A Phase II Trial of Intensive Chemotherapy and Autotransplantation for Patients With Newly Diagnosed Anaplastic Oligodendroglioma

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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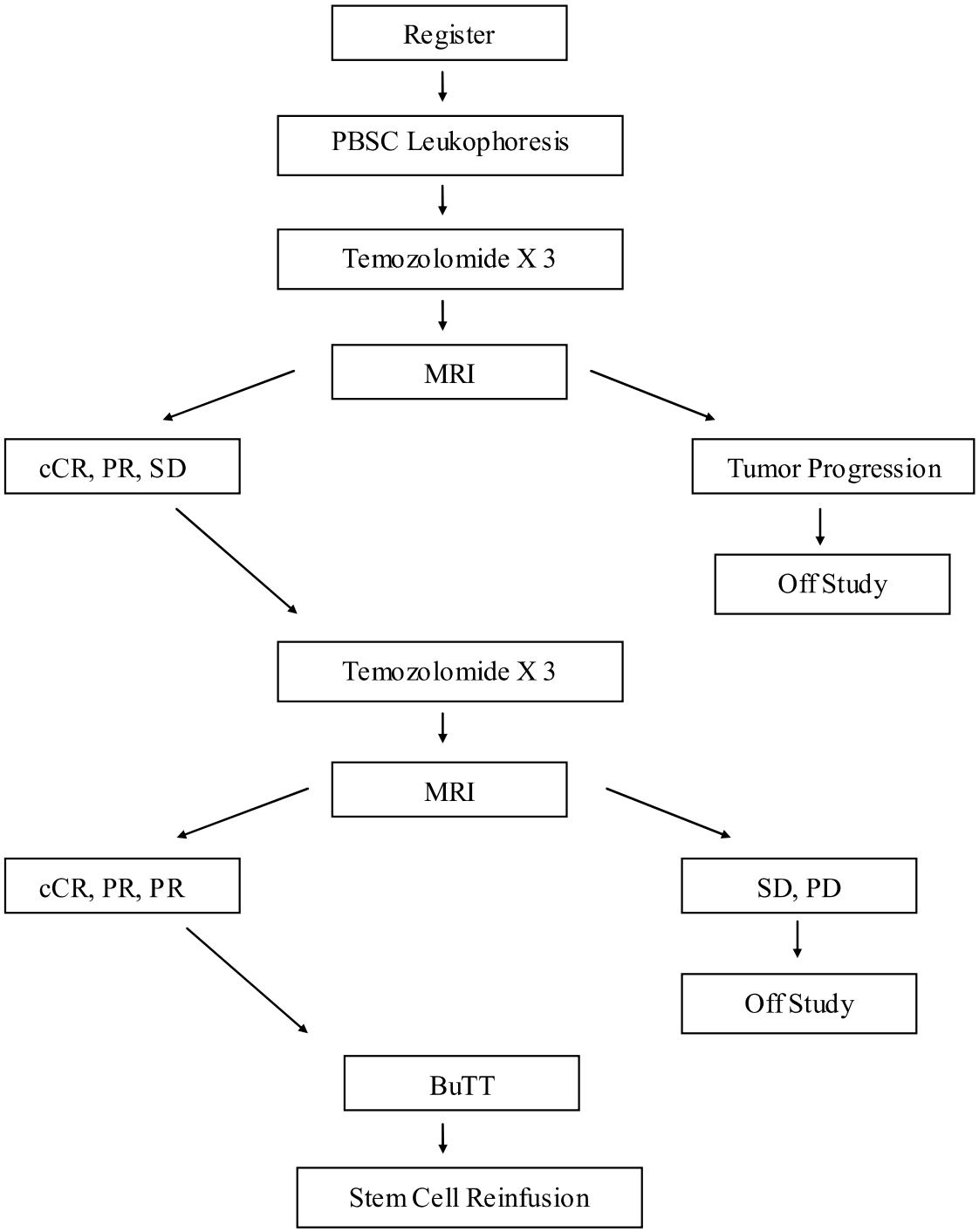
1.0 PROTOCOL SUMMARY AND/OR SCHEMA



2.0 OBJECTIVES AND SCIENTIFIC AIMS

- To determine the duration of disease control of newly diagnosed pure and mixed anaplastic oligodendrogliomas treated with dose-intensive chemotherapy requiring hematopoietic stem cell support. (Primary objective)

- To determine the neurological and systemic toxicities of such treatment. (Secondary objective)

- To prospectively determine the relationship of 1p loss of heterozygosity (LOH) on radiographic response, progression free and overall survival. To prospectively collect and analyze tumor tissue for other potentially important molecular markers including but not limited to p53, 10p, and 19q. (Tertiary objective)

3.0 BACKGROUND AND RATIONALE

Anaplastic gliomas are incurable cancers. Surgery and radiotherapy (RT) prolong life (1), and there is some evidence to suggest that adjuvant treatment with nitrosourea-based chemotherapy may augment tumor control and prolong survival (2,3). For recurrent tumor, reoperation and focussed re-irradiation help some patients but chemotherapy has proved to be of only modest benefit with low response rates and short response durations. The search for effective anti-glioma chemotherapy continues with only occasional signs of progress (4,5). It is in this context that "successful" chemotherapy for oligodendroglioma and mixed gliomas containing oligodendroglial elements (i.e. oligoastrocytoma) emerged ten years ago (6-11).

Oligodendrogliomas are uncommon tumors thought to arise from an oligodendrocyte precursor cell (12). Oligodendroglial neoplasms represented 4.2% of primary brain tumors in a 25-year survey of the Norwegian Cancer Registry (13) and the majority of oligodendrogliomas are low grade. Only a minority of oligodendrogliomas are anaplastic. Anaplastic oligodendrogliomas represented 3.5% of new malignant gliomas seen at one center over 5.5 years (14). Most anaplastic oligodendrogliomas are enlarging, enhancing masses on computed tomographic or magnetic resonance images. They may evolve from benign tumors or appear "de novo". Unlike typical oligodendrogliomas, anaplastic ones have some or all of the following microscopic features: high cellularity, nuclear pleomorphism, endothelial proliferation, mitotic figures and necrosis. Moreover, cytoplasmic clearing, the hallmark of well-differentiated tumors, becomes less conspicuous with increasing anaplasia. Based on these histologic characteristics, oligodendrogliomas can be graded A (low), B, C, or D (high) as proposed by Smith et al (15) or I (low), II, III, or IV (high) using the Kernohan or St. Anne-Mayo systems (16,17). Anaplastic features may not be as reliable an indicator of rapid growth as they are in astrocytomas, but nevertheless, anaplastic oligodendrogliomas usually behave more aggressively than non-anaplastic ones as

illustrated in the following table of median survivals measured in months for patients with oligodendrogliomas of different grades.

Ref.	**Median Survival (months)**				
	A	**B**	**C**	**D**	
Smith et al (18)	94	51	45	17	Smith scale
Kros et al (19)	113	77	83	15	Smith scale
Kros et al (19)	122	67	71	35	Kernohan scale
Shaw et al (20)		116	38		Kernohan scale
Shaw et al (20)		117	47		St. Anne-Mayo
	I	**II**	**III**	**IV**	

Although more aggressive than typical oligodendrogliomas, patients with anaplastic tumors live longer than those with glioblastoma multiforme or anaplastic astrocytoma (14). Longer survival may reflect a better natural history, a better response to contemporary treatment, or both. At one Canadian center patients with anaplastic oligodendroglioma had a median survival of 278 weeks (14) and represented 30% of patients with anaplastic glioma who survived 5 years. As with other gliomas, the survival of patients with oligodendrogliomas is determined by multiple factors, tumor-grading being but one. Age, performance status, extent of resection, and postoperative RT also appear to be important prognostic factors (17). Younger patients, those with good function, those with completely resected tumors, and those who receive RT after partial removal, are likely to live longer. Generally speaking, surgery and RT are regarded as standard initial treatment for anaplastic oligodendrogliomas.

Until recently there was little information about the natural history and response to treatment of anaplastic mixed gliomas, that is anaplastic tumors containing both oligodendroglial and astroglial elements. This is not surprising given the infrequent occurrence of oligoastrocytomas as compared to glioblastomas and anaplastic astrocytomas, and the absence of uniform diagnostic criteria distinguishing them from anaplastic astrocytomas on the one hand, and anaplastic oligodendrogliomas on the other. Two retrospective studies have compared the median durations of survival of patients with anaplastic mixed gliomas to other types of anaplastic glioma. These analyses have yielded conflicting results: Winger et al (14) found the median survival for patients with anaplastic oligoastrocytomas to be inferior to anaplastic

oligodendrogliomas and identical to anaplastic astrocytic tumors (ie. 12 months), while Shaw et al (18) found the median duration of survival of patients with anaplastic mixed tumors to be identical to anaplastic oligodendrogliomas and significantly longer than anaplastic astrocytomas (ie. 34 months using the Kernohan system, 52 months using the St. Anne-Mayo system). Allowing for the fact that diagnostic criteria vary, oligoastrocytomas would appear to be at least as common as pure oligodendrogliomas. In a mixed glioma, either the oligodendroglial or astroglial element may be anaplastic. Surgery and RT are the standard initial treatment for anaplastic oligoastrocytomas.

Chemotherapy for Oligodendrogliomas

There is a substantial body of evidence indicating that pure and mixed anaplastic oligodendrogliomas are chemosensitive tumors. In 1988, based on a small series of consecutive cases, Cairncross and Macdonald (6) reported that recurrent anaplastic oligodendrogliomas respond predictably to nitrosourea-based chemotherapy, especially PCV (procarbazine, CCNU [lomustine], and vincristine), a regimen described eight years earlier by Levin et al (19). Two years later, Macdonald et al (7) reported responses to chemotherapy prior to RT in a small series of patients with newly diagnosed aggressive oligodendrogliomas. By aggressive they meant either histologically anaplastic tumors or non-anaplastic oligodendrogliomas that were symptomatic, enlarging and contrast enhancing on neuroimaging studies. In 1990, Brown et al (8) for the Duke-based CNS Cancer Consortium reported that recurrent anaplastic oligodendrogliomas were more likely to respond to intravenous melphalan than non-oligodendrogliomas. This finding, and a case report by Saarinen et al (9) in 1990, describing a complete response to high-dose thiotepa in a child with a recurrent heavily pre-treated tumor provided further evidence that aggressive oligodendrogliomas were chemosensitive solid tumors. Glass et al (11) in 1992 made the important observation that anaplastic oligoastrocytomas also respond to PCV. They observed durable responses in recurrent tumors and responses prior to RT in newly diagnosed cases. The National Cancer Institute of Canada completed a multicenter phase II trial of intensive-PCV (I-PCV) for new or recurrent anaplastic oligodendrogliomas observing a 75% response rate, and a 40% complete response rate (20). In this study, durations of tumor control were directly related to the completeness of radiographic response, an intuitively obvious result, but one that had not previously been demonstrated in a therapeutic trial for glioma. Subsequently Mason et al (21) demonstrated that symptomatic enlarging low-grade oligodendrogliomas were also sensitive to PCV. This study highlighted the possibility that chemotherapy might be used instead of radiotherapy as the initial non-surgical therapy for patients with oligodendroglial neoplasms requiring additional treatment. Most recently, Chinot et al (22) reported that recurrent anaplastic oligodendrogliomas frequently respond to treatment with temozolomide, a new orally administered DNA methylating agent. Temozolomide has largely replaced PCV as the chemotherapy of choice for anaplastic oligodendroglioma. This change is due in part to the tolerability of temozolomide and comparable response rates of temozolomide and PCV in small trials.[44,45,46,47] This study reaffirmed that oligodendrogliomas are uniquely

drug-sensitive glial neoplasms and added an important new agent to the chemotherapeutic armamentarium of neuro-oncologists confronting such tumors

These initial studies set the stage for a large phase III Intergroup trial by the Radiation Therapy Oncology Group (RTOG) designed to evaluate the role of neoadjuvant I-PCV chemotherapy in the treatment of patients with newly diagnosed pure and mixed oligodendrogliomas. Patients in this study are randomized to I-PCV followed by RT or to RT alone. The principal outcomes of interest are survival, time to tumor progression, and the toxicities of these different treatment approaches. This trial, which will complete accrual shortly, and a similar study by the EORTC, represent a logical next step in the evaluation of nitrosourea-based chemotherapy for newly diagnosed aggressive oligodendroglial neoplasms. However, both studies have the inherent disadvantage of requiring early cranial irradiation for all patients. Although radiotherapy is an effective treatment for aggressive gliomas, it can be neurotoxic. The sequelae of cranial radiotherapy appear months or years later and may include dementia, neuroendocrine disorders, and rarely, cerebral necrosis. Ironically, it is the long-term survivors, those whose tumors have been successfully treated, that develop disabling neurological conditions secondary to radiotherapy. In this regard, patients with oligodendrogliomas may be particularly vulnerable. Oligodendrogliomas are often large or bilateral cerebral lesions at diagnosis and can only be adequately treated with radiotherapy using treatment fields that encompass large volumes of normal brain tissue. Furthermore, oligodendrogliomas and oligoastrocytomas may have a more favorable natural history and better response to treatment than other types of malignant glioma which means that patients with such tumors are precisely the ones at high risk for the serious toxicities of radiotherapy to the brain.

The unusual chemosensitivity of oligodendrogliomas and the potential toxicities of successful radiotherapy for such tumors led our group to examine the role of novel chemotherapeutic strategies in the management of patients with anaplastic pure and mixed oligodendroglial neoplasms (23,24). We chose a dose-intensive chemotherapy strategy, one that, of necessity, would require hematopoietic constitution using bone marrow or peripheral blood stem cells. We reasoned that high doses of drugs might be more effective in controlling tumor growth and that high doses might also be required to ensure adequate drug delivery to tumor cells residing behind the blood-brain barrier. The clinical trial described here builds on our experience using this strategy in patients with both recurrent and newly diagnosed aggressive oligodendrogliomas and will also incorporate a companion molecular analysis. Molecular studies may be of particular interest in interpreting the results of therapeutic strategies for oligodendroglioma because it is becoming increasingly apparent that molecular subtypes exist. These molecular subtypes appear to have distinct natural histories, neuro-imaging characteristics, chemosensitivities and durations of tumor control following therapeutic maneuvers (25-29).

RTOG 94-02 and EORTC 26951

Two recent trials have addressed the role of adjuvant chemotherapy in newly diagnosed anaplastic oligodendrogliomas. In a study conducted by RTOG, 291 patients with new AOs or AOAs were randomized either to treatment with I-PCV followed by RT or to treatment with RT alone. The primary and secondary endpoints were overall survival and progression free survival, respectively. Tissue analysis was included in the study to ascertain the influence of 1p and 19q loss. PCV offered no improvement in overall survival. 148 patients who received PCV had a median overall survival of 4.8 years compared to 4.5 years in those who received RT alone. However, median PFS in the PCV arm was longer at 2.6 years vs. 1.9 years in patients who only received RT. Almost two-thirds of patients who received PCV had grade 3 or 4 toxicity. As expected, patients with allelic loss of 1p and 19q fared better independently of type of treatment. Median survival in this group has not yet been reached but is longer than the 2.8 years reported in patients with no allelic loss. The EORTC, in a similar study, randomized 368 patients to RT followed by PCV or RT alone. No difference in overall survival was observed; 36.8 months in patients who received adjuvant chemotherapy vs. 30 months in patients who had RT alone. Like the RTOG study, median PFS was a secondary endpoint and was statistically longer in patients who received PCV; 24.3 months compared to 13.3 months in the control arm. Notably, 64% of patients who were treated with RT alone ultimately received PCV at relapse. Results of 1p/19q analysis in this study have not yet been reported.

Principles of High Dose Chemotherapy and Autotransplantation

There is a steep dose-response curve for most cytotoxic drugs. Dose intensive chemotherapy is therefore a logical strategy for improving the control of chemoresponsive cancers. Intensive chemotherapy regimens, for which myelosuppression is dose limiting, can now be seriously entertained as a result of advances in stem cell cryopreservation and support of neutropenic patients. Santos et al have developed guidelines for the rational application of autotransplantation technology (bone marrow or peripheral blood stem cell hematopoietic reconstitution) to the treatment of advanced cancers (30). The guidelines are as follows:

- a malignancy responsive to cytoreductive chemotherapy.
- effective treatment whose limiting toxicity is marrow failure.
- performed early when there is minimal tumor burden or resistance to drugs.
- a source of hematopoietic stem cells free of clonogenic cancer cells.

Some patients with leukemia, Hodgkin's disease, and non-Hodgkin's lymphomas meet these criteria and have enjoyed long tumor remissions following high-dose

chemotherapy and hematopoietic reconstitution using bone marrow or peripheral blood stem cells. In some clinical situations, randomized controlled trials have demonstrated that high-dose therapy is the preferred therapy for these cancers. This management strategy has been less efficacious for solid tumors, including relatively chemosensitive malignancies such as breast cancer. In the case of breast cancer, high-dose therapy does not prolong tumor control or patient survival when compared to less morbid treatment methods. Furthermore, this strategy has been entirely unsuccessful for chemoresistant brain neoplasms such as glioblastoma multiforme.

Why then does our group remain interested in dose-intensive chemotherapy for a chemosensitive brain tumor, like oligodendroglioma? Neuro-oncologists are motivated to explore such treatment approaches to oligodendroglioma because the toxicity of standard therapy is excessive, an issue that does not arise routinely in the context of standard treatment for breast cancer, for example. New strategies are needed to improve brain tumor control without destroying intellect and other critical brain functions. For chemosensitive brain tumors, safe and effective high-dose chemotherapy strategies that obviate the need for immediate radiotherapy would represent an important therapeutic advance. In neuro-oncology, equally efficacious, less neurotoxic therapies are also required, even if cure remains elusive.

High-Dose Chemotherapy for Recurrent Oligodendroglioma: Rationale and Experience

Oligodendrogliomas are sensitive to nitrosourea-based chemotherapy. They also respond to other alkylating agents and regimens, including melphalan (8), thiotepa (9), cisplatin/etoposide (31), dacarbazine and temozolomide (4,22). Because there is comparatively little cross-resistance between alkylating agents (perhaps as a result of different DNA repair mechanisms) and because oligodendrogliomas respond to but are seldom cured by standard doses of conventional chemotherapies, cytoreduction by surgery and standard chemotherapy followed by high-dose chemotherapy and autologous bone marrow or peripheral stem cell reconstitution seemed an attractive theoretical strategy for improving the control of aggressive oligodendrogliomas that had recurred following radiotherapy. In our initial evaluation of this strategy we selected for high-dose treatment patients with demonstrably chemosensitive tumors and chose a high-dose agent that crossed the blood-brain barrier. We believed it was critical to choose a drug for high-dose consolidation therapy that would gain access to microscopic tumor “hiding” behind an intact or reconstituted blood-brain barrier. The alkylating agent, thiotepa, which readily crosses the blood-brain barrier attaining high drug levels in brain tissue and cerebrospinal fluid (32,33), seemed an attractive agent for this purpose.

Accordingly, our group (**Oligodendroglioma Study Group**) conducted a trial of intensive chemotherapy with stem cell rescue for patients with recurrent, previously irradiated pure or mixed aggressive oligodendrogliomas (23). Recurrent tumors were treated with either intensive PCV or cisplatin plus etoposide and responders received

high-dose thiotepa (300 mg/m^2 daily x 3). This study suggested the potential for long-term disease control in selected patients (those whose tumors were chemotherapy-naïve at recurrence and who had high performance status), but in general this population of patients, all of whom had had previous brain irradiation, were intolerant of such therapy. Many patients developed profound anorexia or severe encephalopathy, both of which were permanent in some instances, and the duration of tumor control was disappointing for most patients (23). As such, we have abandoned this treatment approach for patients with recurrent, previously irradiated pure or mixed anaplastic oligodendrogliomas.

High-Dose Therapy for Newly Diagnosed Oligodendroglioma: Rationale and Experience

Ordinarily, one would establish that high-dose chemotherapy with stem cell rescue is safe and effective for recurrent disease before using this approach in newly diagnosed cases in an attempt to postpone a standard therapy like RT. However, as Santos et al point out, aggressive chemotherapy with stem cell support is likely to be most effective at an early stage when the tumor burden is small and drug resistance at a minimum (30). There are several reasons to consider dose intensive chemotherapy in patients with newly diagnosed pure and mixed anaplastic oligodendrogliomas. First, although radiotherapy is effective, many patients whose tumors are successfully controlled eventually develop disabling neurological toxicities due to treatment. And second, if oligodendroglial neoplasms behave like other cancers they will be most drug-sensitive at initial diagnosis. It must also be emphasized that radiotherapy is seldom curative for these tumors. The median duration of survival following such treatment for patients with grade B, C and D tumors is 3-4 years (17,18). Patients with longer than average survival develop toxicities of radiotherapy while still being at risk for recurrence, while those who are cured are seldom capable of independent living (34,35). These issues and Fine's comment that "anaplastic oligodendrogliomas are not only one of the most chemosensitive primary brain tumors, but also one of the most chemosensitive solid tumors" (36), prompted the **Oligodendroglioma Study Group** to explore the feasibility of dose intensive chemotherapy with stem cell support as initial treatment for this type of malignant glioma.

We have now completed an initial evaluation of dose-intensive chemotherapy for patients with newly diagnosed anaplastic oligodendrogliomas. Our findings have been submitted for publication (24). Following central pathology review, consenting patients received induction I-PCV chemotherapy (3 or 4 cycles) followed by high-dose thiotepa (300 mg/m2 daily x 3). Radiation therapy was withheld. Sixty-nine patients with a median age of 42 years (range 18-67) and a median Karnofsky performance score of 90 (range 70-100) participated in the trial. Only those patients with demonstrably chemosensitive enhancing tumors or those free of enhancing disease after surgery and I-PCV induction chemotherapy were eligible to receive high-dose thiotepa. Thirty-eight patients received consolidation therapy with thiotepa. Their estimated median progression-free survival time is 69 months; the median overall survival time has not been reached in this cohort. Eleven patients who were treated with intensive-PCV and

high-dose thiotepa have relapsed. Neither histology (oligodendroglioma *versus* oligoastrocytoma) nor prior history of low-grade glioma was associated with duration of disease control; however, the presence of a bulky non-enhancing tumor at the time of high-dose consolidation chemotherapy conferred an increased risk of relapse ($p<0.05$). The transplant regimen was well tolerated. The median hospital stay was 20 days (range 7-43) and the median time to neutrophil and platelet engraftment was ten days. No significant treatment-related neurotoxicity was observed. Thirty-one patients who began I-PCV did not complete protocol therapy because of stable or progressive disease during induction therapy (n=21), excessive toxicity during I-PCV (n=4), refusal of further therapy (n=2), inability to obtain insurance coverage for high-dose therapy (n=2) and other reasons (n=2). The results of this study suggest that high-dose therapy is feasible and safe for selected patients with newly diagnosed pure and mixed anaplastic oligodendrogliomas and is associated that prolonged tumor control occurs in many such patients. Molecular characterization of the cases in this trial was not undertaken, and consequently, the outcomes of patients cannot be interpreted in this regard. Molecular analysis of tumor tissue will be incorporated into this trial, however.

Given the results of this initial trial we have now designed a new trial with the intent of improving disease control in those patients who complete the planned regimen. One of the major concerns with the above trial was that the transplant regimen using single agent thiotepa was inadequate. Therefore, in this trial we will plan to use a conditioning regimen of busulfan and thiotepa. Busulfan is an alkylating agent which freely crosses the blood brain barrier, achieving high drug levels in brain tissue and cerebrospinal fluid (37). The combination of busulfan and thiotepa has been used in the treatment of pediatric brain tumors (39,40,41). Intravenous busulfan can safely be given as a single daily dose (42) and its combination with this dose of thiotepa has been used in the treatment of brain lymphoma (43). A major criticism of our initial trial was the lack of correlative molecular markers and we will collect this information prospectively in this new trial (see below).

Companion Molecular Analysis

The allelic loss of chromosomal arm 1p is increasingly recognized as a marker of chemotherapeutic response and improved survival in patients with anaplastic oligodendroglioma. However, 1p loss does not identify all chemosensitive anaplastic oligodendrogliomas and some patients with 1p loss do not demonstrate durable responses to chemotherapy. Further studies of additional molecular markers suggest that there are at least 4 distinct molecular subsets of anaplastic oligodendroglioma with distinct clinical outcomes (38). The following molecular markers have been identified as having a significant impact on patient survival and response to chemotherapy: 19q LOH, 10q LOH, *PTEN* alteration, CDKN2A deletion, EGFR amplification and TP53 mutation (41).

One weakness of these initial studies reporting the clinical implications of molecular analysis is that they rely on available retrospective data sets of heterogeneous patients.

Therefore it is currently difficult for us to make clinical recommendations on the basis of molecular tumor analysis. One goal in this study is to prospectively collect tissue for molecular analysis and correlate the results of these molecular studies with the clinical outcome of patients. This analysis will be done in the laboratory of David N. Louis, MD at the Massachusetts General Hospital and will include studies of 1p, 19q, 10q, *PTEN*, CDKN2A, EGFR and p53. Tissue will be storedin an anonymized fashion; any additional testing would require IRB approval.

Every effort will be made to include all patients in this part of the study. However, if for any reason a patient does not wish to separately consent to this portion of the study or if tumor tissue is not readily available, this will not exclude a patient from participating in the therapeutic portion of the trial.

4.0 STUDY DESIGN

This is a single arm multi-institution phase II study of temozolomide followed by high dose busulfan and thiotepa for patients with newly diagnosed anaplastic oligodendroglioma/oligoastrocytoma.

All patients will receive an induction chemotherapy with standard dose temozolomide. Patients whose tumors have been completely resected and remain tumor-free after induction chemotherapy and those with residual disease after surgery who have a complete (CR) or partial response (PR) are eligible to receive high-dose busulfan and thiotepa. Subsequent to high-dose treatment, hematopoietic reconstitution is achieved using peripheral blood stem cells or bone marrow. Those who do not respond to or progress on induction chemotherapy are ineligible to receive busulfan and thiotepa and will be removed from the trial. Patients who are removed from the study because of poor response or progression should be considered for immediate radiotherapy because they have demonstrably chemoresistant anaplastic oligodendroglial neoplasms.

Consenting patients completing the pre-treatment evaluation and successful peripheral blood stem cell harvest will be treated as outlined in the study schema. High-dose therapy will be administered only if the tumor has not recurred during the induction phase. Patients whose tumors have been partially resected or biopsied will receive temozolomide induction chemotherapy when the residual tumor is substantially or completely contrast-enhancing. Response will be assessed after three cycles of temozolomide. Those patients who have achieved a complete response (CR) or a partial response (PR) will receive three additional cycles of temozolomide followed by high-dose busulfan and thiotepa. Patients who are stable but have not yet achieved PR status will receive three additional cycles of temozolomide followed by re-imaging. Those who then have a CR or PR will be eligible to proceed to high-dose therapy while all others will be removed from the trial and irradiated or treated in some other fashion.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Temozolomide is an oral cytotoxic alkylating agent which undergoes spontaneous conversion to MTIC, the active metabolite of dacarbazine, at physiologic pH. It has demonstrated activity against breast, ovarian, non-small cell lung, renal cell, colon, prostate and pancreatic cancer as well as melanoma and malignant glioma. Temozolomide is manufactured by Schering Plough, Inc. It is available as 5, 20, 100 and 250mg capsules. The 20mg and 100mg capsules are projected to be stable for at least 30 months when stored between 2° and 30°C in amber glass bottles. The 5mg and 250mg capsules are projected to be stable for at least 12 months under the same conditions. The drug will be made available at no cost by Schering-Plough, Inc. for this study.

Busulfan (Busulfex) is a polyfunctional-alkylating agent that interacts with nucleic acids causing interstrand cross-linking and DNA protein cross-linking. Busulfan is extensively metabolized to inactive compounds that are renally excreted. It is available as a parenteral formulation from Orphan Pharmaceuticals, Inc.

Thiotepa (Thioplex) is a cell cycle non-specific chemotherapeutic agent capable of killing cells in any phase of the cell cycle. Thiotepa forms covalent cross-links with DNA or DNA protein complexes, resulting in cytotoxic, mutagenic and carcinogenic effects. It is administered parenterally and is commercially available from Immunex Inc. in 15mg vials.

6.0 CRITERIA FOR PATIENT/SUBJECT ELIGIBILITY

Any patient with a newly diagnosed anaplastic oligodendroglioma or mixed anaplastic oligoastrocytoma who meets all of the specific eligibility criteria listed below may be enrolled on this study.

6.1 PATIENT/SUBJECT INCLUSION CRITERIA

- Pathologic evidence of an **anaplastic oligodendroglioma**. For this study, World Health Organization classification criteria will be used. Central pathology review must take place prior to high-dose therapy but need not occur prior to study entry and induction therapy.

- Pathologic evidence of an **anaplastic mixed glioma (i.e. oligoastrocytoma).** Again, histopathologic diagnosis will be made using World Health Organization classification criteria. To qualify as a mixed tumor there must be a minimum of 25% oligodendroglial element. Central pathology review must take place prior to high-dose therapy but need not occur in advance of enrollment or induction therapy.

- The diagnostic surgical procedure may have been a complete resection, partial resection, or biopsy.

- Karnofsky performance status $\geq$ 60.
- Granulocyte count $\geq$ 1.5 X 10^9/L.
- Platelet count $\geq$ 100 X 10^9/L
- SGOT $\leq$ 2X upper limit of normal.
- Serum creatinine $\leq$ 1.5X upper limit of normal
- Bilirubin $\leq$ 1.5X upper limit of normal
- All patients must sign written informed consent.

6.2 PATIENT/SUBJECT EXCLUSION CRITERIA

- Systemic or leptomeningeal metastases (excluding contiguous leptomeninges)
- Prior cranial radiotherapy or systemic chemotherapy
- Other concurrent malignancy (with the exception of cervical carcinoma in situ or basal cell carcinoma of the skin) or serious illness if this would interfere with the prescribed treatment
- Pregnant or lactating women
- Refusal to use effective contraception

7.0 RECRUITMENT PLAN

Patients will be recruited to this study from either the outpatient clinic or inpatient hospital setting. All patients will be seen by a Neuro-Oncology attending at one of the participating institutions. Every effort will be made to encourage eligible women and minorities to participate. All patients will be required to sign a written informed consent prior to being registered on this protocol. Every effort will be made to answer questions raised by the patient and their family or advocate regarding the protocol and alternative therapies prior to asking a patient to sign the consent form.

Patients will be recruited from these sites:

Site	Expected Accrual
Memorial Sloan-Kettering Cancer Center	46
NorthShore University HealthSystem	6
Northwestern Memorial Hospital	8

Three patients were recruited from the University of Calgary. The site is now closed.

8.0 PRETREATMENT EVALUATION

8.1 Pretreatment Requirements

The following studies are required within the two weeks prior to starting induction chemotherapy:

- Complete history and physical examination including neurologic exam and MMSE .
- Height and weight
- CBC including: WBC differential and platelet count.
- Urinalysis
- Biochemistry panel including BUN, creatinine, SGPT, SGOT, LDH, alkaline phosphatase, bilirubin, total protein, serum albumin, glucose, electrolytes, calcium, magnesium and uric acid
- Contrast enhanced MRI of the brain (in those patients where an MRI scan is medically contraindicated or unavailable a contrast enhanced CT scan of the brain may be substituted and should then be the preferred imaging study obtained for the remainder of assessments.)
- Serology: Hepatitis B sAb, Hepatitis B sAg, Hepatitis C Ab profile, and HIV I/II Ab

8.2 Central Pathology Review/Tissue for companion molecular analysis

Ideally blood and tumor tissue should be procured from all patients who have consented to the companion molecular analysis portion of the study prior to initiation of therapy. If this is not possible for whatever reason it is acceptable to collect these samples at a later time point.

The following are required. Please send all three items together as one shipment:

1. 10 unstained 5-to-8 micron-thick sections of representative tumor, preferably without extensive necrosis, inflammation or brain infiltration.

2. Surgical pathology report accompanying above slides.

3. Copy of signed consent form.

These items should be sent to the attention of:

David Louis, MD
Molecular Pathology Laboratory, CNY7 Massachusetts General Hospital
East 149 Thirteenth St.
Charlestown, MA 02129
617-726-5690

9.0 TREATMENT/INTERVENTION PLAN

9.1 Induction chemotherapy:

DRUG	DOSE	ROUTE	SCHEDULE
Temozolomide	200mg/m^2	PO	Days 1-5 recycled every 28 days

9.2 Dose modifications

Doses will be modified for hematologic and other toxicities Toxicities will be graded using the NCI common toxicity criteria (version 3.0)

9.2.1 Hematologic Toxicity - ordinarily there will be no dose reductions for low nadir blood counts during induction chemotherapy, but each cycle's start date will be delayed for low treatment day counts as outlined below.

TREATMENT DAY COUNTS

Granulocytes (x 10^9/L)		Platelets (x 10^9/L)	Instructions
1.5	and	100	begin next cycle
< 1.5	or	< 100	delay treatment until recovery

For centers or patients without access to G-CSF, or at the discretion of the investigator, temozolomide may be reduced to 150mg/m^2 for hematologic toxicity as follows:

NADIR COUNTS (Note: CBC pre-treatment and weekly thereafter)

Granulocytes(x 10^9/L)		**Platelets (x 10^9/L)**	**% Dose <u>next</u> cycle**
0.5	and	50	no change
< 0.5	or	< 50	decreased by 25%

9.3 <u>High dose chemotherapy with autologous stem cell support:</u> Busulfan and Thiotepa

The high-dose chemotherapy program will include busulfan and thiotepa administered as follows:

Day minus -8 thiotepa 250 mg/m^2 intravenously

Day minus -7 thiotepa 250 mg/m^2 intravenously

Day minus -6 thiotepa 250 mg/m^2 intravenously

Day minus -5 busulfan 3.2 mg/kg intravenously over two hours

Day minus -4 busulfan 3.2 mg/kg intravenously over two hours

Day minus -3 busulfan 3.2 mg/kg intravenously over two hours

Day minus -2 rest

Day minus -1 rest

Day 0 peripheral blood stem cell or bone marrow reinfusion

Agent	Total Dose	Route	Days
Thiotepa	750 mg/m^2	intravenous	-8, -7, -6
Busulfan	9.6 mg/kg	intravenous	-5, -4, -3

[NOTE: When patient weight exceeds the maximum *large frame* value from the Metropolitan Life table, doses of chemotherapy will be based on ideal body weight, not actual weight (i.e. the maximum large frame weight from said table).]

Stem cell reinfusion occurs on day 0.

All patients should be on prophylactic anticonvulsants prior to the administration of Busulfan. The general recommendation in patients not already on an anticonvulsant is

to use a benzodiazepine (clonazepam 2mg/day or diazepam 10mg/day) starting the first day of buslfan administration and continuing until the day after the last dose of buslfan.

To ensure a urine output ≥100 ml/hr patients will receive normal saline at 200 ml/m^2/hr x 6 hours prior to commencing high-dose chemotherapy with busulfan and thiotepa.

Normal saline plus 20 (milliequivalents) of KCL/l will be infused intravenously between doses of busulfan and thiotepa and during the rest phase prior to stem cell reinfusion. Subsequently, intravenous fluid requirements will be dictated by oral intake and other factors.

Fluid intake and output will be continuously measured. If there is a lag in urine output greater than 800 ml/12 hours, furosemide or an equivalent diuretic should be administered intravenously (± low dose dopamine).

Stem cells will be re-infused in accordance with institutional standard procedures.

All antiemetic prophylaxis and post transplant care will be done according to standard institutional procedures.

9.4 Peripheral Blood Stem Cell Cytophoresis

The peripheral blood stem cell (PBSC) harvest procedure will be performed prior to the start of induction chemotherapy. At the discretion of the treating physician harvest may be delayed until response to induction treatment has been demonstrated. (Note: delayed harvest may compromise a successful harvest or increase the likelihood of engraftment failure.)

PBSCs will be mobilized using G-CSF 10-16ug/kg/day subcutaneously for up to 7 days. Cytophoresis will start on day 4 and repeated daily up to day 7 until a target yield of > 5 X 10^6 CD34+ cells have been collected; the minimum acceptable total yield is 2 X 10^6 CD 34+ cells/kg. If the target yield is not met, a second peripheral mobilization may be attempted at the discretion of the investigator. Bone marrow harvest may be considered if fewer than 2 X 10^6 CD34+ cells are collected then bone marrow harvest is required. The minimum acceptable yield for those patients undergoing bone marrow harvest is 1.5 X 10^8 mononuclear cells/kg/

Some patients will have inadequate peripheral venous access and require placement of a catheter suitable for hemodialysis. All patients will have a 13.5 Fr Davol double-lumen catheter (or similar catheter) placed prior to PBSC leukophoresis. If local circumstances dictate bone marrow rather than peripheral blood stem cells may be harvested for reinfusion after high-dose busulfan and thiotepa.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

The following tests are required prior to each cycle of induction chemotherapy:

- Complete history and physical examination including neurologic exam.
- Weight
- CBC including: WBC differential, and platelet count.
- Biochemistry including: BUN, creatinine, SGPT, SGOT, LDH, alkaline phosphatase, bilirubin, total protein, serum albumin, glucose, electrolytes, calcium, magnesium and uric acid

The following are required prior to high dose busulfan and thiotepa:

- Complete history and physical examination including neurologic exam.
- Weight
- CBC including: WBC differential, and platelet count.
- Biochemistry including: BUN, creatinine, SGPT, SGOT, LDH, alkaline phosphatase, bilirubin, total protein, serum albumin, glucose, electrolytes, calcium, magnesium and uric acid
- Urinalysis
- PT/PTT and INR.
- Chest X ray
- Pulmonary function tests
- EKG, and echocardiogram or MUGA.
- Dental evaluation
- Insertion of a double lumen Hickman (or comparable) venous access.
- Adequate peripheral blood stem cell (or bone marrow) harvest.
- Therapeutic anticonvulsant level or prophylactic anticonvulsants prior to administration of busulfan.

- Central pathology review confirming eligibility.

Post treatment evaluation:

- Follow up neurologic status will be assessed approximately every 3 months after completion of the planned treatment regimen for at least 2 years. Each exam should include a KPS score and MMSE. Follow up beyond 2 years is at the discretion of the treating physician but at a minimum follow up exams and MRIs should be obtained at least twice a year for 5 years and then at least annually.

- MRI scan of the brain will be obtained approximately every 3 months in conjunction with neurologic evaluation.

- Patients who are removed from this study without completing the planned therapy should be followed in a similar fashion whenever possible. If a patient is not available for follow up then an effort should be made to contact the patient or the family by telephone.

11.0 TOXICITIES/SIDE EFFECTS

Toxicity for all phases of the protocol will be recorded using the NCI CTC version 3.0.

11.1 Temozolomide

11.1A Cardiovascular Effects

Cardiovascular finding
Peripheral edema is described with the administration of temozolomide.

Peripheral edema
Peripheral edema was reported in 11% of patients receiving temozolomide in clinical trials (Prod Info TEMODAR(R) CAPSULES, 2005).

11.1B Dermatologic Effects

Alopecia
Alopecia (grade 1 or 2) occurred in 9% of malignant melanoma patients receiving the 5-day regimen of temozolomide in one trial.

Dermatological finding
Alopecia, rash and pruritus are described with the administration of temozolomide.

Rash
Skin rashes may infrequently occur following therapeutic administration of temozolomide (Prod Info TEMODAR(R) CAPSULES, 2005;). Skin rash with PRURITUS has been described occasionally during oral therapy with temozolomide.

11.1C Endocrine/Metabolic Effects

Disease of ovary
Summary - CASE REPORT - A 34-year-old female, with a past history of amenorrhea for 2.5 years, developed severe hot flashes and ovarian suppression approximately 30 weeks after initiating temozolomide therapy. The patient's hormone levels were normal at the beginning of treatment with temozolomide (Brock et al, 1998a).

Electrolytes abnormal
Hypercalcemia is described with the administration of temozolomide.

Endocrine finding
In a single case study, ovarian suppression is described with the administration of temozolomide.

Hypercalcemia
Hypercalcemia has been reported in approximately 1% of patients with the 5-day regimen of temozolomide.

11.1D Gastrointestinal Effects

Constipation
Constipation, (up to 0%), is described with the administration of temozolomide. Constipation has been reported in several patients after beginning temozolomide therapy, and was usually associated with concomitant opiate therapy (Prod Info TEMODAR(R) CAPSULES, 2005).

Incidence: 33%

Gastrointestinal hemorrhage
Gastrointestinal bleeding has occurred with therapeutic use of temozolomide. Gastrointestinal bleeding, presumably related to thrombocytopenia, has been reported rarely with temozolomide therapy (Brock et al, 1998a; Dhodapkar et al, 1997; Woll et al, 1995).

Gastrointestinal tract finding

1) Nausea and vomiting may occur in up to 75% of patients. Mucositis, diarrhea, constipation, anorexia and stomatitis are described with the administration of temozolomide.

2) DIARRHEA and DYSPHAGIA have been reported in up to 16% of patients with temozolomide therapy (Prod Info TEMODAR(R) CAPSULES, 2005).

Inflammatory disease of mucous membrane
Less frequent adverse effects have included mucositis (up to 20%). STOMATITIS has occurred with therapeutic use of temozolomide (Prod Info TEMODAR(R) CAPSULES, 2005).

Loss of appetite
Anorexia (up to 40%) is described with the administration of temozolomide. Anorexia was reported in 7 of 55 patients following therapeutic administration of temozolomide during a phase II clinical trial. (Prod Info TEMODAR(R) CAPSULES, 2005).

Nausea and vomiting
Nausea and vomiting occur in up to 75% of patients with temozolomide therapy, but is not usually severe (mostly grade 1 or 2) (Prod Info TEMODAR(R) CAPSULES, 2005). These symptoms have often been limited to day 1 of the first cycle of temozolomide. Standard antiemetics have been effective in most patients.

Incidence: 42% to 53%

LITERATURE REPORTS:
a) Nausea and vomiting occurred in 53% and 42% of patients, respectively, who received temozolomide therapeutically during a clinical efficacy trial. In a trial of 153 patients treated with a 5-day schedule of temozolomide; grade 3/4 nausea and vomiting occurred in 10% and 6%, respectively (Prod Info TEMODAR(R) CAPSULES, 2005).
b) Moderate to severe nausea and vomiting frequently occurs following therapeutic temozolomide administration and can be controlled with anti-emetics**)** Grade 3 nausea and vomiting occurred in 21% and 23%, respectively, in a trial involving 103 patients; grade 4 nausea was not detected, whereas grade 4 vomiting occurred in one patient (less than 1%).

11.1E Hematologic Effects

Anemia
Anemia has been reported following therapeutic administration of temozolomide, and may be secondary to gastrointestinal bleeding. Anemia frequently coexists with neutropenia and thrombocytopenia, although it is generally less frequent and severe.

Hematology finding
1) Myelosuppression, including anemia, thrombocytopenia and leukopenia are described with the administration of temozolomide.
2) Rare cases of myelodysplastic syndrome and secondary malignancies have been observed.

Myelodysplastic syndrome (clinical)

Very rare cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukemia have been observed (Prod Info TEMODAR(R) CAPSULES, 2005).

Incidence: Very rare

Myelosuppression
Bone marrow depression, including NEUTROPENIA, LYMPHOPENIA, and THROMBOCYTOPENIA, occurs frequently with high-dose therapeutic administration of temozolomide and is dose-limiting. Myelosuppression is predictable, usually occurring within the first few treatment cycles. Women and elderly patients have shown an increased risk of myelosuppression in clinical trials of temozolomide (Prod Info TEMODAR(R) CAPSULES, 2005).

LITERATURE REPORTS:
a) In clinical trials, elderly patients and women appear to be at greater risk for developing myelosuppression. The platelet nadir occurs at a mean of 26 days and the granulocyte nadir occurs at a mean of 28 days (Prod Info TEMODAR(R) CAPSULES, 2005).

b) Neutropenia and thrombocytopenia occurred following single- dose ingestions up to 1000 milligrams/square meter (mg/m(2)) of temozolomide (Prod Info TEMODAR(R) CAPSULES, 2005).

c) Thrombocytopenia and leukopenia reach grade 2 or higher in up to 40% of patients on temozolomide therapy. Leukocyte/platelet nadirs usually occur in 3 weeks (about day 22) with a 5-day schedule, although leukocyte nadirs may be seen slightly later (day 29). Dose-limiting thrombocytopenia has persisted for 7 to 42 days, whereas recovery from leukopenia may be quicker. Bleeding has been infrequent with temozolomide therapy.

d) Myelosuppression has been mild or absent with doses of 750 milligrams/square meter (mg/m(2)) over 5 days in most patients. Hematologic data from continuous dosing studies (e.g., for 6 weeks) are unavailable.

e) In one large trial involving adult patients with malignant glioma, the predominant effect was lymphopenia, which reached grade 3 and grade 4 in 41% and 15%, respectively, receiving a 5-day schedule of temozolomide; however, this may represent a peculiarity of the Clinical Toxicity Criteria (CTC) rating scale. Corresponding incidences of neutropenia were 2% and 4%. The incidence of grade 3 or 4 thrombocytopenia was 11%.

11.1F Hepatic Effects

Liver finding
Mild TRANSAMINASE ELEVATIONS (up to 40% of patients) and HYPERBILIRUBINEMIA (up to 19%) have been reported; increases in alkaline phosphatase have also occurred in some patients. Grade 4 increases in bilirubin have been seen rarely; There are no cases of overt hepatotoxicity.

Elevated hepatic enzymes are described with the administration of temozolomide.

11.1G Neurologic Effects

Ataxia
During a phase I clinical trial of temozolomide in pediatric patients with advanced cancer, 14% of patients (n=16) reported mild to moderate ataxia.

Headache
Headache is among the most commonly reported adverse effects with the use of temozolomide in clinical trials. Headache has been reported in 41% of patients, with 6% of those patients experiencing a grade 3/4 headache, following temozolomide administration during a clinical efficacy trial (Prod Info TEMODAR(R) CAPSULES, 2005).

Incidence: 41%

Neurological finding
Central nervous system effects (CNS EFFECTS) occurring in greater than 5% of patients in clinical trials include ANXIETY, DEPRESSION, INSOMNIA, CONVULSIONS, PARESIS or HEMIPARESIS, DIZZINESS, coordination or GAIT DISTURBANCE, AMNESIA, PARESTHESIA, SOMNOLENCE and ATAXIA. Causality is uncertain in many patients due to the underlying disease or other factors (eg, glioma, other drug therapy) (Prod Info TEMODAR(R) CAPSULES, 2005;). TRANSIENT NEUROLOGIC DETERIORATION was estimated to have occurred in approximately 2% of temozolomide-treated patients (Rosenthal et al, 2002).

Headache, fatigue, convulsions, paresis, hemiparesis, somnolence, dizziness, gait disturbance, amnesia, paresthesia, ataxia, and transient neurologic deterioration are described with the administration of temozolomide.

LITERATURE REPORTS:
Eight cases of transient, profound DETERIORATION OF NEUROLOGIC FUNCTION were reported after temozolomide therapy; in all cases, the compromised neurologic status was fully reversed. The 8 patients had recurrent high-grade gliomas and had undergone prior resection and whole-brain irradiation. Dosing of temozolomide was 150

to 200 mg/m(2)/day for 5 consecutive days every month. Eastern Cooperative Group Performance Status declined to grade 4 (bed-bound) during the period of neurologic compromise (pre-decline grades had been 1 or 2, with 1 patient at grade 3). Symptoms included WEAKNESS, HEADACHE, DYSPHASIA, CONFUSION, and OBTUNDATION; 2 had SEIZURES, though previously well controlled. Duration of deterioration ranged from 5 to 10 days, followed by full recovery, and none had a similar response to subsequent cycles of chemotherapy. During the deterioration, patients received supportive care and increases in dexamethasone. None of 7 who had scans showed evidence of tumor progression or intra-tumor hemorrhage; 3 exhibited modest tumor-related edema. The authors noted that these occurrences did not necessarily confer a poor prognosis and might be considered a temozolomide-induced TUMOR FLARE.

Seizure
Seizures were reported in 23% of patients, with anaplastic astrocytoma, who received temozolomide during a clinical trials (n=153). It is unclear whether the seizures were drug-related or as a consequence of the patients' underlying disease (Prod Info TEMODAR(R) CAPSULES, 2005).

Incidence: 23%

11.1H Psychiatric Effects

Psychiatric sign or symptom
Anxiety, depression, and insomnia are described with the administration of temozolomide.

11.1I Renal Effects

Urinary tract infectious disease
Urinary tract infection and INCREASED URINARY FREQUENCY were reported in 8% and 6%, respectively, of patients receiving temozolomide in clinical trials (Prod Info TEMODAR(R) CAPSULES, 2005).

Urogenital finding
Urinary tract infection and increased urinary frequency have been reported. Testicular function may be affected with the administration of temozolomide.

11.1J Reproductive Effects

Testicular finding, Function
Summary - Testicular function may be affected by temozolomide therapy. Male patients should use effective methods of contraception while undergoing treatment (Prod Info TEMODAR(R) CAPSULES, 2005).

11.1K Respiratory Effects

Respiratory finding
Upper respiratory tract infections, including pharyngitis, sinusitis, and rare cases of Pneumocystis carinii pneumonia (PCP) have been reported with the use of temozolomide (Prod Info TEMODAR(R) CAPSULES, 2005).

Upper respiratory infection
Summary:

Upper respiratory tract infection, PHARYNGITIS, or SINUSITIS were reported in greater than 5% of patients receiving temozolomide in clinical trials (Prod Info TEMODAR(R) CAPSULES, 2005).

Opportunistic infections, including Pneumocystis carinii PNEUMONIA (PCP) have been reported rarely with the use of temozolomide (Prod Info TEMODAR(R) CAPSULES, 2005).

11.1L Other

Fatigue
Summary - Fatigue is among the most commonly reported adverse effect with the use of temozolomide in clinical trials, and is clearly drug-related. Fatigue with temozolomide therapy may be moderate to severe (Prod Info TEMODAR(R) CAPSULES, 2005).

Incidence: 34%

Infectious disease
Opportunistic infections (eg, Pneumocystis carinii pneumonia (PCP)) have been reported rarely with the use of temozolomide (Prod Info TEMODAR(R) CAPSULES, 2005).

11.1M Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy
- **1)** U.S. Food and Drug Administration's Pregnancy Category: Category D (Prod Info Temodar(R) temozolomide, 1999) (All Trimesters)
  - **a)** There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
    See Drug Consult reference: PREGNANCY RISK CATEGORIES
- **2)** Crosses Placenta: Unknown
- **3)** Clinical Management

a) Adequate, well-controlled studies have not been conducted in humans. Due to potential for adverse effects in the fetus, women of childbearing potential should be advised against becoming pregnant while taking temozolomide (Prod Info Temodar(R) temozolomide, 1999), and in the 6 months following the end of treatment (Prod Info Temodar(R), 1999).

4) Literature Reports

a) Temozolomide administration to rats (75 mg/m(2)/day for 5 days) and rabbits (150 mg/m(2)/day for 5 days), at 3/8 and 3/4 the maximum recommended human dose, respectively, resulted in the development of malformations of the external organs, soft tissues, and skeleton (Prod Info Temodar(R) temozolomide, 1999). Temozolomide doses of 150 mg/m(2)/day in rats and rabbits have resulted in embryolethality as indicated by increased resorptions (Prod Info Temodar(R) Temozolomide, 1999).

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus are inconclusive or are inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

2) Clinical Management

a) No reports describing the use of temozolomide during human lactation are available and the effects on the nursing infant from exposure to the drug in milk are unknown. It is unknown whether temozolomide is excreted in human milk; however, breastfeeding is not recommended during treatment due to potential risk to the infant (Prod Info Temodar(R), 1999a).

3) Literature Reports

a) No reports describing the use of temozolomide during human lactation or measuring the amount, if any, of the drug excreted into milk have been located

11.2 Busulfan (Busulfex)

Moderate nausea and vomiting, diarrhea, dose limiting mucositis, and severe myelosuppression with high dose therapy.

Severe or irreversible effects: Veno-occlusive disease (VOD) of the liver, seizures, confusion, hyperpigmentation of the skin, interstitial pulmonary fibrosis (“busulfan lung”), increased incidence of secondary malignancies after prolonged administration. Because of the risk of seizures, prophylactic anti-convulsants are recommended.

11.3 Thiotepa (Thioplex)

Hematopoietic Effects:

Bone marrow depression is dose limiting and requires stem cell support at doses >60 mg/m^2. Neutropenia and thrombocytopenia occur within 7 to 10 days.

Other:

Nausea and vomiting are common but generally mild. Mucositis, esophagitis and enterocolitis are also common side effects.

Central nervous system toxicity characterized by inappropriate behavior, forgetfulness, confusion and somnolence occurs in ~5% patients given 900 mg/m^2.

Dermatological toxicity consisting of an acute erythrodermia with desquamation and peeling of skin of soles and palms is uniformly seen. General darkening of the skin may occur (resembling a mild suntan) which can persist for several months.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUT COME ASSESSMENT

All patients will have their tumor measurements recorded at baseline and at the time of each MRI scan. Lesions must be measured in two dimensions. The dose of gadolinium must be held constant from scan to scan. Every attempt should be made to minimize changes in dexamethasone use during the study so that changes in MRI scans more accurately reflect disease status.

Complete response (CR) is the total disappearance of all measurable radiographic evidence of lesions on MRI or CT. The patient also must have no clinical neurologic deterioration or decrease in performance status attributable to brain tumor. The patient must be off dexamethasone.

Partial response (PR) is at least a 50% reduction in the size of all measurable lesions as measured by the sum of the products of the greatest length and maximum width of all measurable lesions. No lesion may progress and no new lesion may appear. The dose of dexamethasone must be the same or lower than at baseline.

Stable disease exists when a patient fails to qualify for either a response or progressive disease. The dose of dexamethasone must be the same or lower than at baseline.

Progressive disease is an increase of 25% or more in the size of the enhancing or residual non-enhancing lesion as measured by the sum of the products of the greatest length and maximum width, or the appearance of any new lesion(s).

Residual non-enhancing tumor will be assessed on the basis of T2 weighted or FLAIR abnormality. As these lesions are often more difficult to measure precisely they will be assessed at baseline as present or absent. On follow up scans they will be graded as:

Worse: > 25% increase in overall size or the development of new non-enhancing tumor.

Stable: less than a 25% change from baseline.

Improved: >25% decrease in overall size from baseline.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at any time the patient develops progressive disease he/she will be taken off study and referred for alternative therapy.

If at any time the patient develops unacceptable toxicity he/she will be removed from study.

If at any time the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (i.e., a change in diagnosis), the patient will be removed from the study.

Any patient who fails to achieve a CR or PR at the completion of induction chemotherapy will be removed from the study. Patients with an initial complete resection must remain NED.

The patient can be removed from the study at his/her request.

14.0 BIOSTATISTICS

14.1 This is a multicenter phase II study to evaluate the safety and efficacy of temozolomide followed by high-dose busulfan/thiotepa chemotherapy with peripheral blood progenitor cell rescue in patients with newly diagnosed anaplastic oligodendroglioma. Only those patients with a CR or PR following induction chemotherapy or have not progressed after complete resection will proceed to high-dose busulfan/thiotepa. The primary endpoint is efficacy as measured by the 2-year progression-free survival (PFS) rate of patients completing transplant. We plan to accrue 60 patients to this trial. Based on a previous high-dose therapy with stem cell rescue trial recently completed in the same patient population, it is expected that approximately 50% of these patients will be eligible for the high-dose busulfan/thiotepa chemotherapy (i.e., have achieved CR/PR after induction chemotherapy or have not progressed). Therefore, the 2-year PFS will be estimated for these patients. It will take an estimated 3 to 5 years to accrue 60 patients on this study. Enrollment is competitive among the sites and there is no assignment or limit.

14.2 Toxicities will be tabulated according to the NCI/CTC criteria. The study will be stopped early if 3 deaths attributable to treatment-related toxicity are observed in the first 15 patients to complete the planned therapy (both temozolomide and Busulfan/thiotepa). If $\leq$ 2 treatment-related deaths are observed in these first 15 patients, then an additional 15 patients will be accrued. However, if at any time during this second accrual phase the total number of treatment-related deaths (including those observed in the first 15 patients) reaches 4, then the study will be stopped. The probability of stopping the trial early is .07 if the true risk of treatment-related death is 5% and is .38 if the true risk of treatment related-death is 20%.

14.3 The third objective of this study is to obtain preliminary prospective information regarding the relationship between various molecular markers (e.g., loss of heterozygosity of 1p, 10p, and 19q, p53, PTEN, CDKN2A, and EGFR). Statistical analysis of these data will depend on how many patients have simple tumor tissue available for this molecular analysis, and may just be descriptive.

14.4 All patients will be included in the analysis of toxicity.

15.0 RESEARCH PARTICIPANT REGISTRATION

15.1 RESEARCH PARTICIPANT REGISTRATION

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.1.1 FOR PARTICIPATING CENTERS:

Central registration for this study will take place at Memorial Sloan Kettering Cancer Center.

To complete registration and enroll a patient from another institution, the study staff at that site must contact the designated staff at MSKCC to notify him/her of the patient registration. The site staff then needs to fax registration/eligibility documents to the **Neurology department** at MSKCC fax # **(646) 227-2461.**

The following documents must be sent for each enrollment within 24 hours **of the informed consent form being signed:**

- The completed or partially completed MSKCC eligibility checklist

- The signed informed consent and signed HIPAA Authorization form (Research Authorization)
- Supporting source documentation for eligibility questions (laboratory results, pathology report, radiology reports, MD notes, physical exam sheets, medical history, prior treatment records, and EKG report).

Upon receipt, the research staff at Memorial Sloan Kettering Cancer Center will conduct an interim review of all documents. If the eligibility checklist is not complete, the patient will be registered PENDING and the site is responsible for sending a completed form within 30 days of the consent.

If the eligibility checklist is complete, participant meets all criteria, all source documentation is received, the participating site IRB has granted approval for the protocol, and the site is in good standing with MSKCC, the MSKCC research staff will send the completed registration documents to the MSKCC Protocol Participant Registration (PPR) Office to be enrolled as stated in section 15.1. The participant will be registered.

Once eligibility has been established and the participant is registered, the participant will be assigned an MSKCC Clinical Research Database (CRDB) number (protocol participant number). This number is unique to the participant and must be written on all data and correspondence for the participant. This protocol participant number will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

Data will be collected centrally at Memorial Sloan Kettering Cancer Center.

16.0.1 DATA AND SOURCE DOCUMENTATION FOR PARTICIPATING SITES

Data

Standardized Case Report Forms (CRFs) and directions for use as well as sign off requirements have been generated for this study. Blank case report forms will be sent to the study staff at each participating site for use. The participating Site PI is responsible for ensuring these forms are completed accurately, legibly and in a timely manner.

Source Documentation
Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into CRFs. Relevant source documentation to be submitted throughout the study includes:

- Baseline measures to assess pre–protocol disease status (ex. MRI, Medical History, Pathology report)
- Treatment records
- Grade 3-5 toxicities/adverse events not previously submitted with SAE Reports
- Response designation and MRI reports
- Lab results
- MD notes

16.0.2 Data and Source Documentation Submission for Participating Sites

Participating sites should fax CRFs and source documentation to MSKCC to the contact provided below. Submissions should include a cover page listing all CRFs enclosed per

	Baseline	*Cycle 1*	*Cycle 2*	*Cycle 3*	*Cycle 4*	***Cycle 5***	***Cycle 6***	***Post Induction***	***Transplant***	***Follow-up***

participant.

FAX: *(646) 227-2461* to the attention of *02-089* Research Staff

[OR]

MAILING ADDRESS:
02-089 Neurology RSA
633 3rd Ave, 12th Fl
MSKCC
New York, NY 10017

Participating sites are required to keep copies of each form that is sent via postal mail.

16.0.3 Data and Source Documentation Submission Timelines for Participating Sites

Data and source documentation to support data should be transmitted to MSKCC according to chart below:

Submission Schedule										
Source Documentation	**Within 24 hours (see section 15.1.1)**	**within 14 days of visit**							**Within 14 days of discharge**	**within 14 days of visit**
CRFs	**Within 7 days of visit**									
Required Forms										
On Study Form	**X**									
Patient Disease Form	**X**									
Central Pathology Review	**X**									
Pre-Treatment Evaluation Form I	**X**									
Co-Morbidity Form	**X**									
Concomitant Drug Form	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Physical Exam Form	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Neurological Exam Form	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**
Treatment Form		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Laboratory Form	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Lesion/EOD Form				**X**				**X**		**X**
Toxicity Form	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Serious Adverse Event Form										
Hospitalization Form									**X**	
Patient Status & Outcome Form				**X**				**X**		**X**
Leukapheresis/ Transplant Form	**X**								**X**	
Pre-Treatment Evaluation Form II								**X**		

Data and Source Submission Requirements and Timelines for Therapeutic Studies

16.0.4 Data Review and Queries for Participating Site Data

Research staff at MSKCC will review data and source documentation as it is submitted. Data will be monitored against source documentation and discrepancies will be sent as queries to the participating sites. Queries will be sent by MSKCC Research staff twice a month.

Participating sites should respond to data queries within 14 days of receipt.

16.1 QUALITY ASSURANCE

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.1.1 Quality Assurance for Participating Sites

Each site participating in the accrual of participants to this protocol will be audited by the staff of the MSKCC study team for protocol and regulatory compliance, data verification and source documentation. Audits may be accomplished in one of two ways: (1) selected participant records can be audited on-site at participating sites or (2) source documents for selected participants will be sent to MSKCC for audit. Audits will usually be determined by participant accrual numbers and rate of accrual, but can also be prompted by reported SAEs or request of MSKCC PI.

Audits will be conducted at least once shortly after initiation of participant recruitment at a site, annually during the study (or more frequently if indicated), and at the end or closeout of the trial. The number of participants audited will be determined by available time and the complexity of the protocol.

The audit will include a review of source documentation to evaluate compliance for:

- Informed consent documents and procedures
- Adherence to eligibility criteria
- Protocol defined treatment
- Required baseline, on study and follow-up protocol testing
- IRB documents (submitted amendments, annual continuing review reports, SAEs)
- Required specimen submission
- Pharmacy review, if applicable
- Case Report Form submissions to MSKCC: timelines and accuracy

A wrap-up session will be conducted at the participating site and preliminary findings will be discussed with the participating site PI and research team. The preliminary results will be sent to the MSKCC PI.

Each audit will be summarized and a final report will be sent to the PI at the audited participating site within 30 days of the audit. The report will include a summary of findings, participant by participant case review, specific recommendations on any performance and/or shortcomings and request for corrective action, when necessary. When corrective action is required, the participating site must reply within 45 days of receipt of audit report with their corrective action plan.

A copy of the audit report and corrective action plan (if applicable) submitted by the participating site must be sent to the MSKCC IRB/PB, CRQA and maintained in the department's protocol regulatory binder.

16.1.2 RESPONSE REVIEW

Since therapeutic efficacy is a stated primary objective, all sites patient's responses are subject to review by MSKCC's Therapeutic Response Review Committee (TRRC). Radiology, additional lab reports and possibly bone marrow biopsies and/or aspirates will need to be obtained from the outside sites for MSKCC TRRC review and confirmation of response assessment. These materials must be sent to MSKCC within sixty days of request to the site.

16.2 Data and Safety Monitoring

Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: *http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1*. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at:
https://one.mskcc.org/sites/pub/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH

sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

16.3 Regulatory Documentation

Prior to implementing this protocol at MSKCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC Institutional Review Board/Privacy Board (IRB/PB). Prior to implementing this protocol at the participating sites, approval for the MSKCC IRB/PB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to MSKCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, MSKCC will formally contact the site and grant permission to proceed with enrollment.

16.3.1 Amendments

Each change to the protocol document must be organized and documented by MSKCC and first approved by the MSKCC IRB/PB. Upon receipt of MSKCC IRB/PB approval, MSKCC will immediately distribute all non expedited amendments to the participating sites, for submission to their local IRBs.

Participating sites must obtain approval for all non expedited amendments from their IRB within 90 calendar days of MSKCC IRB/PB approval. If the amendment is the result of a safety issue, sites will not be permitted to continuing enrolling new participants until the participating site IRB approval has been granted.
The following documents must be provided to MSKCC for each amendment within the stated timelines:

- Participating Site IRB approval
- Participating Site IRB approved informed consent form and HIPAA authorization

16.3.2

Continuing Review Approval
The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to MSKCC within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of study activities.

Deviations and Violations

A protocol deviation on this study is defined as a request to treat a research participant who does not meet all the eligibility criteria, pretreatment evaluation, or who requires alteration in their study plan. If a deviation from this protocol is proposed for a potential or existing participant at MSKCC or a participating site, approval from the MSKCC IRB/PB is required prior to the action. Participating sites should contact the MSKCC PI who will in turn seek approval from the MSKCC IRB/PB.

A protocol violation is anything that occurs with a participant, which deviated from the protocol without prior approval from the MSKCC IRB/PB. For protocol violations that are identified after they occur, the participating site should report to MSKCC as soon as possible. The MSKCC PI will in turn report the violation to the MSKCC IRB/PB.

Participating sites should report deviations and violations to their institution's IRBs as soon as possible per that site's institutional guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations and violations should be submitted to MSKCC as received.

Other correspondence
Participating sites should submit other correspondence to their institution's IRB according to local guidelines, and submit copies of that correspondence to MSKCC.

16.3.3 Document maintenance

The MSKCC PI and the Participating Site PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

The participating sites will ensure that all participating site IRB correspondence (IRB approval letters referencing protocol version date and amendment number, IRB

approved protocol, informed consent forms, deviations, violations, and approval of continuing reviews) is maintained in the regulatory binder on site and sent to MSKCC.

A regulatory binder for each site will also be maintained at MSKCC; this binder may be paper or electronic.

After study closure, the participating site will maintain all source documents, study related documents and CRFs for *3 years.*

16.4 Noncompliance

If a participating site is noncompliant with the protocol document, accrual privileges may be suspended and/or contract payments may be withheld (if applicable), until the outstanding issues have been resolved.

17.0 PROTECTION OF HUMAN SUBJECTS

17.1 Privacy

It is the responsibility of the Research Staff to ensure that Memorial Sloan-Kettering Cancer Center has on file a written acknowledgment of receipt by the subject of the Center's Notice of Privacy Practices. If the subject has not already done so, he/she must sign such an acknowledgment before participating in this study.

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

Potential risks to human subjects include drug related toxicity, pain and discomfort associated with phlebotomy, and possible psychologic discomfort while obtaining MRI scans.

The side effects and potential toxicities of all chemotherapeutic agents are listed in section 11. All efforts will be made to avoid any complication by completely reviewing patients' symptoms and monitoring blood tests.

Periodic phlebotomy is necessary to monitor for the potential treatment related toxicities; trained phlebotomy technicians or nurses will perform all phlebotomy.

MRI scans are the accepted and best method for assessing central nervous system tumors and patients with substantial anxiety can be treated with an anxiolytic prior to the study. In those patients where an MRI is not possible for medical

reasons (e.g. pacemaker, ferromagnetic intracranial aneurysm clips) a CT scan will be substituted.

Potential benefit to society will be the establishment of an effective medical therapy, which may offer prolonged survival or improved quality of survival to other patients with this disease.

Potential benefit to society will be the enhanced productivity and decreased cost of any individual spared progressive neurologic impairment.

If an adverse medical event occurs, the patient will first contact the principal investigator or treating physician. At nights and on weekends, there is a neuro-oncology physician on call at all times. Patients may either call or come directly to the urgent care center at Memorial Hospital (or their collaborating institution) to be seen.

Costs to the patient will include the cost of the chemotherapy, MRI scans, office visits, blood tests and any hospital admission including those admissions as a consequence of treatment-related complications.

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled

- A description of the subject's condition
- Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

All serious adverse experiences and relevant laboratory findings must be reported to Dr. Antonio Omuro immediately. An adverse experience is considered serious if death occurs, the condition is life threatening, hospitalization is required, prolonged hospitalization results, or there is permanent disability or incapacity. All information regarding serious adverse experiences must be recorded on the form provided. Patients suffering serious adverse reactions must be carefully followed and all follow-up information also recorded. In addition:

All life threatening and lethal (grade 4 or grade 5) known, unknown, or suspected reactions (toxicities) must be reported to Dr. Antonio Omuro by telephone (212) 639-5122, or fax (917) 432-2310. A written report must be sent within ten days to Dr. Antonio Omuro, Department of Neurology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

Any death, regardless of cause, must be reported to Dr. Omuro by telephone or fax and in writing. It is the treating physician's responsibility to investigate and report the date and cause of death of any patient entered on this trial.

All unusual reactions (grade 2 or 3 toxicities) must be reported in writing within 10 days to Dr. Omuro.

To protect patient confidentiality, names or other identifying characteristics will not be used in any reports or publications resulting from this study. Patient records relating to this study will be stored in the department of Neurology; access to these records will be restricted to study investigators, appropriate institutional and federal review agencies.

Germline DNA from peripheral blood and tumor DNA will be anonymized and stored in the laboratory of Dr David Louis at the Massachusetts General Hospital.

17.3 SERIOUS ADVERSE EVENT (SAE) REPORTING FOR PARTICIPATING SITES

Responsibility of Participating Sites

- Participating sites are responsible for reporting all SAEs to the MSKCC PI via fax or e-mail within 3 calendar days of learning of the event.

- Participating sites should notify the MSKCC PI of any grade 5 event immediately.
- Participating sites should use the SAE Report Template to report SAEs to MSKCC (a copy of the site's institutional SAE report is acceptable as a substitute).

SAE contact information for the Coordinating Center is listed below:

Dr. Antonio Omuro, Phone # 212-639-752, Fax # 646-422-0626
02-089 RSA, Fax # 646-227-2461

Responsibility of MSKCC

- The MSKCC Research Staff is responsible for submitting all SAEs to the MSKCC IRB/PB as specified in 17.2 and to Schering Plough per section 17.4.
- The MSKCC PI is responsible for informing all participating sites about unexpected SAEs within 30 days of receiving the stamped SAE from the MSKCC IRB/PB.
- Any report pertaining to a grade 5 event will be distributed to the participating sites as soon as possible.

17.4 SCHERING ADVERSE EVENT REPORTING

Adverse events (AE) will use the descriptions and grading scales found in the revised NCI Common Toxicity Criteria (CTC). This study will utilize the CTC version 3.0 for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTC version 3.0.

Each serious adverse event must be reported by the investigator to **Schering's Drug Safety Surveillance (DDS) [see DDS fax coversheet]** with a completed **Medwatch Form 3500** and faxed to **(973)-921-7424** within 24 hours of learning of its occurrence, even if it is not felt be treatment-related. Follow-up information about a previously reported serious adverse event must also be reported within 24 hours of receiving it. If the serious adverse event has not been previously documented (new occurrence) and it is thought to be related to study drug, the Drug Safety Surveillance (DSS) Department may contact the investigator to obtain further information. If warranted, an investigator alert may be issued, to inform all investigators involved in any study with the same drug that this serious adverse event has been reported.

All serious adverse events will be reported to the FDA within 24 hours of notification by calling 1-800-FDA-1088. A FDA MedWatch , Form 3500, will also need to be completed and forwarded to the FDA in a timely fashion. The FDA Form 3500 can be found on the FDA website, www.fda.gov.

DEFINITIONS

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product/biologic (at any dose) or device and which does not necessarily have to

have a causal relationship with this treatment. An **AE** can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example) a symptom or disease temporally associated with the use of a medicinal product whether or not considered related to the medicinal product:

- occurring in the course of the use of a drug, biological product, or device,
- associated with, or observed in conjunction with product overdose, whether accidental or intentional,
- associated with, or observed in conjunction with product abuse, and/or
- associated with, or observed in conjunction with product withdrawal.

An adverse event is also any failure of expected pharmacological or biologic therapeutic action (with the exception of such failure occurring in a clinical trial).

Serious or non-serious follows:

Serious - Any adverse drug, biologic or device experience occurring at any dose that

results in any of the following outcomes: death, a life threatening adverse drug experience, requires or prolongs in-patient hospitalization, a persistent or significant disability/incapacity or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

Non-serious - Any AE which does not meet the criteria for a serious adverse event.

Life-threatening - the patient/subject was at immediate risk of death from the AE as it occurred.

Although not considered a serious adverse event (unless an event occurs with a serious outcome), pregnancy information on clinical study subjects is collected by Schering-Plough's Drug Safety Surveillance department. If a subject, incuding the female partner(s) of male study subjects, should become pregnant during the course of the study, the principal investigator or designee must contact Schering-Plough's Drug Safety Surveillance department within 5 working days of the principal investigator or designee first becoming aware of the pregnancy (if a serious adverse event occurs in conjunction with the pregnancy, then the reporting time frame for a serious adverse event must be met). Follow-up information on the outcome of the pregnancy should also be forwarded.

Overdose – we acknowledge that these are not serious, unless a serious outcome occurs.

Attribution

The Principal Investigator or his designee will document his/her opinion and any supporting laboratory and clinical information of the potential attribution of the study drug to any grade 3 or greater toxicity based on the following guidelines:

Unrelated

This category applies to those toxicities that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.)

Unlikely (*must have any two criteria*)

In general, this category can be considered applicable to those toxicities that are judged to be unrelated to the test drug. A toxicity may be considered unlikely if or when:

1. It does not follow a reasonable temporal sequence from administration of the test drug;
2. It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
3. It does not follow a known pattern of response to the test drug;
4. It does not reappear or worsen when the drug is re-administered.

Possible (*must have any two criteria*)

This category applies to those toxicities for which a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. A toxicity may be considered possibly related if and when:

1. It follows a reasonable temporal sequence from administration of the test drug;
2. It could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
3. It does follow a known pattern of response to the test drug.

Probable (*must have any two criteria*)

This category applies to those toxicities that are felt with a high degree of certainty to be related to the test drug. A toxicity may be considered probably related if and when:

1. It follows a reasonable temporal sequence from administration of the test drug;
2. It could not reasonably be explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
3. It disappears or decreases on cessation or reduction in dose. There are important exceptions when a toxicity does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (e.g. bone marrow depression, fixed drug eruptions, tardive dyskinesia);
4. It follows a known pattern of response to the test drug.

Definite (*must have all four criteria*)

This category applies to those toxicities that are felt to be incontrovertibly related to the test drug. A toxicity may be considered definitely related if and when:

1. It follows a reasonable temporal sequence from administration of the test drug;
2. It could not reasonably be explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
3. It disappears or decreases on cessation or reduction in dose with re-exposure to drug. (Note: this is not to be construed as requiring re-exposure of the subject, however, a category of definitely related can only be used when a recurrence is observed.);
4. It follows a known pattern of response to the test drug.

17.5 Safety Reports

- MSKCC will distribute outside safety reports to the participating sites immediately upon receipt.
- MSKCC must submit safety reports to the MSKCC IRB/PB according to institutional guidelines.
- Participating sites must submit safety reports to their institution's IRBs within 30 days of receipt from MSKCC or per participating site guidelines.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

18.1 For Participating Sites

The investigators listed on the protocol cover page and their qualified designees at each participating site may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines.

Signed copies of the informed consent should be distributed as follows: One copy will be given to the participant to be retained for their personal records. One copy will be maintained on file at the MSKCC. The third copy will be confidentially maintained by the participating institution.

A note will be placed in the medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

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