which is a cascade of biochemical events that promote tumor cell metabolism, growth, and survival (Yap et al. 2008) (Figure 1). Some of these targets include epidermal growth factor receptor (EGFR) and EGFRvIII – a common EGFR variant found in GBM, farnesyl transferase, histone deacetylases (HDAC), heat-shock protein 90 (HSP-90), integrins, mammalian target of rapamycin (mTOR), phosphatidylinositol 3-kinases (PI3K), and vascular endothelial growth factor (VEGF) (Nakada et al. 2011). Research has also shown that similar to other cancers, deregulation of the p53 and retinoblastoma genes plays a critical role in GBM, as well as the loss of function of the tumor suppressor genes, RB, p16 (both cell cycle inhibitor) and PTEN (negative regulator of PI3K production and cellular proliferation) (Meir et al. 2010).

PROGNOSTIC INDICATORS

Prognostic indicators are clinical, genetic, or biomarkers that help physicians predict treatment effectiveness and/or outcomes. The two most common prognostic indicators used to predict treatment response of GBM patients are DNA methylation status and the genetic categorization of the resected tumor.

DNA METHYLATIONS STATUS

MGMT methylation status is used as a key indicator to determine the likelihood that a patient will respond to temozolomide treatment. MGMT methylation status refers to the chemical state of a specific gene that controls the production of O6-methylguanine DNA methyltransferase (MGMT) protein. This gene is commonly referred to as the MGMT promoter.

MGMT is a DNA repair protein that can reverse the effects of temozolomide and other drugs with a similar mechanism of action. Temozolomide works by depositing alkyl groups onto DNA. DNA alkylation of genes that play important roles in tumor proliferation can disrupt tumor survival mechanisms and result in tumor cell death. Tumors can evade the therapeutic effects of DNA alkylation by inducing the production of MGMT proteins, which repair the DNA by removing alkyl groups deposited by temozolomide and other alkylating agents.

When the MGMT promoter gene is methylated, the gene is referred to as "silenced" and cannot induce the expression of MGMT proteins. On the contrary, when the promoter gene is not methylated, the gene can induce the expression of MGMT proteins. Consequently patients with unmethylated MGMT promoters are

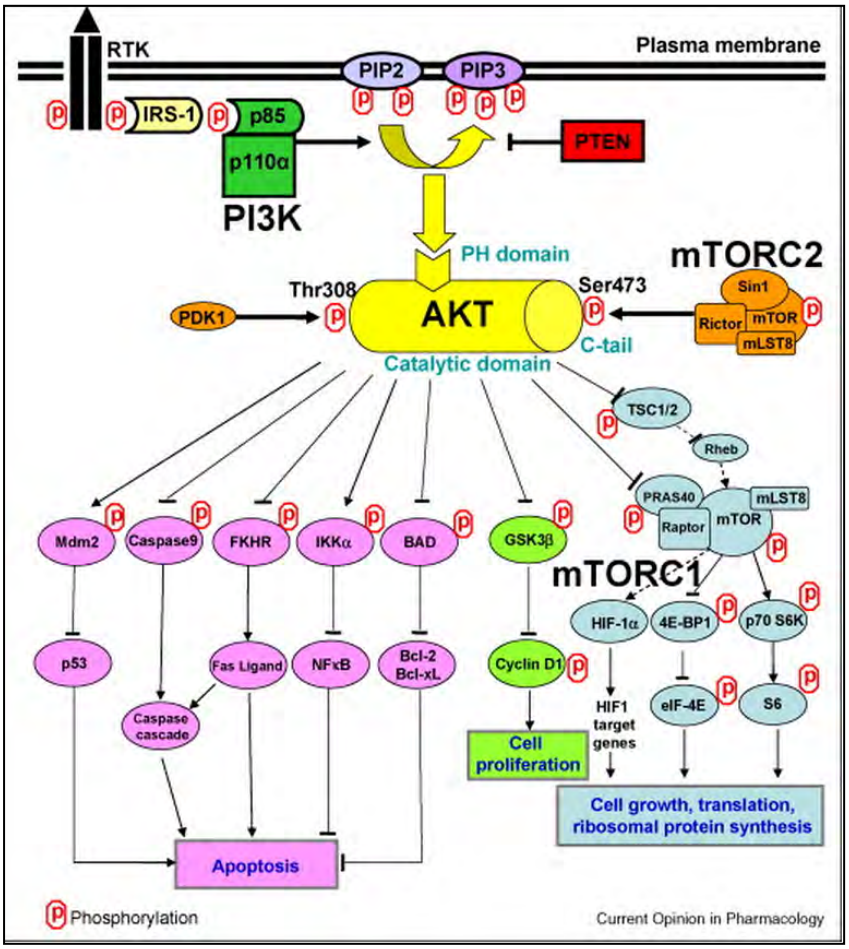

Figure 1: PI3K/Akt/mTOR pathway is an intracellular molecular signaling pathway that is a key regulator of cell growth and death. Aberrations in this pathway can lead to tumor development and or survival. ***Adapted from Curr Opin Pharmacol. 2008 Aug; 8(4):393-412***

more resistant to treatment with temozolomide and other alkylating agents, whereas patients with methylated MGMT promoters are more responsive to these types of treatments.

GBM TUMOR SUBTYPES

There are four subtypes of GBM tumors: classical, proneural, mesenchymal, and neural (Verhaak et al. 2010). These subtypes are generally defined by specific genetic abnormalities that are linked to a patient's clinical profile. This profile includes patient age, treatment response, and survival length. These subtypes also correlate to patient outcomes and are sometimes used as prognostic indicators, which help predict tumor aggressiveness and can help physicians determine how aggressive the treatment plan should be. Genetic features of each tumor type are listed below:

Classical

- Carries extra copies of epidermal growth factor receptor (EGFR) gene (DNA) and consequently expresses abnormally high levels of EGFR protein
- Lacks mutation in *TP53* gene, which is the most frequently mutated gene in GBM
- Research shows that patients with classical tumors survived the longest of the subgroups in response to aggressive treatment

Proneural

- Highly mutated TP53, platelet-derived growth factor receptor-type A (PDGFRA), and isocitrate dehydrogenase 1 (IDH1) genes
- Most frequent mutations in IDH1 gene compared to other tumor subtypes
- PDGFRA protein expressed at abnormally high amounts in proneural tumors, but not other subtypes
- Research shows that patients with proneural tumors tend to survive longer; however, unlike other subgroups, this survival rate is not dependent on the degree of treatment aggressiveness

Mesenchymal

- Most frequent number of mutations in the Neurofibromatosis type 1 (NF1) tumor suppressor gene
- Fewer mutations in EGFR gene and less expression of EGFR protein compared to other tumor subtypes
- Clinical research shows that patients with mesenchymal tumors had significant increases in survival after aggressive treatment

Neural

- This tumor subgroup has many of the same gene mutations as the other tumor subtypes. The neural subgroup is primarily categorized by the expression of several genes that are typical of normal cells in the brain
- Data from patients with neural tumors demonstrated some improvement in survival after aggressive treatment, but not as much as the classical and mesenchymal groups

INTERVENTIONS

DIAGNOSIS

Diagnostic tests are important not only for accurately identifying disease but also for helping to understand disease progression and the impact of treatment. To obtain an accurate diagnosis of GBM, physicians execute the following:

- Neurological exam – During this exam, neurologists look for signs of unsteadiness or imbalance, changes in vision, hearing loss, and speech difficulty. In many cases, these symptoms are in conjunction with headaches, confusion, disorientation, and memory loss.
- Imaging scans of the brain – GBM and other brain tumors are detected by computed tomography (CT) scans or magnetic resonance imaging (MRI). These scans enable determination of the size and location of the tumor and allow the physician to predict the type of tumor (e.g., malignancy, grade, etc.) prior to pathological confirmation. They may also be helpful to define the margins of the tumor for surgical resection.
- Brain tissue analysis – Accurate diagnosis of brain tumors requires maximal surgical resection of the tumor, which is then analyzed to confirm the pathogen (tumor cell type and grade). Often, more than one tumor cell type exists within the same tumor, thus it is important to remove and analyze as much brain tissue as possible in order to correctly diagnose the tumor. The tumor cell type that dominates the majority of the resected tumor determines final diagnosis.

TREATMENTS

There are currently five FDA-approved treatment methods for GBM: surgery, radiation therapy, chemotherapy, targeted therapy, and tumor treatment fields. Each method is described below, and FDA-approved drugs and devices are listed in Table 1.

- Surgery – In addition to enabling definitive pathological diagnosis, surgery is also the first stage of GBM treatment. Surgery usually alleviates symptoms and can prolong patient survival.
- Radiation – In this form of treatment, the area around the original tumor is subjected to an external beam of photons, which in turn kill remaining tumor cells. Following tumor resection, most patients undergo six weeks of external beam radiation five times per week.
- Chemotherapy – Chemotherapy agents are generally agents that deter cell division, thereby limiting the propensity of cancer cells to multiply and spread. The disadvantage of these drugs is that they also interfere with cell division of normal cells, which leads to unwanted toxicities. Chemotherapy drugs can be used differently throughout the course of treatment. For instance, it may be used before surgery to shrink the tumor (referred to as neoadjuvant therapy) or after surgery to kill additional cancer cells (referred to as adjuvant therapy).

- Targeted therapy – Targeted therapies are agents that inhibit specific molecular targets involved in signaling pathways (cascades of biochemical events that regulate cellular development and behavior) that have been identified as abnormal and shown to play a key role in the development and/or survival of tumor cells. Some of the most common targets include EGFR (epidermal growth factor receptor), mTOR (mammalian target of rapamycin), PI3K (phosphatidylinositol 3-kinase), and VEGF (vascular endothelial growth factor).

- Tumor treatment fields (TTF) – TTF is an electric field applied to the head of the patient by insulated surface electrodes attached to a medical device. These fields stop the growth of tumor cells by interfering with the cell division process. The geometrical shape and scattering of the electrical charges within the dividing tumor cells allows TTF electrical fields to physically break up the tumor cell membrane.

Table 1: FDA-approved treatments for GBM

Name (Brand Name, Manuf.)	Treatment Type	Method of Action	Delivery
Carmustine (Gliadel, Eisai)	Chemotherapy	Cross-links DNA and RNA, leading to the inhibition of DNA synthesis, RNA production, and RNA translation (protein synthesis). Also binds to and modifies glutathione reductase to cause cell death	Surgical Implant
Temozolomide (Temodar, Merck)	Chemotherapy	Alkylates DNA to cause double-strand breakage and cell death	Intravenous or Oral
Bevacizumab (Avastin, Genentech/Roche)	Targeted Therapy	Monoclonal antibody that targets VEGF and prevents angiogenesis	Intravenous
NovoTTF	Tumor Treating Field	Head gear device applies an electric field that hinders tumor growth by interfering with the cell division process	N/A

Cancer immunotherapy is an additional treatment option; however, this method is not currently FDA-approved. In this treatment method, the immune system is stimulated using a vaccine or some other immune-modulation agent such that the immune system is able to recognize, attack, and destroy tumor cells. Tumors can evade treatments and become resistant by changing its genetics and/or morphology. A key advantage of immunotherapy is that these treatments train the immune system so that it is able to recognize tumors even as they attempt to change their "appearance."

It is important to note that a treatment plan for GBM may include one or more of these methods and is highly dependent on the stage of disease progression, previous treatments, health, and treatment tolerance.

INVESTIGATIONAL THERAPIES AND CLINICAL TRIALS

CLINICAL TRIALS - OVERVIEW

Clinical research is research in human subjects aiming toward approved products for use in patients. Clinical trials determine whether a particular product is as effective in people as it is in the laboratory or in animal models, which often fail to adequately mimic human responses. Further, clinical trials provide information on potential adverse reactions or side effects that need to be weighed against the potential benefits.

Pre-registration clinical research for drugs and vaccines is broken into four key phases. Each phase is described in the table below.

Table 2: Phases of clinical development

Clinical Phase	Description	Number of Patients
Phase I	Examines the safety of the product in a very small group of healthy volunteers or patients afflicted with a specific disease. Also used to determine appropriate dose ranges.	20-80
Phase II	Evaluates the safety and efficacy of the product at a pre-determined dose in comparison to the standard of care treatment (commercially available therapies commonly used to treat the same disorder or disease).	100-300
Phase III	Evaluates the product compared to the standard of care in a large diverse population to determine broader efficacy and develop usage guidelines.	1000-3000
Phase IV	Evaluates the long term effects of a drug post-FDA approval for public use.	All patients prescribed the drug by a treating physician

KEY EMERGING THERAPIES

As of July 2014, there were 77 products in clinical development for GBM. Figure 2 illustrates the distribution of these trials by phase of clinical development.

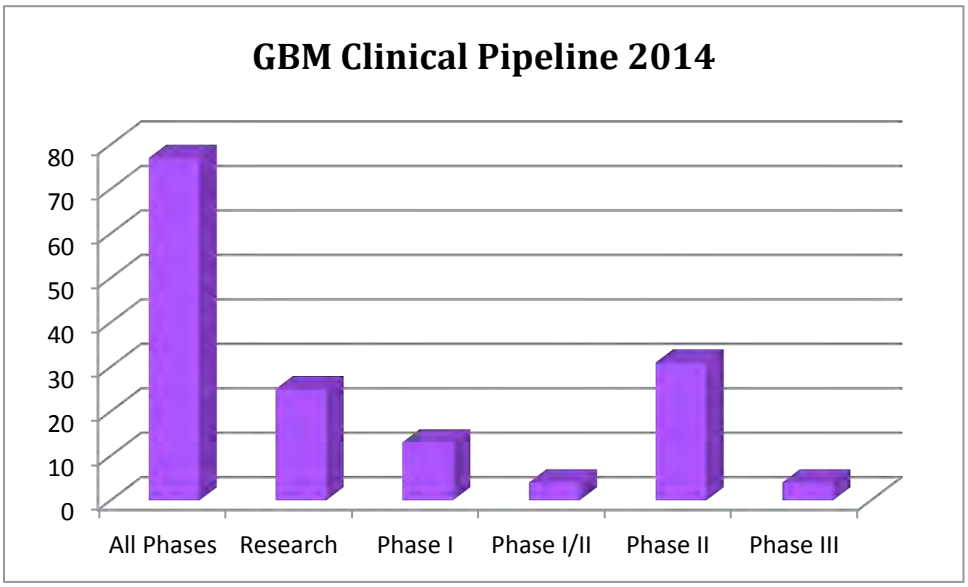

Figure 2: Agents in clinical development for newly diagnosed and/or recurrent GBM

In the sections below we discuss key therapeutics that are currently in clinical development for GBM; meaning that they are in active and ongoing clinical trials exploring the use of these agents in GBM patients and a few that are not officially in clinical development for GBM but will likely be considered in the near future.

CHEMOTHERAPY

Chemotherapy drugs are drugs that interfere with the process of cell division. Chemotherapeutic agents can somewhat target cancer cells because these cells divide more frequently than normal cells; however, these effects are not exclusive to cancer cells. The off-target effects on normal cells can cause a number of unwanted side effects that can diminish quality of life.

Chemotherapy drugs used in the GBM setting are often used differently throughout the course of treatment. For instance, these drugs can be used before surgery to shrink the tumor. This is referred to as adjuvant therapy. Conversely, chemotherapy drugs can be used as neoadjuvant therapy, which means that the agents are administered after surgery to kill additional cancer cells.

VAL-083

Treatment Type: Chemotherapy

Mechanism of Action: DNA alkylating agent

Sponsor/Developer: DelMar Pharmaceuticals – Canada; USA

Clinical Development Stage: Phase I/II

Clinical Development Indications: GBM; chronic myelogenous leukemia; acute myelogenous leukemia; lung cancer

Key Clinical Data: VAL-083 is currently in Phase I/II development for GBM. Interim data from a Phase I/II open-label, dose-escalation trial in four cohorts of patients with recurrent GBM or progressive secondary brain tumors was presented at the 2013 Society for Neuro-oncology meeting.

GBM patients enrolled in this study were previously treated with surgery and/or radiation if appropriate, and failed both bevacizumab and temozolomide (unless contraindicated). According to DelMar, enrollment in all four cohorts of the trial has been completed. In addition, in Cohorts 1-3 twenty five percent of evaluated patients exhibited stable disease or tumor-regression and improved disease symptoms. Also there were no significant adverse events or dose limiting toxicity was observed in these cohorts. Evaluation and clinical observations of Cohort 4 is ongoing.

TARGETED THERAPY

Targeted therapies are agents that inhibit specific molecular targets involved in abnormal signaling pathways (cascades of biochemical events that regulate cellular development and behavior). Examples of molecular targets include EGFR (epidermal growth factor receptor), mTOR (mammalian target of rapamycin), PI3K (phosphatidylinositol 3-kinase), VEGF (vascular endothelial growth factor), etc. Targeted therapies are often used in combination with chemotherapy drugs. Table 1 describes the only targeted therapy currently approved for GBM, bevacizumab (Genentech's Avastin), which targets VEGF.

TRC-105

Treatment Type: Targeted Therapy

Mechanism of Action: Endoglin (CD105)

Sponsor/Developer: Tracon Pharmaceuticals – USA

Clinical Development Stage: Phase II

Clinical Development Indications: Recurrent GBM; Metastatic Kidney Cancer; Solid tumors

Key Clinical Data: TRC-105 is currently in Phase II development for GBM patients with recurrent disease. The agent will be evaluated in the following patient populations and combinations with Avastin:

- Avastin-naïve patients – TRC-105 only
- Avastin-naïve patients – TRC-105 plus Avastin
- Patients previously treated with Avastin with progressive disease – TRC-105 plus Avastin

Trial designs for the evaluation of TRC-105 in GBM are based on Phase Ib data of TRC-105 in combination with Avastin for the treatment of advanced solid tumors. This data showed that TRC-105 at a dose of 10mg/kg administered in combination Avastin is well tolerated when TRC-105 is staggered by one week following the initial 10mg/kg dose of Avastin, which was split into 2 doses of 5mg/kg over two days. Evaluation of anti-tumor activity by radiography showed that treatment with TRC-105 and Avastin led to longer periods of progression free survival (PFS) compared to the patients' previous treatment regimens that only included Avastin.

GBM trials will be conducted in collaboration with the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) and data is expected from these studies in the second half of 2014.

GENE THERAPY

The term oncolytic virus applies to viruses that are able to replicate in tumors and destroy their cells. As the infected cancer cells are destroyed, new infectious virus particles are released to destroy additional tumor cells. Efforts to harness viruses for cancer therapy are based on viruses with inherently low human pathogenic potential or pathogens that are genetically engineered to selectively kill cancerous cells without concomitant toxicity in normal cells.

There are two primary approaches for generating tumor selectivity in genetically modified viruses, which are transductional and non-transductional targeting. The transductional targeting approach requires the modification of proteins that coat the surface of the virus to such that the virus primarily targets the tumor and has a low rate of entry into non-tumor cells. The non-transductional approach involves altering the genes of the virus so that it can only replicate (make copies of itself) in cancer cells. Most oncolytic viruses are genetically engineered for tumor selectivity; however, there are some examples of viruses that are inherently tumor-selective, such as Poliovirus, Reovirus, and Senecavirus.

In addition, some viruses can be used as delivery vehicles for genes that can metabolize (change the chemical structure) of a separately administered non-toxic drug that converts to a chemotherapy agent that is sequestered to the tumor cells, thereby minimizing toxicity to normal cells (Freeman 1996; Duarte 2012).

Profiles for oncolytic viruses that are currently in clinical development for GBM are provided below.

VB-111

Treatment Type: Gene Therapy

Mechanism of Action: Dual anti-angiogenic and vascular disruptive agent; molecular target unknown

Sponsor/Developer: VBL Therapeutics Ltd – Israel

Clinical Development Stage: Phase I/II

Clinical Development Indications: GBM

Key Clinical Data: VB-111 is currently in Phase I/II trials for GBM. VB-111 is an anti-angiogenic gene-therapy tool that targets endothelial cells in the tumor vasculature. This technology uses a non-replicating adenoviral vector that harbors a uniquely modified transcriptional promoter which regulates transcription of a Fas-Chimera transgene. The proprietary promoter specifically targets expression of the Fas-Chimera transgene to angiogenic tumor blood vessels, which leads to exclusive killing of tumor cells, with no harm to normal vasculature and non-cancerous tissues in the body. VB-111 is the first agent based on transcriptional targeting of tumor endothelium to be assessed in a clinical trial.

At the 2013 American Society of Clinical Oncology (ASCO) annual meeting, data from a dose-escalation, open-label, U.S. Phase I/II trial in 28 recurrent GBM patients were presented. This data showed that VB-111 was safe and well

tolerated with repeat doses of up to $1x10^{13}$ viral particles. This study also showed that VB-111 produced responses that were dose dependent. The median overall survival (OS) for patients that received at least one high-dose ($1x10^{13}$ viral particles) of VB-111 was 360 days. Progression free survival was 87 vs 55 days for patients who received high dose vs. lower dose ($3x10^{12}$), respectively. Twenty-one out of twenty-eight patients eventually progressed after VB-111 treatment. These patients received Avastin off study; however 15 of these patients remained eligible for evaluation. Nearly 47% of these patients achieved a partial response (PR) compared to a 30% expected PR rate according to studies documented in research literature.

TOCA 511

Treatment Type: Gene Therapy

Mechanism of Action: Replicating oncolytic virus

Sponsor/Developer: Tocagen – USA

Clinical Development Stage: Phase I

Clinical Development Indications: GBM

Key Clinical Data: Toca 511 is a special virus that can deliver genes to cells. More specifically, Toca 511 is a retroviral replicating vector (RRV) that is designed to deliver a gene called cytosine deaminase (CD) selectively to cancer cells. The virus is injected into the brain and deposits genetic material for the cytosine deaminase gene into cancer cells. After the virus is administered into the tumor or the resected tumor cavity within the brain, the virus is then given time to spread throughout the tumor or any residual tumor cells within the resected cavity. The treatment then continues with the oral administration of the FDA approved antifungal, flucytosine (5-FC also referred to as Toca FC). This agent is converted by the cytosine deaminase gene at the site of the tumor to the anti-cancer drug, 5-fluorouracil (5-FU). This local production of 5-FU using cytosine deaminase gene therapy has the potential to produce much higher intratumoral concentrations of 5-FU than can be currently attained with systemic administration; however, intravenous administration of Toca 511 followed by oral Toca FC is also currently under clinical investigation.

Toca 511 is currently in Phase I clinical trials and has been tested in approximately 60 recurrent high grade glioma patients (including GBM patients) as of November 2013. Preliminary studies show that the agent is well-tolerated as no dose-limiting toxicities or drug-related serious adverse events have been observed. In addition, evidence of antitumor activity and symptomatic improvement in some patients was reported at the 2013 Society for Neuor-oncology meeting.

IMMUNOTHERAPY

Immunotherapy refers to therapeutic strategies that stimulate a patient's immune response to attack and destroy tumor cells. The immune system works by actively surveilling cells in the body to detect and destroy cells that are foreign. Cells are identified as foreign or non-foreign based on molecules expressed on the surface of the cells called antigens. In the context of tumor cells, the immune system can naturally identify and eliminate some of these cells based on antigen expression; however, tumors are sophisticated such that they can change the

expression of some of their surface antigens to resemble non-foreign cells. This process is often referred to as immune editing.

T-cells are the primary arsenal of the immune system. These cells contribute to immune defense by either directing the immune response by sending signals to other molecules (helper T-cells), or by directly attacking infected or cancerous cells (killer T-cells).

Cancer immunotherapy treatment strategies address this issue by boosting the immune system in a general way or by training the immune system to attack specific tumor cell antigens. These approaches include the use of vaccines, immune checkpoint inhibitors, and adoptive cell transfer.

Many of the current approaches to cancer immunotherapy focus on enhancing T-cell function by stimulating their activation against tumors. This approach is most commonly employed in the use of cancer vaccines and adoptive cell transfer. Inhibiting the mechanisms that tumors use to suppress the immune response (i.e., displaying key non-foreign antigens) is also a key treatment strategy that is quickly gaining traction in the oncology setting. In this approach, monoclonal antibodies are used to block specific cellular antigens identified as "immune checkpoints" normally used by the body to attenuate immune response in order to prevent autoimmunity. Agents commonly referred to as immune checkpoint inhibitors are generally used in this approach.

The following sections will discuss each of these immunotherapy strategies in more detail as well as provide information on specific immunotherapy agents in clinical development.

VACCINES

Cancer vaccines are active immunotherapeutic approaches that are intended to activate and expand tumor specific T cells to induce an anti-tumor response. Many cancer vaccines are made by expanding and stimulating a type of immune cell called dendritic cells (DCs).

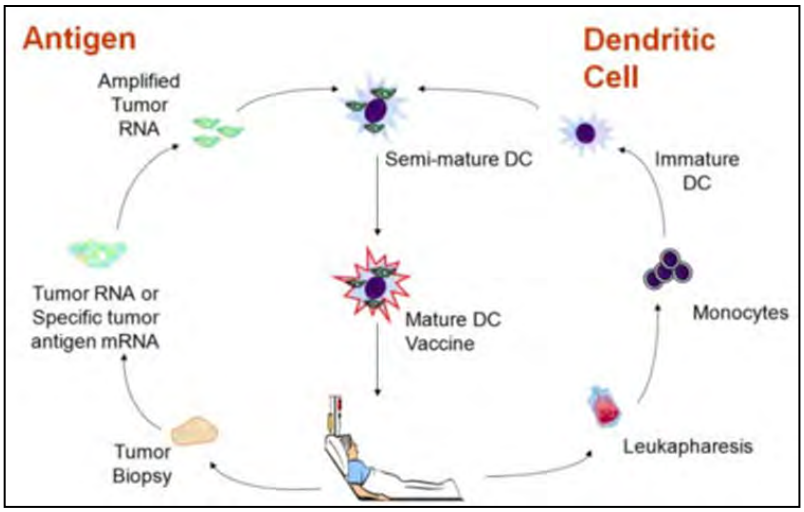

Figure 3: Dendritic vaccine preparation. ***Adapted from www.sciences.surgery.duke.edu***

DCs are key components of the immune system in that they direct all ensuing activities of the immune response. When DCs encounter a foreign cell, they consume the cell and process it into smaller pieces. The DC then travels to the lymph nodes to present the antigens that were displayed on the consumed foreign cell to T-cells and other types of immune cells. Once the antigens are presented to the immune army of cells, this elicits a cascade of events that leads to a full immune response.

As mentioned, many cancer vaccines in development are based on the use of dendritic cells. These DC vaccines are autologous, meaning that they are derived from the same individual's body. While dendritic cells exist naturally in

the body, there are usually not enough of them to complete the immune system's destruction of cancer cells. In addition, they may not be able to recognize the specific antigens necessary to identify the tumor. As a result, researchers have discovered a way to not only expand the population of DCs, but also to train them to efficiently identify tumor cells.

Therapeutic dendritic cell vaccines are prepared by harvesting blood cells from patients and stimulating these cells ex vivo (outside of the body) with molecules that will promote the development of DCs. The DCs are then treated with tumor specific antigens, which are obtained from a liquid preparation of the patient's dissolved tumor or small proteins called peptides that resemble the antigens displayed on the tumor cell. Treating the DCs with tumor specific antigens trains them to recognize and send signals to other immune cells to attack the tumor. Once the DCs are expanded and trained, they are then added back into the patient's body as a vaccine, where they can instigate an immune response to the tumor.

Profiles for cancer vaccines that are currently in clinical development for GBM are provided below.

DCVAX-BRAIN

Treatment Type: Immunotherapy - Vaccine

Mechanism of Action: Dendritic cell vaccine

Sponsor/Developer: Northwest Biotherapeutics - USA

Clinical Development Stage: Phase III

Clinical Development Indications: GBM; melanoma; non-small cell lung cancer; renal cell cancer; colorectal cancer; prostate cancer

Key Clinical Data: DCVax-Brain is currently in Phase III clinical development for GBM. In 2010, Northwest Biotherapeutics announced positive long-term data from Phase I and Phase I/II trials of DCVax-Brain in patients newly diagnosed with GBM. The data showed that 33 percent of patients reached 4-year survival and 27 percent reached or exceeded 6-year survival (PRNews Wire, August 3, 2010). The longest surviving patient to date has exceeded 10 years.

DCVax-Brain is approved in Switzerland for use at selected centers to treat malignant brain cancers, including GBM. The vaccine has Orphan Drug designation in the United States and European Union. The ongoing Phase III trial was adopted as a high priority clinical trial by the United Kingdom's National Institute for Health Research (NIHR) in April 2013 (NWBio, April 16, 2013).

RINDOPEPIMUT (CDX-110)

Treatment Type: Immunotherapy - Vaccine

Mechanism of Action: EGFRvIII Vaccine

Sponsor/Developer: Celldex Therapeutics

Clinical Development Stage: Phase III for newly diagnosed GBM, Phase II for recurrent GBM

Clinical Development Indications: GBM

Key Clinical Data: Rindopepimut targets the tumor specific gene EGFRvIII, which is a mutated form of the EGFR gene. Expression of EGFRvIII has been associated with tumor aggressiveness and poor long term survival in GBM patients. This agent is currently in Phase III clinical development for GBM patients with tumors that express EGFRvIII.

Three Phase II trials of rindopepimut have been completed in newly diagnosed GBM patients with EGFRvIII tumors, ACTIVATE, ACTII, and ACTIII. All three studies generated consistent results which demonstrated that rindopepimut is generally well tolerated and can generate a specific and durable immune response against EGFRvIII. The median overall survival (OS) ranged from 24.4 – 24.6 months compared to historical controls (historical patient data that was matched to the study cohort with respect to eligibility criteria) where the median survival was only 15.2 months. The median progression free survival (PFS) of the study cohort was 12.3 – 15.3 months compared to only 6.4 months as documented for historical controls (Reardon 2012).

Data for an additional Phase II study was presented recently at the 2013 Society for Neuro-Oncology meeting. ReACT is a Phase 2 exploratory study designed to determine if adding rindopepimut to standard of care bevacizumab improves the outcomes for patients with EGFRvIII-positive recurrent glioblastoma across multiple measures. There are two cohorts in this study:

- Cohort 1 – Patients that have never been treated with Avastin that are randomized to receive either rindopepimut or placebo, in addition to Avastin; target number of patients = 70
- Cohort 2 – Patients that have progressed on Avastin tha are randomized to receive rindopepimut plus bevacizumab in a single treatment arm; target number of patients = 25

Interim data for Cohort 1 showed an OS of 12 months in the study arm (Rindopepimut + Avastin) compared to 7.9 months in the control arm (placebo + Avastin). In addition PFS was 3.7 months in the study arm compared to only 2 months in the control arm. Also, 78 percent of patients with measurable disease on the rindopepimut arm experienced tumor shrinkage versus 56 percent of patients on the control arm of the study, and 70 percent of these patients had stable disease or better for greater than 2 months versus 55 percent in the control arm. Further emphasizing the benefit in disease control, only 5 percent of patients treated with rindopepimut required an increase in steroids versus 35 percent of patients on the control arm.

Interim data for Cohort 2 showed a median OS of 5.6 months and median PFS of 1.9 months. The primary endpoint for this arm is f progression-free survival of twenty percent at 6 months. Only eight percent of patients are progression free at six months; however it is important to note that there was no comparative data available to define expected outcome for EGFRvIII-positive patients who have failed on Avastin. Only six out of 24 patients with

measurable disease experienced any tumor shrinkage; however 32 percent of patients had stable disease or better for greater than 2 months.

The currently ongoing Phase III study of rindopepimut, referred to as ACT IV, is a randomized, double-blind, controlled study of rindopepimut plus granulocyte macrophage colony-stimulating factor (GM-CSF) administered in addition to temozolomide in patients with newly diagnosed, surgically resected, EGFRvIII-positive GBM. The primary objective of the study is to determine whether rindopepimut plus GM-CSF improves the overall survival of patients with newly diagnosed EGFRvIII-positive glioblastoma after gross total resection (GTR) when compared to treatment with the current standard of care, temozolomide. Secondary endpoints include: progression free survival; safety and tolerability of rindopepimut and GM-CSF in combination with temozolomide; neurologic status and quality of life.

ICT-107

Treatment Type: Immunotherapy - Vaccine

Mechanism of Action: Dendritic cell vaccine

Sponsor/Developer: Immunocellular Therapeutics

Clinical Development Stage: Phase II

Clinical Development Indications: GBM

Key Clinical Data: ICT-107 is a six-antigen dendritic cell vaccine targeting cancer stem cell antigens found in a high proportion of GBM tumor cells. Phase I data evaluating the safety and immune response of ICT-107 in both newly diagnosed and recurrent GBM patients showed that at 40.1 months, there were no signs of tumor recurrence in 37% of the newly diagnosed patients. The median progression free survival and overall survival was 16.9 months and 38.4 months respectively, in newly diagnosed patients. The data also showed that the expression of four ICT-107 targeted antigens in the pre-vaccine tumors correlated with longer overall survival and progression free survival in newly diagnosed GBM patients. All patients evaluated had at least three of the targeted antigens and 75% had all six of the antigens targeted by ICT-107 (ImmunoCellular Therapeutics, 2012).

In December 2013, results of the phase II data showed that ICT-107 demonstrated a statistically significant increase in progression free survival, but did not reach the primary endpoint of a nine month improvement in median overall survival in the study group compared to the control. The median survival advantage reached only 2 months – based on the intent to treat analysis of all 124 patients enrolled or 3 months – based on the per protocol analysis of 117 patients. Despite the disappointing results, the data is not yet mature and ImmunoCellular suspects that the median survival estimates may improve as the study continues. Based on this expectation the company is in talks with the FDA and the European Medicines Agency (EMA) to stay the course and initiate a Phase III study (ImmunoCellular Therapeutics, 2013).

TRIVAX (FORMERLY AV00113)

Treatment Type: Immunotherapy - Vaccine

Mechanism of Action: Dendritic cell vaccine

Sponsor/Developer: Activartis Biotech

Clinical Development Stage: Phase II

Clinical Development Indications: GBM

Key Clinical Data: Trivax is currently in Phase II clinical development. Preliminary results from the current randomized Phase II study were presented at the 2013 AACR Annual Meeting. This data showed that 64 percent of patients treated with Trivax were alive at 12 months, compared to only 48% of patients in the non-treated control group. At 18 months, 50% of patients in the treatment group were still alive, compared to 33% of patients in the control group. Curiously, patients treated with Trivax experienced signs of relapse earlier compared to patients in the control group; however, this observation can be potentially explained by inflammation in the tumor tissue triggered by Trivax treatment. This phenomenon is commonly observed in other cancer immunotherapy clinical trials (B3C Newswire, 2013).

ADOPTIVE CELL TRANSFER

Adoptive cell transfer involves the transfer of immune cells with antitumor activity into cancer patients. There are two primary methods used to execute this type of treatment; one requires the surgical removal of the patient's tumor (autologous) and the other only requires the patient's blood (genetically engineered) (Figure 4). Both processes are dependent upon lymphocytes (also known as white blood cells) (Rosenberg 2011).

In the autologous process, white blood cells that have migrated into the tumor (also known as tumor infiltrating lymphocytes or TILs) are isolated from the resected tumor. The cells are then expanded ex vivo and treated with IL-2, a natural chemical that stimulates the growth, proliferation, differentiation, and survival of tumor antigen specific T-cells. After the cells are expanded and treated with IL-2 to promote immunologic memory against tumors, they are then re-infused into the patient to facilitate an immune response against tumor cells.

In the genetically engineered process, adoptive cell transfer is achieved by isolating lymphocytes from the blood and then

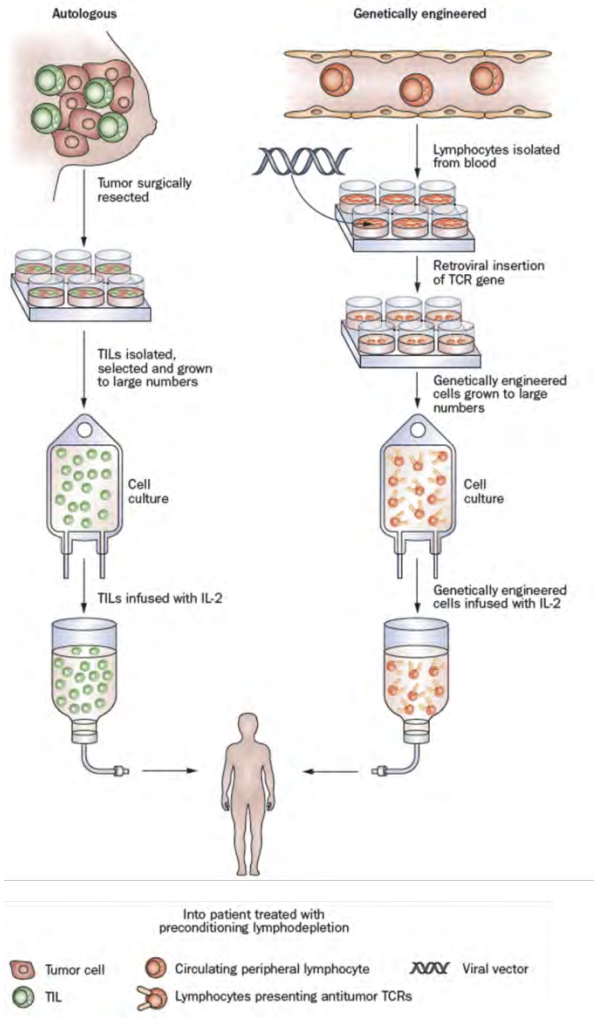

Figure 4: Autologous and Genetically Engineered Adoptive Cell Transfer are the primary methods used to execute this type of treatment.

transferring artificial T-cell receptors (molecules that recognize tumor antigens) onto lymphocytes, giving them a new and enhanced function. This method is sometimes referred to as the CAR method, where CAR stands for Chimeric Antigen Receptors.

The key challenge with adoptive cell transfer is that a new drug is created for each patient, therefore creating a huge manufacturing and logistical challenge for pharmaceutical companies. As a result, this treatment method is offered in only a few academic centers throughout the country. According to Steven Rosenberg, a leading cancer researcher and a pioneer of the use of adoptive cell transfer, recent simplifications of the methods for cell growth could enable the production of pharmaceutical-grade cells by academic blood banks or individual academic laboratories in the near future, thereby opening up this investigational treatment option to more patients.

IMMUNE CHECKPOINT INHIBITORS

As mentioned previously, tumor cells can change the expression of some of molecules on their cell surface antigens to resemble the surfaces of non-foreign cells. More specifically, tumor cells will often express molecules that serve as "immune checkpoints," meaning that when expressed these molecules send the message to the immune system that an immune response is *not* necessary. Researchers have discovered that developing drugs that can block these immune checkpoint molecules from binding to their molecular partners can effectively "release the breaks" on the immune system to allow the body to mount an immune response against the tumor. These types of drugs are called immune checkpoint inhibitors.

The two immune checkpoint molecules that have been most actively studied in the context of cancer immunotherapy are cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed cell death ligand 1 (PD1).

While there are a number of immune checkpoint inhibitors in clinical development to treat various cancers, none of these agents are in clinical development for GBM. The following table lists the leading checkpoint inhibitors currently in clinical development.

Table 3: Immune checkpoint inhibitors in clinical development for various cancers

Agent	Manufacturer	Molecular Target	Clinical Development Therapeutic Areas	Latest stage of clinical development
Ipilimumab	Bristol-Myers Squibb	CTLA-4	Melanoma	Marketed
Nivolumab	Bristol-Myers Squibb	PD-1	Melanoma; NSCLC[1]; renal cell cancer; CRC[2]; prostate cancer	III
Lambrolizumab	Merck	PD-1	Kidney cancer; NSCLC; breast cancer; melanoma; non-Hodgkin's lymphoma; and Hodgkin's lymphoma; prostate cancer CML[3]; hepatocellular carcinoma	III
Amp-224	Amplimmune/GlaxoSmithKline	PD-1	Melanoma; lymphoma; VAST[4]	I
BMS-936559	Bristol-Myers Squibb	PD-L1	Melanoma; NSCLC; renal-cell cancer; ovarian cancer; colorectal cancer; pancreatic cancer; gastric cancer; breast cancer	I
MEDI-4736	Medimmune	PD-L1	Melanoma; renal cell carcinoma; NSCLC; colorectal cancer	I
MPDL3280A	Genentech/Roche	PD-L1	Melanoma; NSCLC; VAST	III
CT-011	CureTech	PD-L1	AML; GBM	2

[1] NSCLC – Non Small Cell Lung Cancer

[2] CRC – Colorectal Cancer

[3] CML – Chronic Myelogenous Leukemia

[4] VAST – Various Advanced Solid Tumors

UNMET NEEDS

TUMOR RECURRENCE

While many patients respond to initial treatment (surgical resection, radiation, TMZ) in most patients, the tumor eventually returns within two years of their original diagnosis. This process, commonly referred to as recurrence, is believed to be a result of residual tumor cells (cancer stem cells) being left behind during resections. Unfortunately, the infiltrative nature of GBM cells, along with the restraints associated with cutting into the brain, make it very difficult to eliminate all tumor cells.

Many believe that GBM tumor recurrence is significantly driven by cancer stem-like cells (CSCs) that express the antigen, CD133 (Li 2012). Various studies have shown that these cells have the ability to initiate tumors in vivo (Galli 2004; Zeppernick 2008). Studies have also shown that patients whose tumors express CD133 antigen have worse outcomes than patients with tumors that do not express this antigen (Beier 2008; Rebetz 2008; Zhang 2008). In addition, CD133 expressing GBM cells contribute to resistance to radiation and chemotherapy as well as overall tumor aggressiveness (Liu 2006; Eramo 2006; Kang 2007).

GBM Tumor Associated Antigens

Tumor antigens are protein molecules expressed on the surfaces of tumor cells. There are two types of tumor antigens

Tumor specific antigens – expressed only on tumor cells

Tumor associated antigens – expressed on some tumor cells as well as normal cells.

The following list includes some key antigens that researchers are exploring as immunotherapy targets

CD133	*Her2/neu*
TRP-2	*AIM-2*
MAGE1	*IL13RA2*
gp100	

Various research groups are exploring immunotherapy strategies that target CD133 and other antigens that are overexpressed on CSCs (Cho 2011; Zhang 2007; Saikali 2007; Liu 2004). These immunotherapy strategies generally consist of an autologous vaccine containing dendritic cells treated with synthetic forms of the target antigens so that the dendritic cells can recognize these antigens when re-introduced into the patient.

As mentioned previously, immunotherapy strategies present a promising approach to deterring and possibly preventing tumor recurrence. While great strides have been made in other areas of oncology, significant progress in GBM is currently lacking. This is in part due to a lack of financial resources that could accelerate translational GBM immunotherapy research, which would in turn provide proof-of-concept data that would encourage investment by pharmaceutical manufacturers of immunotherapy agents.

AVASTIN CONTROVERSY / AVASTIN REFRACTORY GBM

In 2009, bevacizumab (Genentech's Avastin) was approved for the treatment of recurrent glioblastoma. This agent was approved through the FDA accelerated approval process, which allows for marketing approval based on a

surrogate or intermediate endpoint that is representative or predictive of clinical benefit. Examples of surrogate endpoints include laboratory measurements or radiographic imaging. Similarly, any measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug (i.e., effect on morbidity or mortality) can be considered an intermediate endpoint.

Accelerated approval requires the sponsor to continue clinical trials post marketing, completing at least one clinical trial that will validate that the drug provides meaningful benefit on tangible measures of clinical benefit. Post approval, there were two ongoing trials for bevacizumab, one conducted by Genentech to satisfy the criteria for accelerated approval, AVAglio, and the other conducted by the Radiation Therapy Oncology Group (RTOG). The primary endpoints for both studies were progression-free survival and overall survival.

Recent data from both studies presented at the 2013 American Society for Clinical Oncology annual meeting showed that bevacizumab does not increase overall survival in GBM patients. In addition, the RTOG study showed that patients treated with bevacizumab have a significant deterioration in neurocognitive function (NCF) and quality of life. The AVAglio study did not evaluate NCF or quality of life. Data from both studies indicate that the drug can improve progression-free survival; however, the controversy is whether or not this modest clinical benefit is enough to convince the FDA not to recall the drug's approval in GBM patients. The brain cancer advocacy group, Accelerate Brain Cancer Cure (ABC2) responded to this controversy by immediately writing a letter to the FDA requesting that the agency independently evaluate the AVAglio and RTOG data sets in order to reconcile differences between the two studies.

In addition to this controversy, bevacizumab is sometimes associated with increased tumor cell invasion in GBM patients. Bevacizumab works by restricting the blood supply to tumors; however, tumors are highly adaptive and can send migratory signals that will enable cells to travel away from the tumor origin to search for new blood supplies. As a result in some cases, when the tumor returns it does so in a more diffuse and invasive pattern than the original tumor (de Groot 2010).

Overall, experts agree that Avastin has a role in the treatment of GBM; however, additional research is necessary to better define the characteristics of bevacizumab and to define the patient population that will benefit the most from this drug.

ALTERNATIVE CLINICAL TRIAL ENDPOINTS

One of the major impediments on the development of new therapies for GBM and other types of brain tumors is the narrow focus on overall survival (also referred to as survival rate) as the primary metric (endpoint) used to evaluate efficacy of these drugs in clinical trials. Overall survival is defined as the percentage of subjects in a study who have survived for a defined period of time (usually starting from the date of diagnosis). The use of this metric as a primary endpoint is mandated through guidance by the FDA.

The advantage of using overall survival as a primary endpoint for neuro-oncology trials is that it is an objective and straightforward measurement of efficacy. However, because this endpoint is a direct measure of mortality, which takes longer to observe, in order to measure statistically significant differences among patient groups these trials have long durations. These overtly time-consuming trials often translate into prohibitive costs for the manufacturer. In addition, upon recurrence, physicians will often discontinue the patient in the trial and administer last resort treatment options that can potentially delay or deter tumor growth (these therapies are

usually not FDA-approved treatments for GBM). The result is that it becomes more difficult to determine the absolute contribution of the study drug to overall survival because of the administration of subsequent treatments, which may or may not be the same among patients within a study cohort of a trial. Various researchers and other stakeholders have proposed using alternative endpoints such as imaging-related endpoints, progression-free survival, response duration, and time to progression, as well as quality of life and functional endpoints such as patient-reported outcomes, neurocognitive function, and other symptom-specific measures (Polley et al. 2010 and Braintumor.org 2013).

Recently two high-profile drugs in clinical development for GBM, Cilengitide (Merck) and Avastin (Genentech) failed to show improvement in overall survival in GBM patients when compared to the standard of care – temozolomide and radiotherapy (Reuters 2013 and PharmaTimes 2013). The disappointing results from these two otherwise promising drugs, underscore the challenge that researchers and drug manufacturers face in demonstrating clinical benefits for new GBM therapies when using overall survival as the primary endpoint.

In 2012, the National Brain Tumor Society catalyzed open conversation around this challenge through the creation of the "Clinical Trial Endpoints Initiative." The purpose of this effort is to explore the potential impact of "alternative endpoints" for increasing brain tumor-specific drug development. The effort is led by a strategic Steering Committee that includes leading medical researchers, physicians, and biostatisticians. In June 2013, the National Brain Tumor Society met directly with the FDA to continue this discussion around identifying alternative clinical trial endpoints and to discuss how various stakeholders in brain tumor drug development could work together to increase the volume and speed of approvals for new treatments for this disease.

EVALUATING TREATMENT RESPONSE

RECIST CRITERIA

The majority of clinical trials evaluating cancer treatments for response in solid tumors utilize a set of criteria referred to as the Response Evaluation Criteria in Solid Tumors (RECIST). These criteria define when cancer patients improve (respond), remain the same (stable), or worsen (progression). Under these criteria, response is evaluated as a function of direct measurements of solid tumors – which are also referred to as target lesions. The four categories of response outlined by RECIST are as follows:

- Complete Response - Disappearance of all target lesions
- Partial Response - At least a 30 percent decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum of the LD of target lesions
- Stable Disease - Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum of the LD of target lesions since the treatment started
- Progressive Disease - At least a 20 percent increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions

IMMUNE-RELATED RESPONSE CRITERIA

While the RECIST criteria are indeed useful to detect early effects of cytotoxic chemotherapeutic agents, these rules may not allow for adequate assessment of immunotherapeutic agents. Experts note that clinical response to immunotherapy can manifest after an initial increase in tumor size, or after the appearance of new lesions – both of which are categorized as progressive disease according to RECIST. It has been shown that an increase in tumor volume after immunotherapy treatment can be attributed to lymphocyte (a type of white blood cell) infiltration into the tumor, and not actual disease progression (Ribas et al. 2009).

Consequently, there is a shifting paradigm among oncologists in the evaluation of response to immune therapies. In 2009, Wolchock et al. published a paper that proposes a new set of criteria referred to as immune-related Response Criteria (irRC) (Wolchok et al. 2009). Under the proposed irRC, the appearance of new lesions do not always represent progressive disease, which is the case according to the RECIST rules. Instead, new lesions are to be measured and factored into the overall tumor burden prior to officially categorizing the response as progressive disease. The irRC also does not unequivocally regard an initial increase in tumor size as an indicator for progressive disease. The clinical utility of irRC has been evaluated using data from ipilimumab Phase II clinical trials in patients with advanced melanoma, and is currently under evaluation in Phase III trials with ipilimumab.

BRAIN TUMOR FOUNDATIONS

There are several non-profit organizations specifically focused on charitable giving to support brain tumors. The majority of these organizations are focused on improving awareness, providing patient support, and or aiding research for cures.

Using desktop research and guidestar.org, we identified national organizations that support brain tumors with revenues greater than $200,000. All of these organizations provide direct support for brain tumor research. Financial information for these organizations from fiscal year 2011 is provided in the table below.

Table 4: Charitable organizations supporting brain tumor research with revenues greater than $200,000.

Organization	Revenue	Research Support	Research/Expense Ratio
Ben & Catherine Ivy Foundation	$3,985,984	$8,588,478	87%
Translational Genomics Research Institute (TGen)	$6,025,718	$6,629,446	82%
American Brain Tumor Association	$4,245,612	$2,440,775	53%
Accelerate Brain Cancer Cure (ABC^2)	$1,872,056	$813,600	41%
National Brain Tumor Society	$7,439,676	$752,337	8%
Voices Against Brain Cancer	$509,930	$143,858	52%
The Musella Foundation	$401,101	$130,000	30%
Chris Elliot Fund	$211,722	$40,000	19%
Sontag Foundation	$1,253,409	$7,263,116	94%

COLLABORATIVE INITIATIVES AND CONSORTIA

DATA PLATFORM EFFORTS

In response to revolutionary advances in DNA sequencing technologies, multiple large-scale efforts have been initiated to centralize cancer genomic data and create an infrastructure for making the data publicly accessible. The motivation behind these efforts is to accelerate the understanding of the molecular basis of cancer through the application of genome analysis technologies.

While there are many repositories housing cancer genomic data, the largest repository is The Cancer Genome Atlas (TCGA), which houses extensive data charting genomic changes involved in more than 20 types of cancer, including glioblastoma. The Repository of Molecular Brain Neoplasia Data (REMBRANDT) is the largest data repository specific to brain cancers. This database includes glioblastoma data as well as data specific to low grade and mixed gliomas.

Additionally, the Ivy Genomics Based Medicine (GBM) Consortium and the Ivy Glioblastoma Atlas Project are also noteworthy collaborative efforts. The focus of the Ivy GBM Consortium is to pool and profile a collection of 60 preclinical models of human GBM to evaluate anti-tumor activity of current and early-stage drugs. The Ivy Glioblastoma Atlas Project (GAP) is a major research initiative focused on creating three-dimensional maps of gene activity in GBM tumors by specifically targeting 1,000 genes selected by GBM experts. Each initiative is described in greater detail below.

THE CANCER GENOME ATLAS (TCGA)

TCGA is a large-scale collaborative effort to characterize the genomic changes that occur in various types of cancer. The project is co-funded by the National Cancer Institute and the National Human Genome Research Institute (NHGRI); and led by Kenna Shaw, Ph.D., Director of The Cancer Genome Atlas Program Office, Brad Ozenberger, Ph.D., TCGA Program Director for NHGRI, and Liming Yang, Ph.D., Bioinformatics Program Director for TCGA.

The TCGA project solicits participation of a national network of research and technology teams working on distinct but related projects. The aim is to bring together data from these projects to create a publicly accessible repository that is available to researchers around the world in order to help them make and validate important discoveries.

In an effort led by Lynda Chin, M.D., Ph.D., MD Anderson Cancer Center, and Matthew Meyerson, M.D., Ph.D., Dana-Farber Cancer Institute, GBM was the first cancer studied using TCGA resources. Analysis of DNA copy number, gene expression, and DNA methylation aberrations were analyzed in 206 GBM tumors. Nucleotide sequence aberrations were analyzed in 91 of the 206 glioblastoma samples. Key findings from this study include:

- Identification of mutation patterns in genes coding for ERBB2, NF1, TP53, and PIK3R1 proteins, which occur with significant frequency in GBM.
- The elucidation of the mechanics of signaling pathways altered in the development of GBM (i.e., RB, p53, and RTK/RAS/PI3K pathways).

- The observation that MGMT methylation in conjunction with treatment with alkylating agents (i.e., temozolomide) may lead to other mutations that may cause patients to become resistant to this class of drugs.

The availability of this extensive genomic data has led to many additional discoveries, including the identification of molecular subtypes of GBM – proneural, neural, classical, and mesenchymal (Verhaak, 2010); the development of new data analysis tools that can identify gene combinations that are important for tumor development and progression (Masica, 2011); and the discovery that microRNA, miR-26a, contributes to GBM development by turning off tumor suppressor genes (Kim, 2010). As the cancer genomics community continues to unveil the genetic intricacies of GBM and other cancers, a clearer picture of these complex diseases will undoubtedly lead to improved treatments and increased survival.

REPOSITORY OF MOLECULAR BRAIN NEOPLASIA DATA (REMBRANDT)

REMBRANDT is a repository for molecular research and clinical trials data related to brain cancers. REMBRANDT is a joint initiative of the NCI and the National Institute of Neurological Disorders and Stroke and was developed to support the Glioma Molecular Diagnostic Initiatives (GMDI) led by NCI's Center for Cancer Research Neuro-Oncology Branch. The primary goal of GMDI is to develop a clinically and biologically meaningful molecular classification system based on genomic data from gliomas isolated from patients whose progress will be followed throughout treatment. GMDI also aims to explore gene expression profiles to correlate patient response with chromosomal abnormalities.

Similarly, the focus of REMBRANDT is to molecularly characterize a large number of adult and pediatric primary brain tumors, and to correlate those data with extensive retrospective and prospective clinical data. REMBRANDT hosts various data types that include gene expression profiles, real time PCR assays, comparative genomic hybridization and single nucleotide polymorphism array information, sequencing data, tissue array results and images, proteomic profiles, patient response to various treatments, and clinical trial information and protocols. A key differentiator of REMBRANDT compared to TCGA data is that REMBRANDT contains clinical and molecular data from low grade gliomas in addition to glioblastoma. As a result, researchers often use REMBRANDT in compliment with TCGA GBM data. Key findings based on the use of the REMBRANDT dataset include:

- The identification of molecularly distinct subclasses of lower grade gliomas.
- Studies providing evidence that STAT6 (Signal Transducer and Activators of Transcription 6) plays a key role in enhancing GBM cell proliferation and invasion, and identifying this protein as a novel therapeutic target (Merk, 2011).
- The elucidation of the role of myristoylated alanine-rich C-kinase substrate (MARCKS) in GBM growth, radiation sensitivity, and clinical outcome (Jarboe, 2012).

IVY GENOMICS BASED MEDICINE PROJECT

The Ivy Genomics Based Medicine Project is a collaboration among nine U.S. institutions working to molecularly profile 60 xenograft models of human glioblastoma to evaluate vulnerability to current and early-stage targeted therapies. In the process, the consortium is building a database housing genomic profiling data (copy number,

gene expression, and gene sequencing) of each preclinical model. The primary aim of this profiling is to discover patterns in the tumor profiles that can be used to predict the most effective therapy based on tumor type. In addition, results will lead to a pilot study utilizing the alignment of molecular profiling of patients' tumors to xenograft models to select treatments for their recurrent tumor.

This effort is led by Michael Berens, Ph.D., Deputy Director for Research Resources, Translational Genomics Research Institute (TGen). Project leaders and participating institutions include Antonio Chiocca, M.D., Ph.D., and Sean Lawler, Ph.D., Ohio State University; Howard Colman, M.D., Ph.D., MD Anderson Cancer Center; G. Yancey Gillespie, Ph.D., University of Alabama at Birmingham; C. David James, Ph.D., University of California, San Francisco; Tom Mikkelsen, M.D., Henry Ford Hospital; Jann Sarkaria, M.D., Mayo Clinic, Rochester Minnesota; Andrew Sloan, M.D., Case Western Reserve University School of Medicine; and Craig Webb, Ph.D., Van Andel Research Institute.

THE IVY GLIOBLASTOMA ATLAS PROJECT

The Ivy GAP project is a major research initiative focused on creating three-dimensional maps of gene activity in GBM tumors. The primary aim of this initiative is to develop a better understanding of the role of previously identified aberrant genes by evaluating where these aberrations take place within the tumor. Comparison of the tumor maps with similar maps of gene activity in normal brain tissue will allow researchers to develop new diagnostic tools and treatments that target abnormal genes. The Atlas Project specifically targets 1,000 genes, which were selected for study by an expert panel of neuro-oncologists and genomic researchers, led by Greg Foltz, M.D., director of the Ivy Center for Advanced Brain Tumor Treatment and a principal investigator on the Atlas Project.

KEY ACTIVITIES AND STRATEGIC PARTNERSHIPS

NATIONAL BRAIN TUMOR SOCIETY ANNOUNCES LAUNCH OF 'DEFEAT GBM RESEARCH COLLABORATIVE

The National Brain Tumor Society announced the formation of the Defeat GBM Research Collaborative. The objective of this strategic research initiative is to double the five-year survival rate of patients with GBM in five years. To achieve this goal, the Defeat GBM Research Collaborative will connect leading brain tumor researchers from top cancer institutions around the world, in a tightly focused and goal-driven research effort. The collaborative will combine synergistic projects led by investigators with proven track records of high-impact results to significantly improve patient survival. Data will be shared among all projects within Defeat GBM to better inform the overall effort and to quickly advance the clinical development of promising therapies (National Brain Tumor Society, 2013).

"Defeat GBM draws upon successful science and proven funding models from other disease populations that have yet to be utilized in brain tumor research," said N. Paul TonThat, Executive Director of the National Brain Tumor Society. "The brain tumor community can no longer spend years and millions of dollars to achieve only incremental progress in this deadly disease."

A team of senior neuro-oncology experts will serve as the Strategic Scientific Advisory Council (SSAC) that will oversee the collaborative. The advisors will chart the strategic direction of Defeat GBM research, regularly review Defeat GBM's achievements and progress, and hold the project teams accountable for attaining key milestones and annual goals during the five-year project, which will also determine continued financial support. The advisors will also be responsible for reviewing any additional and complementary research projects that may be integrated into Defeat GBM in the future.

The advisors and research leaders will partner with Defeat GBM's Managing Director, Carrie Treadwell (National Brain Tumor Society, Director of Research) and its Scientific Director, Dr. W.K. Alfred Yung, Margaret and Ben Love Chair of Clinical Cancer Care, and Professor of Neuro-Oncology and Cancer Biology at The University of Texas MD Anderson Cancer Center, to direct the overall research initiative.

Additional members of the SSAC include:

- Dr. Webster Cavenee - Director, Ludwig Institute for Cancer Research, San Diego, and Distinguished Professor at the University of California, San Diego
- Dr. Anna Barker - Director of Transformative Healthcare Networks, and Co-Director of the Complex Adaptive Systems Initiative at Arizona State University
- Dr. Richard Gaynor – Director of Clinical Development & Medical Affairs at Eli Lilly and Company
- Dr. Mitchel S. Berger – Chairman of the Department of Neurological Surgery, Director of the Brain Tumor Surgery Program, and Director of the Neurosurgical Research Centers at the Brain Tumor Research Center at University of California, San Francisco
- Dr. Darrell D. Bigner – Director of The Preston Robert Tisch Brain Tumor Center at Duke University
- Dr. George D. Demetri – Director of the Ludwig Center at Dana-Farber/Harvard Cancer Center and Professor of Medicine, Dana-Farber Cancer Institute/Harvard Medical School
- Dr. William C. Hahn – Senior Associate, Broad Institute of Harvard and MIT, and Professor of Medicine, Dana-Farber Cancer Institute/Harvard Medical School

NATIONAL BRAIN TUMOR SOCIETY PARTNERS WITH NATIONAL FOUNDATION FOR CANCER RESEARCH ON GBM BRAIN CANCER INITIATIVE

The collaboration will allow the organizations to create a unique effort to drive the development of targeted new brain cancer therapies, with a specific focus on GBM. This initiative will address some of the research and organizational gaps that impede medical progress in this area. Additional details regarding this strategic collaboration, as well as complete project descriptions and research goals will be announced later in 2013 (National Brain Tumor Society, 2012).

TGEN RECEIVES A $10 MILLION AWARD FROM THE BEN AND CATHERINE IVY FOUNDATION TO CONTINUE GBM RESEARCH AND INITIATE A PERSONALIZED MEDICINE STUDY IN BRAIN-CANCER PATIENTS

TGen will use funding from the Ivy Foundation to complete a five-year genomic study aimed to identify key genetic fingerprints specific to various subtypes of GBM tumors. This study will be conducted in two stages. The first stage will focus on the development of xenograft models using tumors provided by the Ivy GBM Consortium to study the behavior of GBM tumors in vivo. Deep sequencing (whole genome, whole exome, methylation, and

phosphorylation) will be performed on the tumors to look for biochemical mechanisms that drive tumor behavior. The primary aim of the second stage of the project will be to conduct a randomized Phase II clinical trial comparing patient treatment plans based on genomic profiling of tumors to physician selected treatment plans (TGen, 2012).

ACCELERATE BRAIN CANCER CURE AND EXOSOME DIAGNOSTICS COLLABORATE WITH LEADING ACADEMIC MEDICAL CENTERS TO DEVELOP NEW BLOOD AND CEREBROSPINAL FLUID-BASED DIAGNOSTIC TECHNOLOGY FOR BRAIN CANCER

Accelerate Brain Cancer Cure and Exosome Diagnostics are collaborating with leading academic medical centers to accelerate clinical validation of Exosome's blood and cerebrospinal fluid-based molecular diagnostics technology in brain cancer. This technology can sensitively detect rare gene transcripts and the expression of genes responsible for cancer and other diseases. The collaboration between ABC2, Exosome Diagnostics, and various academic centers will explore the capabilities of the RNA biofluid-based diagnostic technology for early identification, disease risk stratification, and progression monitoring. Initial studies conducted at Massachusetts General Hospital and University of California, San Diego have demonstrated that genetically rich exosome populations can be accessed safely multiple times through treatment courses without the need for surgical procedure. Additional studies are ongoing at Memorial Sloan-Kettering Cancer Center, Johns Hopkins, Yale University, MD Anderson Cancer Center, Mt. Sinai Hospital, Henry Ford Hospital, University of Miami, University of Florida, and Dana-Farber Cancer Institute (Exosome 2012).

COVANCE AND THE INSTITUTE FOR SYSTEMS BIOLOGY COLLABORATE TO ELUCIDATE THE COMPLEXITIES OF GBM GENE EXPRESSION

In March 2011, Covance's Seattle-based Genomics Laboratory collaborated with the Institute for Systems Biology, also based in Seattle, to collectively unravel the complex regulation of gene expression in GBM, one of the most common and aggressive forms of brain cancer (GenomeWeb, 2011).

THE NATIONAL BRAIN TUMOR SOCIETY LAUNCHES THE $5 MILLION MARY CATHERINE CALISTO SYSTEMS BIOLOGY INITIATIVE

Brain tumors are complex, highly variable among and within types and subtypes, and their locations beyond the blood-brain barrier make it difficult for therapies to penetrate. Given these challenges, a systems biology approach is essential. Systems biology recognizes that brain tumors are complex, dynamic systems. The various parts of the system work together to keep the tumor going. To come up with effective treatments, scientists must study the entire system, not just one or two parts. With this newfound understanding, researchers can now apply a predictive approach to the development of new therapies and treatments.

The Mary Catherine Calisto Systems Biology Initiative mandates that grantees form a team of researchers and scientists, which include experts outside of their own specialties. The first grants were awarded in September 2011. Seed funding of $600,000 was provided to six leading researchers. All the researchers will meet with National Brain Tumor Society advisors in a symposium to fully discuss their findings and potential. The six researchers will then be able to apply—individually or in collaboration with each other—for three $1.5 million ($500,000 per year) three-year grants to advance their research toward clinical trials (National Brain Tumor Society, 2011).

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Research on the latest approaches for the diagnosis, treatment, and management of GBM was presented at the American Society of Clinical Oncology 2014 Annual Meeting held May 30 – June 3, 2014, in Chicago, IL. Highlights from key presentations are outlined below:

Novocure Announces New Survival Data for Recurrent GBM Patients Treated with NovoTTF™ Therapy: Based on patient registry data of 147 female and 310 male patients (n=457) who were treated with this device, recurrent glioblastoma patients treated with NovoTTF Therapy achieved a median overall survival of 9.6 months (95% confidence interval [CI] 8.0 to 13.7), which is the longest median overall survival yet shown in non-experimental use for patients with recurrent glioblastoma. The median treatment duration was 4.1 (95% CI 3.5 to 4.8) months. The most common device-related adverse events include skin reaction (24.3%), neurological disorders (10.4%), heat sensation (8.9%), electric sensation (7.7%) and headache (5.7%). Adverse events seen in this study were consistent with the findings from the therapy's registration trial. Details of the abstract presented at ASCO 2014 can be found here.

Progression vs. Pseudoprogression - FLT-PET Imaging Fails to Distinguish between the Two: Positron emission tomography (PET) using 18F-fluorothymidine (FLT) as a tracer failed to distinguish true progression of glioblastoma from pseudoprogression in a small single-center study presented at the 2014 ASCO Annual Meeting. FLT is a tracer that is taken up by proliferating tumors cells. The study, conducted by Martha W. den Hollander, MD, of University Medical Center Groningen, the Netherlands, included 30 patients, 28 with glioblastoma and 2 with gliosarcoma. In this study 24 patients underwent assessment for pseudoprogression. The researchers compared changes in maximum standardized uptake value (SUV_{max}) and tumor to normal brain tissue ratios between patients with pseudoprogression and true progression. True progression was defined as progressive disease after chemoradiotherapy and further progression after three courses of temozolomide.

Of the 24 patients analyzed for pseudoprogression, 10 had stable disease or complete response after chemoradiotherapy and 14 had progressive disease. Of the 14 patients found to have progressive disease, 7 had pseudoprogression and 7 had true progression.

The researchers found no difference in the key metrics, SUV_{max} and tumor to normal brain tissue ratios on FLT-PET, between patients with true progression compared with pseudoprogression. However, the researchers did find that baseline FLT uptake was associated with overall survival. The median uptake of all patients in the study was 1.59 SUV_{max}. According to den Hollander, patients with an uptake lower than 1.59 had a higher overall survival than patients with a SUV_{max} higher than 1.59.

In a discussion of the results of this study, Elizabeth Robins Gerstner, MD, of Massachusetts General Hospital, commented on the increasing interest in looking at PET imaging in brain cancers. Gerstner acknowledged that PET does provide information about metabolism that is unavailable with MRI; however, she also pointed out that PET has several limitations as well, including being nonspecific, providing only a static picture of the tumor's metabolism, and a lack of standardization of acquisition protocols.

GLOSSARY

Adjuvant Chemotherapy	Additional treatment given after surgery to lower the risk of the cancer returning
Angiogenesis	The physiological process through which new blood vessels form from pre-existing vessels
Apoptosis	Genetically determined process of cell self-destruction
Benign	Abnormal growth of body tissue that is not cancerous
Biobanking	A type of repository that stores biological samples
Chemotherapy	The use of one or more drugs that are toxic to cells with the purpose of preventing the spread or growth of tumor cells
Downregulated	Refers to underactive expression of genes or proteins
Etiology	The cause or causes of a disease or abnormal condition
Genomic Profiling	Information about all the genes in an organism, including variations, gene expression, and the way those genes interact with each other and with the environment
Helper T cells	T-helper cells (Th cells) are a sub-group of white blood cells that help the activity of other immune cells by releasing T cell cytokines
Immunotherapy	Treatment of a disease by inducing, enhancing, or suppressing an immune response
Killer T cells	A sub group of white blood cells that kill damaged, infected and cancerous cells
Malignant Growth	A cellular growth that develops quickly and uncontrollably that has the ability to destroy tissues and/or travel to other parts of the body
Metastasis	The movement of cancer cells to other parts of the body
Molecular Pathway	A series of interaction within a cell that directs various cell processes and phenomena
Monoclonal Antibody	Antibody obtained from immune cells that were cloned from a unique parent cell
Mouse Xenograft (Avatar Mice)	Mice into which human tumor cells are transplanted either under the skin or into the organ
Neoadjuvant Chemotherapy	Treatment given to patients before the primary chemotherapy
Oncogenes	Genes that speed up cell division

Pathogenesis	The mechanism by which a disease is caused
Phase I	Examines the safety of the product in a very small group of healthy volunteers or patients afflicted with a specific disease. Also used to determine appropriate dose ranges
Phase II	Evaluates the safety and efficacy of the product at a predetermined dose in comparison to the standard of care treatment (commercially available therapies commonly used to treat the same disorder or disease)
Phase III	Evaluates the product compared to the standard of care in a large diverse population to determine broader efficacy and develop usage guidelines
Phase IV	Evaluates the long term effects of a drug post FDA approval for public use
Pre-clinical	A stage of research before clinical trials where feasibility and drug safety data is collected
Recombinant DNA	DNA molecules formed in the laboratory by bringing together genetic material from multiple sources
Tumor suppressor genes	Genes that slow down cell growth and control cell death
Standard of care treatment	Commercially available therapies commonly used to treat the same disorder or disease
Systems Biology	An interdisciplinary field of study that focuses on complex interactions within biological systems
T-Cells	A type of white blood cell (also called lymphocytes) that plays a central role in cell mediated immunity
Tumorigenesis	The formation of tumors tissue or cells
Upregulated	Refers to overactive expression of genes or proteins
Vaccine Adjuvants	A substance that is added to a vaccine to increase the body's immune response to the vaccine

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