

Life Sciences Case Example

U.S. Market Overview for TSC as a Radiation Sensitizer in GBM Patients
(Used With Permission from Diffusion Pharmaceuticals)

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Diffusion Pharmaceuticals is developing a drug to treat oxygen deprivation, a condition with significant unmet need

Diffusion Pharmaceuticals

– Overview –

- **Diffusion Pharmaceuticals is a private, clinical-stage drug company developing small-molecule therapeutics that enhance oxygen diffusion to oxygen-deprived (hypoxic) tissues**
 - The company expects its lead product candidate, *trans sodium crocetin* (TSC) to have applications across a variety of life-threatening diseases related to hypoxia
- **There is a substantial unmet need for a pharmacological treatment for hypoxia**
 - When deprived of oxygen, cells quickly begin to die
 - Severe cases of hypoxia can cause loss of consciousness, seizures, coma, neurological incapacitation, or death
 - Acute hypoxia often occurs when the flow of oxygenated blood to a local region is restricted by trauma, blood clots, or some other obstruction (e.g., PAD, stroke)
- **The potential clinical applications for a novel therapy that addresses hypoxia are significant**
 - Critical/Acute Care: Trauma, hemorrhage, stroke, heart attack
 - Chronic Care: Cardiovascular disease, respiratory disorders, peripheral vascular disease
 - Oncology: Radiosensitizer to support radiation therapy for solid malignant tumors
- **Diffusion Pharmaceuticals is pursuing clinical trials for multiple indications, including glioblastoma multiforme (GBM), a type of brain cancer**
 - The U.S. market potential for this indication is expected to exceed \$200MM annually
- **Successful clinical trials would lead to expansion to other solid tumor radiation therapies; lung, head and neck, uterine/cervical, and other brain cancers appear most promising**

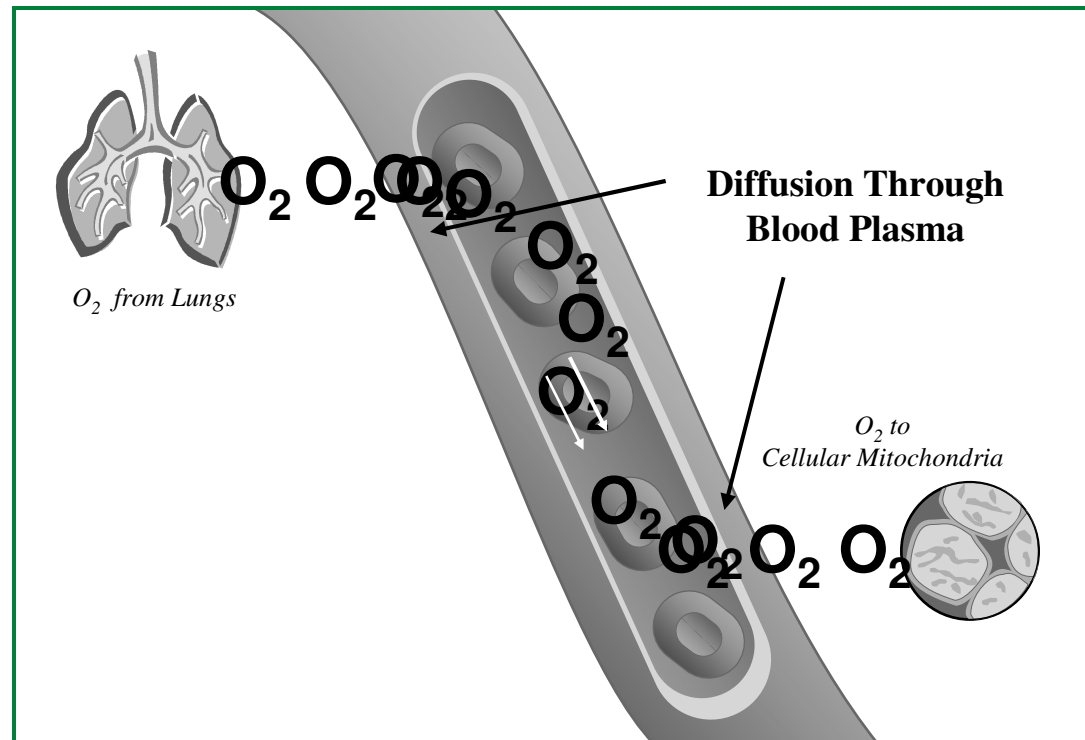
TSC uses a novel method of action to enhance oxygenation that has been proven effective in animal models and safe in humans

TSC Drug Profile Overview

- **TSC increases the amount of oxygen available for use by cell tissue by reducing the resistance the oxygen encounters when it moves through the blood plasma**
 - Diffusion of oxygen through the blood plasma is the “rate-limiting” step in the oxygen pathway
 - TSC alters the arrangement of water molecules in the plasma, so that the resistance to oxygen diffusion is reduced by about 30%, allowing for a more rapid movement of oxygen to the deprived tissue cells
- **TSC is differentiated from most other current and pipeline treatments for hypoxia in two ways:**
 - As a small-molecule drug, TSC is expected to have a better side effect profile than hemoglobin-based therapies, which often cause vascular inflammation
 - TSC tries to prevent and mitigate the underlying condition of oxygen deprivation, whereas many other pipeline treatments attempt to prevent the negative physiological consequences of oxygen deprivation, which is more complex and difficult to achieve
- **Early clinical testing of TSC has yielded positive results**
 - Pre-clinical trials in animal models of hemorrhagic shock, acute lung injury, radiation oncology, and ischemic stroke have demonstrated therapeutically significant results
 - Phase I trials demonstrated that the drug is well-tolerated in humans at doses significantly higher than the amount estimated necessary to be efficacious

TSC reduces resistance that occurs within the blood plasma; by doing so, more oxygen can make its way to the tissue

TSC Mechanism of Action



A novel treatment for hypoxia could have broad clinical application; this analysis evaluates the indication for sensitizing radiation-resistant glioblastoma multiforme (GBM) cancerous tumors

Potential Applications for Hypoxia Treatments

– Potential Indications for TSC –

Radiation-Resistant Cancerous Tumors

Peripheral Arterial Disease (PAD)

Stroke, Cardiovascular, and Respiratory Disease

Hemorrhagic Shock

Background:

- Cancerous tumors often grow faster than their ability to form new blood vessels, leading to hypoxic cells
- The non-responsiveness of cancerous tumors to radiation therapy is linked to oxygen deficiency within the cells of the tumor

- Peripheral Arterial Disease (PAD) refers to the narrowing of blood vessels outside of the heart and brain
- This often occurs when fatty deposits build up in the inner lining of artery walls
- The American Heart Association estimates that PAD affects up to 12 million Americans

- Ischemic conditions caused by stroke, myocardial infarction and respiratory disease where blood flow to a vital organ is restricted:
 - Strokes affect 600,000 to 750,000 Americans each year
 - Cardiovascular disease affects ~22 million Americans and is the leading cause of death in the U.S.
 - Respiratory disease covers a wide range of conditions, ranging from asthma to lung cancer

- Hemorrhagic shock occurs when blood loss exceeds the body's ability to compensate and provide adequate tissue oxygenation
- Death due to blood loss is the major cause of death on the battle field

Opportunity:

- Pre-clinical data shows TSC improves oxygen flow to the tumor, increasing the effectiveness of radiation therapy—and survival and/or quality of life

- TSC may improve oxygen flow to muscle tissue that may relieve the pain of peripheral arterial disease, in both acute and chronic situations

- Pre-clinical data indicates TSC improves oxygen flow that can protect tissue that otherwise would be damaged when blood flow is blocked, improving prospects for recovery

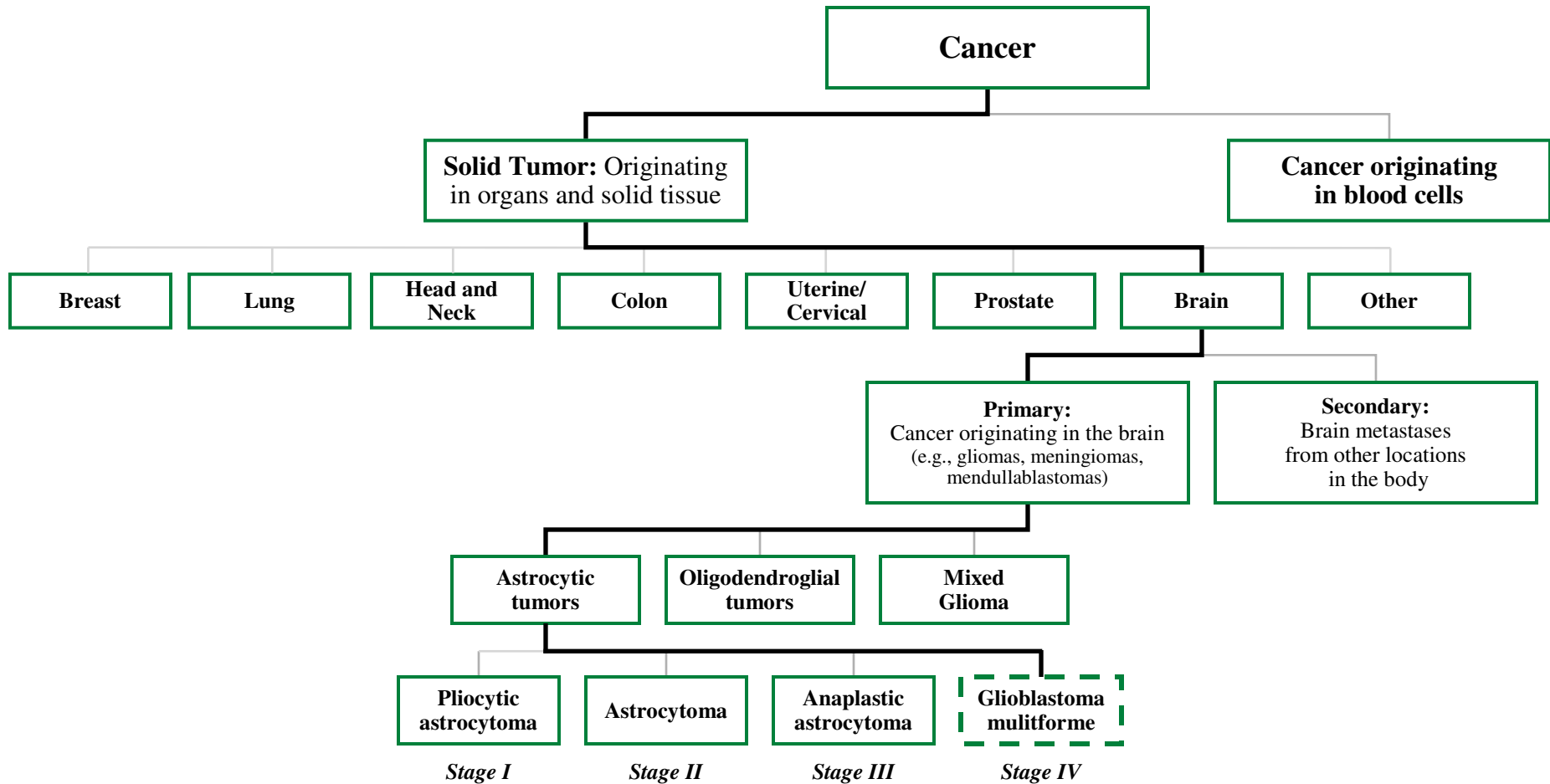
- Pre-clinical data shows TSC acts as a resuscitation agent in severe blood loss or other trauma, improving oxygen flow that may prevent tissue damage and increase the chances of survival

Focus of this analysis

Source: American Heart Association, WebMD entry on Hemorrhagic Shock, Diffusion Pharmaceuticals company website, CDC

Glioblastoma multiforme (GBM) is an aggressive and fatal form of brain cancer

Types of Cancer



Source: National Cancer Institute; University of Maryland Medical Center; Datamonitor Primary Brain Cancer Report 6/2007

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Due to the aggressive nature of GBM, standard treatment typically requires surgery followed by radiation and chemotherapy

Current Standard of Care

– GBM –

Surgery

- Surgery is used to physically remove as much of the tumor as possible in order to:
 - Confirm histological diagnosis using an obtained tissue sample
 - Alleviate symptoms associated with intracranial pressure or compression caused by the tumor
 - Increase survival by slowing/preventing further tumor growth

Radiation

- Radiation damages both cancerous and healthy cells, but the latter are able to repair themselves and regain function
- Oxygen deprived cells often found with solid tumors can, however, lead to radiation resistance

and

Chemotherapy

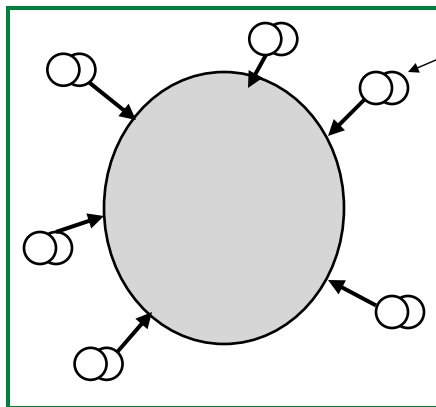
- Chemotherapy primarily consists of small-molecule drugs that act chemically on cells to impair division; tumor cells grow more rapidly than normal cells, and thus, are affected to a greater extent by chemotherapy
- Chemotherapy drugs can also enhance the effectiveness of radiation therapy

The effectiveness of radiation can be limited by a lack of oxygen in cells; since up to 80% of tumor tissue can be hypoxic, this can lead to radiation resistance, and an opportunity for oxygenation therapies like TSC

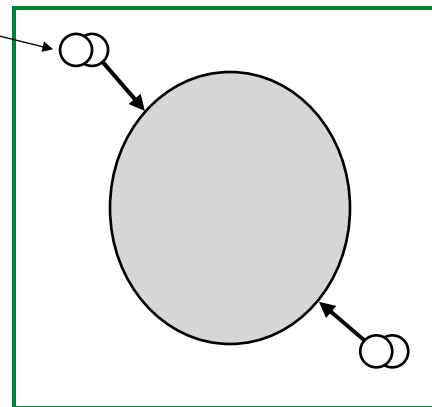
Comparison of Normal and Tumor Cells

– Oxygen Levels –

Normal Cell



Tumor Cell (Hypoxic)



Oxygen

- Though lack of oxygen is deadly to most normal cells, tumor cells frequently mutate and manage to thrive in a hypoxic state
- Radiation is generally less effective in cells with inadequate oxygen supply

The use of chemotherapy drugs to enhance the efficacy of radiation therapy has been practiced for years; TSC holds significant promise as an adjunct therapy in combination with other chemotherapy radiosensitizers

Radiation Sensitizers

	<i>Chemotherapy and Radiation Sensitizers</i>				<i>Radiation Sensitizer Only</i>
	Traditional Chemotherapy Drugs	DNA Targeting Drugs	Epidermal Growth Factor Receptors	Tumor Vasculator Targeting Drugs	Oxygenation Agents
Examples:	<ul style="list-style-type: none"> Alkylating agents (e.g., Temodar) Antimetabolites Cytotoxic drugs 	<ul style="list-style-type: none"> Topoisomerase 1 inhibitors (e.g., Topotecan) 	<ul style="list-style-type: none"> Tyrosine kinase inhibitors 	<ul style="list-style-type: none"> CI monoclonal antibodies/Anti-angiogenesis drugs (e.g., Avastin) 	<ul style="list-style-type: none"> Hemoglobin-based therapies TSC
Mechanism of Action:	<ul style="list-style-type: none"> Enhances formation of toxic intermediates Inhibits DNA repair Radiation induces increase in cellular drug uptake Promotes cell cycle arrest 	<ul style="list-style-type: none"> Interferes with DNA metabolism <ul style="list-style-type: none"> – RNA transcription – DNA replication – Regulation of DNA supercoiling 	<ul style="list-style-type: none"> Inhibits tumor cell growth kinetics, through inhibition of downstream induction of mitogenic signals Inhibits post radiation repair and angiogenesis Enhances radiosensitivity Promotes radiation-induced apoptosis 	<ul style="list-style-type: none"> Inhibits development of blood vessels in tumor, reducing provision of nutrients to cells, slowing growth Concern that inhibition of tumor angiogenesis could increase fraction of hypoxic tumor cells and, as a result, induce radiation resistance 	<ul style="list-style-type: none"> Increases oxygen flow to hypoxic cancer cells, enhancing efficacy of radiation therapy

Combining drugs that have unique mechanisms of action and absence of overlapping toxicities with radiation therapy should support continued clinical trials—and an opportunity for TSC

The current “gold standard” of chemotherapy drugs for GBM is Temodar, which is only able to increase survival by ~2.5 months

Current Drug Therapies for Primary GBM

– FDA Approved –

Treatment	Company	Description	Indication	Notes
<ul style="list-style-type: none"> • Temodar (temozolomide) 	Schering-Plough	<ul style="list-style-type: none"> • Orally administered cytotoxic alkylating agent 	<ul style="list-style-type: none"> • In combination with radiation therapy for newly diagnosed GBM, as well as other indications related to astrocytoma and recurrent GBM 	<ul style="list-style-type: none"> • Considered the gold standard in treatment—demonstrated a 2.5 month survival improvement in newly diagnosed GBM patients compared to radiation alone
<ul style="list-style-type: none"> • Gliadel (carmustine polymer wafer) 	MGI Pharma	<ul style="list-style-type: none"> • Biodegradable wafer containing the cytotoxic alkylating agent carmustine, implanted into the resection cavity following tumor resection 	<ul style="list-style-type: none"> • Newly diagnosed patients with high-grade malignant glioma as an adjunct to surgery and radiation; recurrent glioblastoma multiforme patients as an adjunct to surgery 	<ul style="list-style-type: none"> • Demonstrated a 2.1 month survival improvement in newly diagnosed GBM patients compared to radiation alone
<ul style="list-style-type: none"> • Other chemotherapy drugs 	—	<ul style="list-style-type: none"> • Most commonly nitrosureas or a regimen of procarbazine, lomustine and vincristine (PCV regimen) 	<ul style="list-style-type: none"> • Glioblastoma multiforme 	<ul style="list-style-type: none"> • Considered to be of very limited or no survival benefit with higher toxicity

While hemoglobin-based therapies may also improve tissue oxygenation, none are likely to compete as radiation sensitizers

Hemoglobin-Based Oxygenation Therapies

	Drug Type	Example	Description
<p><i>Failed to reach radiation sensitizer endpoints in Phase III trials</i></p>	Allosteric Molecules	<ul style="list-style-type: none"> Efaproxyn (Allos) 	<ul style="list-style-type: none"> Modifies hemoglobin to reduce its ability to bind to oxygen, and thus releases more oxygen into the bloodstream Efaproxyn failed to show statistically significant improvement in overall survival compared to patients receiving radiation alone
<p><i>Not relevant to radiation sensitizer indication</i></p>	Human Blood Substitutes	<ul style="list-style-type: none"> Recycled bovine blood, e.g., Hemopure (Biopure) 	<ul style="list-style-type: none"> Increases blood volume with the intention to increase the level of hemoglobin to increase oxygen in the bloodstream, as hemoglobin is the protein in red blood cells that carries and releases oxygen to the body's tissues
	Modified and Artificial Hemoglobin	<ul style="list-style-type: none"> Perfluorocarbon compounds 	<ul style="list-style-type: none"> Increases hemoglobin volume without the associated blood volume increase of blood substitutes, to increase oxygen in the bloodstream

Hemoglobin-based therapies that improve oxygenation of the tissue by increasing the oxygen concentration in the blood, appear less effective than TSC, which promotes oxygen diffusion

Current pipeline drugs indicated for primary GBM may have synergies with radiation therapy, but likely still could be used concurrently with a radiation sensitizer like TSC

Relevant Pipeline Therapies in the U.S.

– With Primary GBM Indication –

Relevant Drugs	Company	GBM Indication	Currently Marketed Indication	GBM Phase	Drug Type
Xeytrin	Pharmacyclics	In combination with radiation therapy for treatment of brain metastases from NSCLC	None	NDA filed over FDA protest	Texaphyrin-tumor targeted reactive oxygen species (ROS) generator
CDX-100	Celldex Therapeutics	In combo with radiation therapy and TMZ for GBM patients (potentially only targeting those who express EGFRvIII)	None	Phase II/III	Therapeutic Peptide Vaccine
Enzastaurin	Eli Lilly	Before and in combo with radiation therapy in newly diagnosed GBM as first line treatment and Enzastaurin maintenance therapy until progression/unacceptable AEs	Non-Hodgkin's Lymphoma, pending successful Phase III outcomes; additional ongoing trials for additional indications	Recruiting Phase II	Serine-Threonine Kinase Inhibitor
Lenalidomide (Revlimid)	Celgene	In combo with radiation therapy in patients with newly diagnosed GBM	In combo with dexamethasone for multiple myeloma patients who have received at least one prior therapy	Recruiting Phase II	Immunomodulatory
Cilengitide	Merck KGaA	In combo with radiation therapy and TMZ in newly diagnosed GBM; various other monotherapy studies for GBM	None	Phase I/IIa completed	Anti-Angiogenesis
Elotinib (Tarceva)	Genentech/(OSI)oncology	In combo with radiation therapy in newly diagnosed young patients (3-25)	Non-Small Cell Lung Cancer and Pancreatic Cancer (in combination with gemcitabine)	Recruiting Phase I/II	EGFR-Tyrosine Kinase Inhibitor
Zarnestra (tipifarnib)	Johnson & Johnson	Radiosensitizing effect of Zarnestra in patients with GBM	Granted fast-track status for acute myeloid leukemia (AML)	Recruiting Phase I/II	Farnesyltransferase Inhibitor
G207	MediGene	Following radiation therapy in malignant glioma	In additional clinical trials for other indications	Phase I	Oncolytic Virus
Interferon Beta-1a	Biogen Idec (Avonex); Serono and Pfizer (Rebif)	Standard radiation therapy followed with recombinant Interferon Beta-1a in newly diagnosed GBM with necrosis	MS		

Source: Datamonitor "Stakeholder opinions: Primary brain cancer" 06/2007; Clinical trials gov.; company websites

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A number of factors contribute to the market potential for an effective radiosensitizer for the treatment of GBM

Therapies Related to GBM

– Market Potential Overview –

- **Since radiation therapy is part of the standard treatment of care for GBM, most patients will be candidates for a drug that improves the effectiveness of radiation**
- **Currently few drugs exist in the GBM market, and those available show limited efficacy**
 - Temodar, the current gold standard chemotherapy drug for glioblastoma multiforme, has demonstrated an average increased survival rate of only 2.5 months
- **Radiation sensitizers and chemotherapy drugs should be complementary, especially given the current trend of “cocktail therapies” in cancer treatment**
 - Clinical trials must be used to demonstrate both the safety and incremental therapeutic benefit of concurrent use of radiosensitization and chemotherapy drugs
- **Drugs developed for GBM are likely to achieve Orphan Drug status and/or Fast Track status as well as insurance reimbursement**
 - In the past, radiation sensitizers in clinical development have been granted one or both of these designations (e.g., Efavoxyn)
 - Historically, Medicare has favorably reimbursed GBM therapies, such as Temodar, due to the devastating nature of the disease and relatively small number of patients

To support initial market size projections, we developed a set of steady state assumptions around addressable market, pricing, and market share

Steady State Market Opportunity Projection for TSC

– Key Assumptions –

	Assumptions	Source/Rationale
Addressable Market	<ul style="list-style-type: none"> In 2007, over 19,000 cases of primary brain cancer were expected to be diagnosed in the U.S. Over 50% of primary brain cancer tumors are classified as GBMs Nearly all GBM patients will be treated with radiation therapy, as it is considered standard care for such tumors 	<ul style="list-style-type: none"> Datamonitor Datamonitor; eMedicine Medical research
Pricing	<ul style="list-style-type: none"> Price per course of therapy can be compared to other chemotherapy/radiosensitizer agents (e.g., Temodar) used to treat GBMs (~\$25,000 course/patient) A course of radiation therapy typically involves one to two treatments per day, five days a week, for five to seven weeks Annual price increase of 5% 	<ul style="list-style-type: none"> Comparable therapy/efficacy Market benchmarks
Competition/Market Share	<ul style="list-style-type: none"> No other radiosensitizers exist on the market, and no direct competition is currently foreseen As physicians become comfortable with TSC's safety and efficacy, market share will increase rapidly in early years, and then plateau 	<ul style="list-style-type: none"> Competitive landscape analysis Benchmark against Temodar and Efaproxyn

Insurance companies have shown the willingness to reimburse therapies that can extend life beyond radiation treatment alone

Estimated Cost of Current GBM Therapies

– Chemotherapy Products –

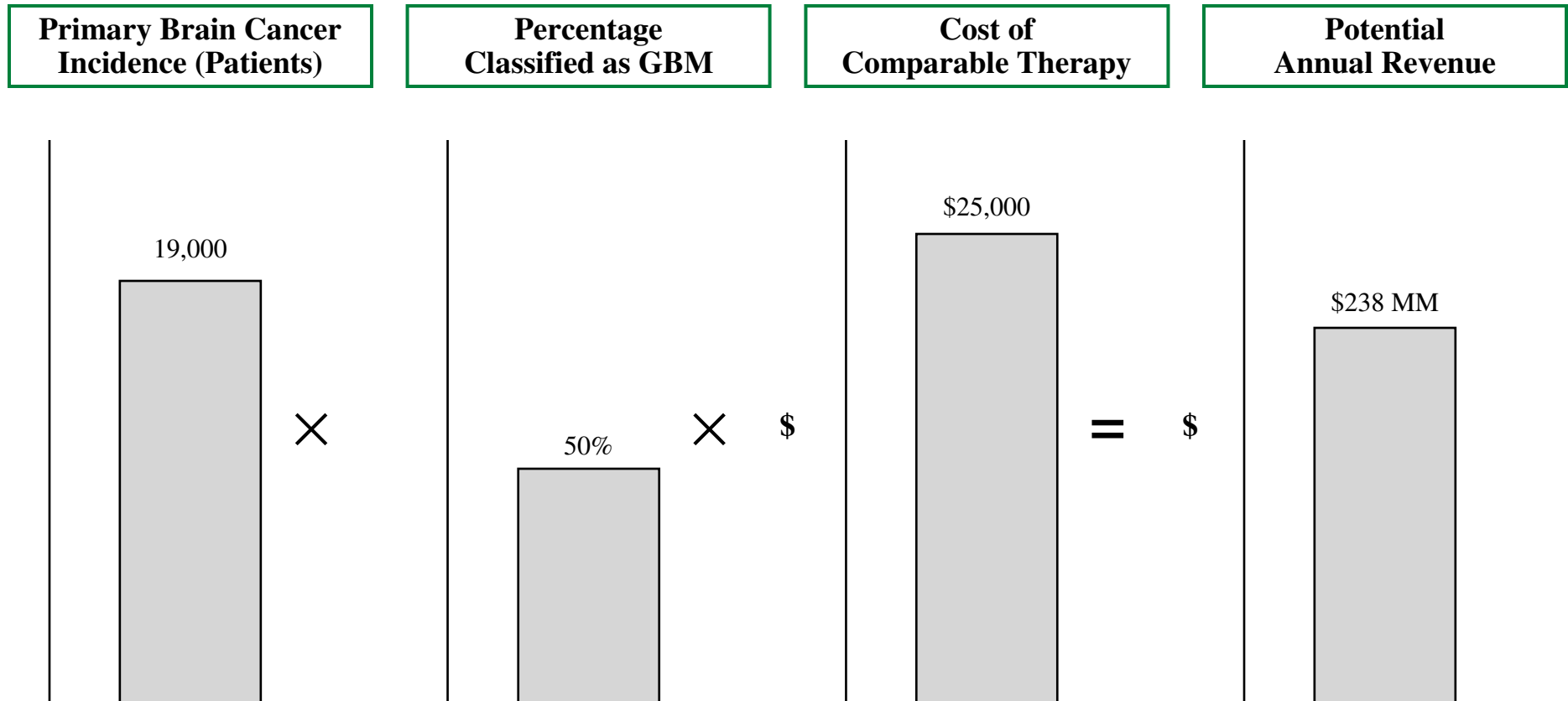
Therapy	Incremental Cost over Radiotherapy	Incremental Life-Expectancy over Radiotherapy
• Radiotherapy + Gliadel	>\$25,000	~2.1 months
• Radiotherapy + Temodar	~\$25,000	~2.5 months

- **If radiotherapy + Temodar + TSC shows improved survivability over radiotherapy + Temodar, it is reasonable to assume a \$25,000/treatment base price for TSC**
 - Radiotherapy + Temodar is the current “gold-standard” of treatment for GBM

Annual revenue potential could be as high as \$238 million

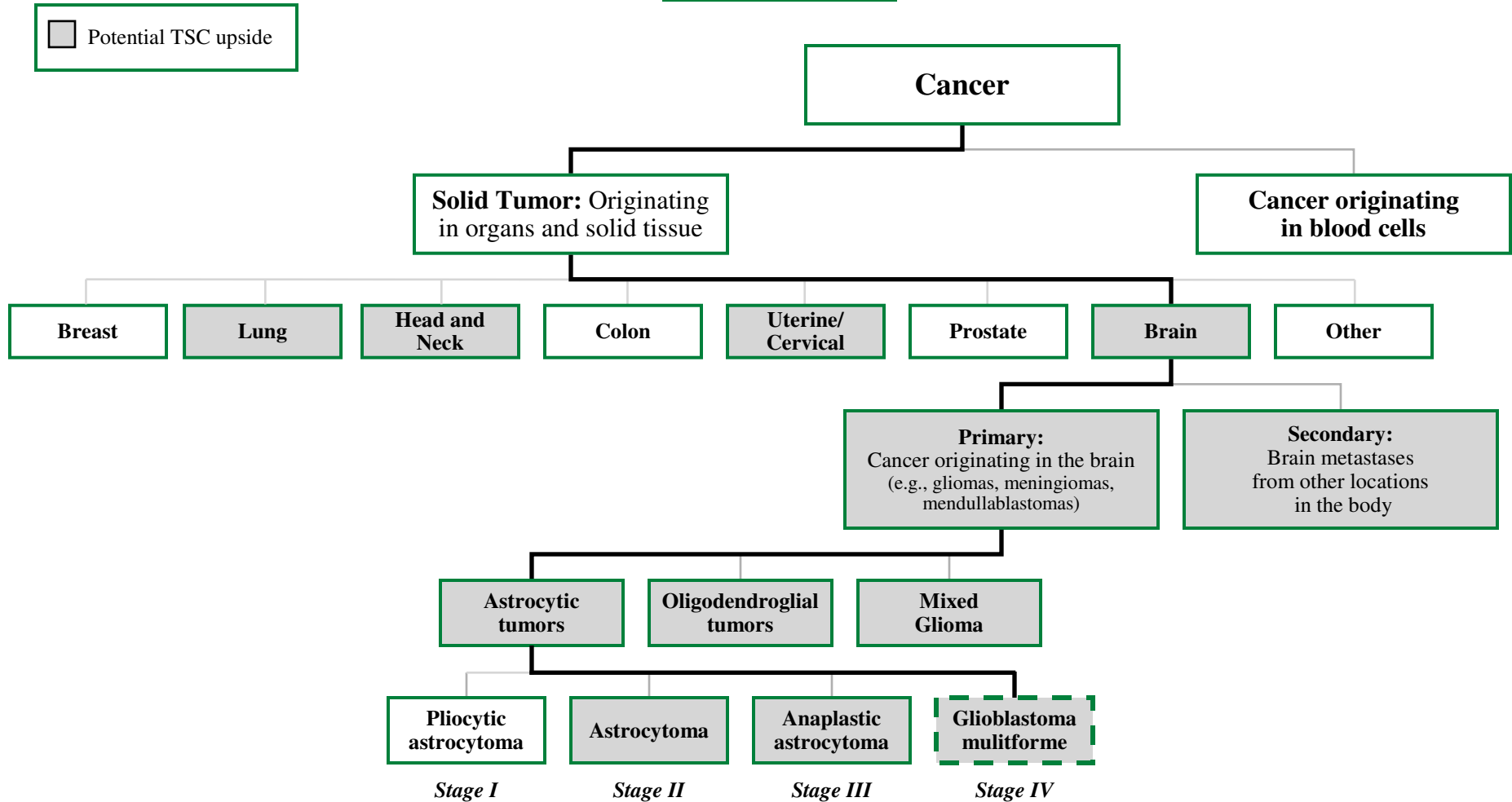
Total Market Opportunity for New Radiosensitizer Drugs for GBM

– U.S. Annual Revenue –



Positive results treating GBM with TSC would lead to expansion to other solid tumor radiation therapies; head and neck, lung, uterine/cervical, and other brain cancers are particularly promising future indications

Types of Cancer



Source: National Cancer Institute; University of Maryland Medical Center; Datamonitor Primary Brain Cancer Report 6/2007

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