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North Central Cancer Treatment Group

Phase III Intergroup Study of Radiotherapy versus Temozolomide Alone versus Radiotherapy with Concomitant and Adjuvant Temozolomide for Patients with 1p/19q Codeleted Anaplastic Glioma

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Add 1

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CANCER TRIALS SUPPORT UNIT (CTSU)
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Questions:	Contact:
The CTSU Public Web site is located at: www.ctsu.org The CTSU Registered Member Web site is located at http://members.ctsu.org CTSU logistical information is found in Appendix IV.	
Submit study data to NCCTG Operations Office unless otherwise indicated in protocol, Section 18.0:	NCCTG Operations Office RO FF 03 24-CC/NW Clinic 200 First Street SW Rochester, MN 55905 ATTN: QCS for N0577 Fax: (507) 293-3536
For questions unrelated to patient eligibility, treatment, or data submission:	Contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923 or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.
For questions related to patient treatment, follow-up, or data submission:	Refer to the Protocol Resource table on page 2.

Add 1

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

All North American institutions, including NCCTG, will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical Appendix VII.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://members.ctsu.org
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical Appendix VII for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the NCCTG. **Case report forms** (with the exception of patient enrollment forms)**, clinical reports, and transmittals** must be sent to NCCTG unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations. DO NOT copy the CTSU on data submissions. NCCTG institutions will do remote data entry per standard operating procedures.
- **Data query and delinquency reports** will be sent directly to the enrolling site by the NCCTG Operations Office. Please send query responses and delinquent data to the NCCTG and do not copy the CTSU Data Operations.

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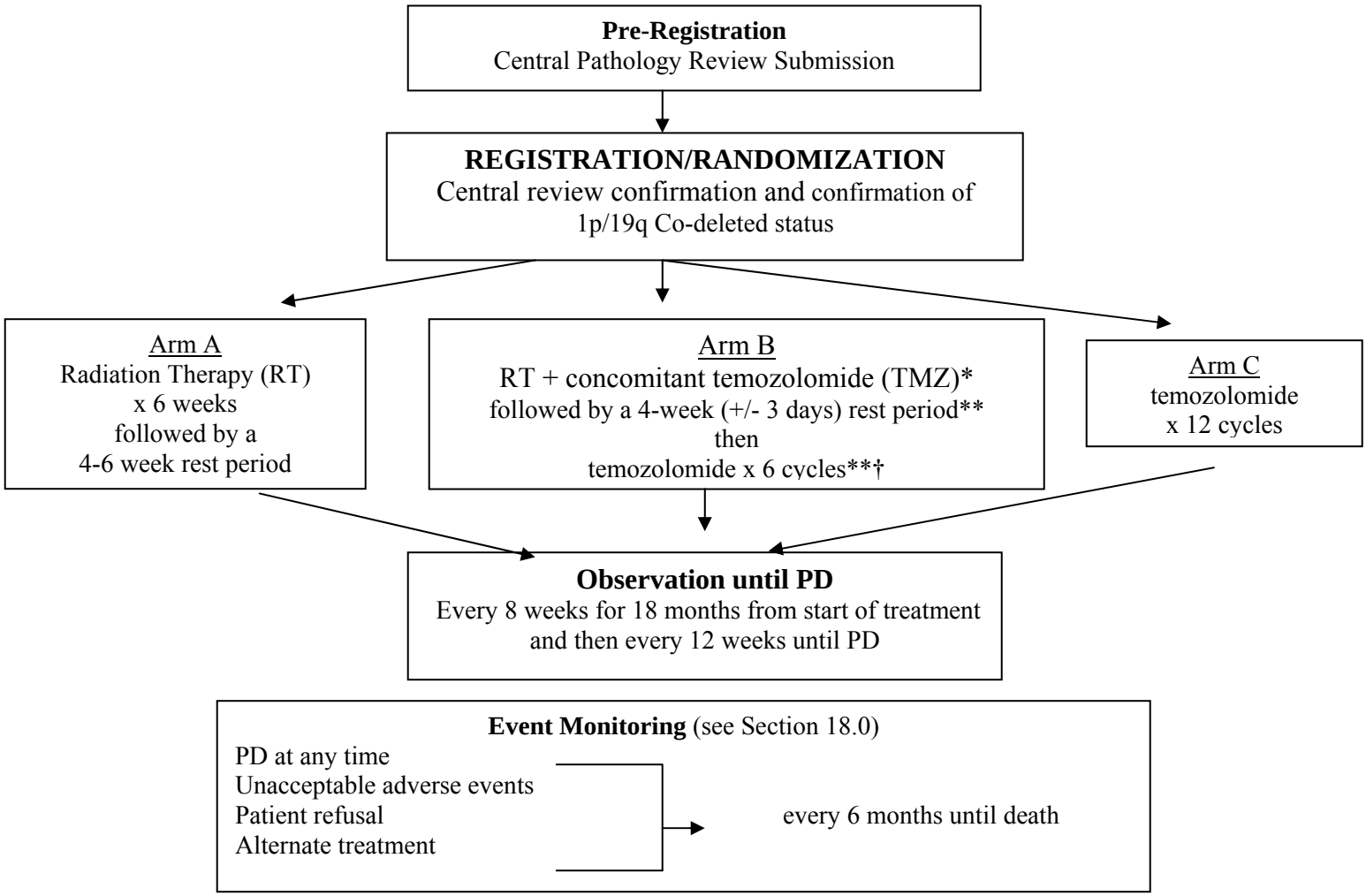
Schema



Arm A: Cycle = 10-12 weeks (depends on whether or not the patient takes the full 6-week rest period)

Arm B: * Cycle 1 length = 10 weeks
** Cycles 2-7 length = 4 weeks
† Option to extend to 12 cycles (cycle = 4 weeks)

Arm C: Cycle = 4 weeks

If a patient is deemed ineligible or a cancel, please refer to Section 13.0 for follow-up information.

NCCTG and CTSU institutions EXCEPT NCIC CTG: ***One-Time Submission - Study Agent Shipment Form*** has been emailed to Clinicaltrials@biologicstoday.com (see Section 15.14 for complete instructions) prior to registration of the first patient to allow enough time (7-10 days) for Biologics, Inc. to process the form for drug shipment. Biologics, Inc. will confirm receipt of the SASF by email to the site.

Generic name: temozolomide Brand name: Temodar (North America); Temodal (Europe) NCCTG abbreviation: TMZ Availability: Schering Plough via Biologics, Inc.

1.0 Background

There is increasing data which suggests that both low grade and anaplastic oligodendrogliomas (AO) are responsive to treatment. Unlike most gliomas, response rates of up to 70% have been observed following radiotherapy and PCV (procarbazine, lomustine (CCNU) and vincristine) chemotherapy. Attempts have been made to correlate clinical outcome with specific predictive markers, including genetic deletions (particularly of 1p, 10q, and 19q), hypermethylation / gene silencing of specific promoters (methylguanine methyltransferase (MGMT), gene amplification (particularly growth factor receptors) and cell cycle regulatory events. In particular, data suggest that 1p and 19q loss of heterozygosity (LOH) may be predictive of superior outcome. To date, it is still unclear whether the 1p and 19q deletions simply represent a molecular signature in AO which reflects a favorable natural biological behavior, or whether these markers are mechanistically related to response to therapy. The data has suggested that tumor response, even when 1p/19q deletions are present, may be independent of timing of PCV chemotherapy treatment type (Cairncross, 2004; van den Bent, 2005). The specific genes involved, and the mechanism that results in improved outcome in patients with 1p/19q deletions, have yet to be characterized.

In early uncontrolled trials, the observation of response of AO to treatment with nitrosoureas resulted in a modification of clinical practice. In the early 1990s, physicians began treating most AO patients with PCV (procarbazine, CCNU, and vincristine) chemotherapy, despite the lack of convincing data supporting this practice. To study this issue, in the United States a prospective randomized Phase III Radiation Therapy Oncology Group (RTOG) study (R9402) was initiated as an intergroup effort between RTOG, NCCTG, SWOG and ECOG. A similar Phase III study with a slightly different design was also initiated by the European Organisation for Research and Treatment of Cancer (EORTC). RTOG 9402 randomized AO patients, following surgical resection or biopsy of their neoplasm, to either radiotherapy (RT) alone or RT + PCV chemotherapy. The main objectives of R9402 were to determine whether there was evidence of a survival advantage when PCV chemotherapy was added to radiotherapy in initial treatment, and to explore the predictive value of certain molecular markers, specifically 1p and 19q gene deletions, with outcome. The results showed no clear evidence of superior survival of patients receiving RT + PCV as compared to RT alone. However, those patients with co-deletions for 1p and 19q had significantly longer progression-free survival (PFS) and overall survival (OS) over those with one or no deletions, regardless of treatment arm (Cairncross, 2004a). It should be pointed out that although RTOG 9402 was a prospective study, the study did not randomize patients on the basis of the 1p and 19q status, and tissue for analysis was informative in slightly over one-half of the patients. In Fall 2004, an update of RTOG 9402 was presented (Cairncross, 2004b), which added the observation that PFS, but not OS, was prolonged in PCV+RT -treated patients as compared to those treated with RT alone, and that the bulk of this difference was accounted for by the patients who had both 1p and 19q deletions. However, the PFS benefit was gained at the cost of significant toxicity with the PCV regimen.

Similar results were also reported by the EORTC in a contemporaneous study (26951) which compared RT alone to RT followed by adjuvant PCV chemotherapy for AO/AOA patients. No differences in survival were observed between treatment arms (van den Bent, 2005). Patients with combined 1p and 19q deletions had significantly longer OS and PFS than those with one or no deletions regardless of treatment arm. In the EORTC study, an increase in PFS was observed in the PCV-treated patients, which primarily accounted for by the cohort of 1p/19q co-deleted patients who more often showed the extension of PFS than those without deletions, suggesting (but not proving) that this group may potentially be the most likely group to derive any benefit from addition of chemotherapy to RT.

In both trials, patients with single deletions of either 1p or 19q had intermediate survival that fell between that of co-deleted and of undeleted patients. However, there was a subtle difference between the trials, in that patients with 19q single deletions fared better than those with 1p single deletions in the RTOG study, whereas in the EORTC study those with 1p deletions alone fared better. The reason for this difference is not yet known.

Based on the Phase III data from the RTOG and EORTC studies, investigators feel that it is now possible to define a subgroup of AO/AOA patients (1p/19 q co-deleted) with superior survival, and it has been proposed (van den Bent, Cairncross, Jaeckle, Mehta and others) that this cohort should be studied separately from patients without 1p and 19q deletions. Importantly, there is a suggestion from both RTOG 9402 and EORTC 26951, and from several earlier Phase II or uncontrolled studies, that this cohort is more responsive to treatment, and appears to have a longer progression-free survival when treated with RT and chemotherapy, either administered before or following the RT.

Recently, discussions were held in a series of Working Group meetings between key investigators of NCCTG, RTOG, ECOG, NCIC and EORTC. The purpose of these meetings was to identify a strategy for treatment of AO and anaplastic mixed gliomas, in the wake of the data presented from RTOG 9402, EORTC 26951, and the Stupp GBM study data. It was felt that there was a need to determine whether the survival of newly patients with AO could be improved with the addition of temozolomide chemotherapy to radiotherapy as compared with radiotherapy alone, the control standard utilized in RTOG 9402 and EORTC 26951. In addition, data to date (Cleveland Clinic experience, Vogelbaum, personal communication) has shown that patients with AO and combined deletions ("co-deletions") of chromosomes 1p and 19q in tumor tissue, infrequently progress during the first few years. Given the potential of neurotoxicity in patients treated early in their course with RT, who experience long-term survival, the working group decided that an important question to answer was whether radiotherapy could be delayed in these favorable-risk patients, treating with temozolomide alone until progression (or 12 cycles), including a comparative analysis of neurocognitive function following such treatment versus early treatment with RT.

Prior clinical trials have suggested less toxicity with temozolomide than with PCV (utilized in RTOG 9402 and EORTC 26951), and a potential for greater efficacy of temozolomide, observed in treatment of another malignant glioma, newly diagnosed glioblastoma (GBM) (Stupp, 2004). In the wake of these reported findings, the concomitant use of temozolomide with RT for treatment of other newly diagnosed malignant gliomas including AO is currently widespread (data from Society of Neuro-oncology Survey, Lisa DeAngelis, personal communication), albeit in the absence of Level 1 evidence of benefit supporting this approach. As such, it was felt that this question should be answered scientifically in the context of a clinical trial. In addition, inclusion of an RT-containing control arm seemed critical, as the best available databases for this tumor type are derived from RTOG 9402 and EORTC 26951; these studies included RT as part of treatment for all patients on all arms. In the end, consensus was reached within the Working Group that the study design for this Phase III clinical trial for co-deleted AO and mixed AOA patients would be a three-arm randomized Phase III trial comparing RT alone vs RT plus concomitant and adjuvant temozolomide vs temozolomide alone.

There are several reasons at this time to proceed with a Phase III trial. Unlike PCV, temozolomide has shown Phase III evidence of benefit in GBM, a related tumor, when administered as concomitant and adjuvant therapy to RT. Furthermore, neither RTOG 9402 nor EORTC 26591 actually evaluated the administration of concomitant and continuous chemotherapy during RT, which although unproven, has been postulated by some to be a primary reason for the observed benefit of temozolomide in the EORTC Phase III GBM study. Finally, as stated above, definitive data is needed to support or refute the current community practice of

utilization of combined RT + temozolomide in treatment of AO/AOA (e.g., determination that addition of temozolomide does more than add toxicity to RT alone). Such data is also needed to determine whether temozolomide alone can produce similar or superior survival to RT alone, or allow the RT to be delayed, The 1p/19q deleted population would appear to be a key target for such a Phase III investigation, since data suggests that this cohort may be the most responsive; in the recent RTOG 9402 and EORTC 26951 studies, this cohort that showed a significant increase in progression free (but not overall) survival with the addition of PCV to RT.

There are valid concerns shared by CTEP and the cooperative groups that accrual might be challenging for this relatively modest group of codeleted AO/AOA patients, and that cooperation between several groups is necessary. As such, NCCTG, RTOG, ECOG, NCIC, and EORTC have indicated willingness to collaborate on this Phase III trial, and the intention of the group is also to list this trial on the CTSU.

Several key translational correlative studies are incorporated into this study, including association of outcome endpoints with tumor 1p/19q status, p53 and PTEN status, other downstream signaling events, other candidate gene expression profiles, and methylguanine methyltransferase, (MGMT) gene promoter methylation status. Based on recent observations presented at ASCO and AACR (see Supporting data, Section C below) by Dr. Robert Jenkins of NCCTG (Jenkins 2006), analysis for CEP1/19p12 fusion and the t(1;19)q10;p10) translocation will also be correlated with 1p and 19q co-deletions and outcome endpoints. Finally a critical component will be the ongoing assessment and comparison of quality of life and neurocognitive status between treatment arms.

1.1 Rationale for selected approach and trial design (Including choice of both clinical and correlative study designs)

The response of AO to temozolomide chemotherapy has been reported in up to 70% of oligodendroglioma patients. Even in patients with progression of their tumors following prior RT and PCV chemotherapy, the response rate (CR+PR) has been favorable (approximately 25%) (Van den Bent 2003; Soffietti; Chinot 2004). There is a significant amount of data correlating outcome with 1p/19q deletion status in AO patients treated with RT or RT+PCV, but only limited data in patients treated with temozolomide or RT + temozolomide. In a small reported retrospective series of 16 patients, response to temozolomide was observed in 9/10 patients with losses of chromosome 1p, whereas only 2/6 patients with an intact chromosome 1p responded (p=0.04) (Chahlavi, 2003).

Recently, the EORTC concluded a Phase III trial providing evidence that chemoradiotherapy with temozolomide and RT followed by 6 cycles of temozolomide prolongs the survival of patients with newly diagnosed grade 4 astrocytomas (Stupp, 2004). It is reasonable to speculate that extension of survival may also be observed in patients with AO treated with a similar regimen, particularly since the response rate of newly diagnosed AO patients to treatment exceeds 70% as compared to 20-30% of patients with glioblastoma. However, to date there is no Level 1 evidence of benefit of chemoradiotherapy in AO, despite the widespread use in clinical practice of combined RT+temozolomide for treatment of patients with non-GBM histologies, including AO and AOA. Such a trial is warranted, particularly in this responsive histology. Furthermore, the data from RTOG 9402 and EORTC 26951 supports evaluation of AO/AOA patients with 1p /19q deletions as a separate cohort, due to the observed

differences in survival as compared with those AO/AOA patients without deletions (Cairncross 2006; van den Bent 2006). We therefore propose a Phase III trial design powered to determine whether RT plus concomitant and adjuvant temozolomide produces superior survival of patients with AO/AOA and co-deletion of 1p and 19q as compared to treatment with RT alone (control arm). In addition, since several investigators feel that temozolomide alone until progression may be a reasonable option for these patients with favorable survival, this Phase III design will also address whether temozolomide alone produces superior survival over RT alone, and provide objective data on whether RT can be delayed, and for what interval, in this population. It is recognized that many patients on temozolomide alone will receive RT at progression, and similarly patients randomized to RT alone will likely receive a temozolomide-containing regimen at progression. As such, progression free survival will be a particularly important secondary endpoint in this trial. Survival information is needed on patients receiving temozolomide alone, as robust data is not available utilizing temozolomide alone in this population, and it must be remembered that all patients on RTOG 9402 and EORTC 26951 received radiotherapy up front.

In RTOG 9402, 201 AO/AOA patient specimens were available for analysis of LOH by FISH (fluorescent *in-situ* hybridization, co-deletion for both 1p and 19q was present in 92 (46 %). Single deletions for 1p occurred in 16 (8 %) and for 19q in 33 (16%); 60/201 (30 %) had neither deletion (Cairncross, 2004). In EORTC 26951, 200/368 (54%) AO/AOA specimens were available for 1p/19q analysis. Of the 200, there was co-deletion for 1p and 19q in 50 (25%), 1p only in 30 (15%), 19q only in 25 (13%) and neither deletion in 95 (47%) (van den Bent, 2005). The reasons for the differences in percentage of 1p/19q co-deleted patients reported in these studies is unclear, but may reflect differences in assay technique ,or differences in the proportion of mixed gliomas (which less commonly have do-deletions) between the studies, that were not otherwise captured (e.g., differences in pathologic interpretation, or tissue sampling errors).

It is not clear what exactly should be done with the singly-deleted patients. In RTOG 9402 and EORTC 26951, patients with single deletions of 1p or 19q had intermediate median OS, falling between those with both deletions and those without either deletion. It is likely this group is heterogeneous, and this problem was inadvertently complicated by the inclusion of patients with mixed AOA in addition to "pure" AO within the two Phase III trials (at the time of design, it was felt by most that these patients had similar survivals; later it has been shown that pure AO patients have superior survival (Buckner, 2002). From RTOG 9402, the relative frequency of single deletions for 1p and 19q as a function of histology (pure AO or mixed AOA) is shown below:

1p del	**Pure AO**	**Mixed AOA**	**19q del**	**Pure AO**	**Mixed AOA**	**1p and 19q del**	**Pure AO**	**Mixed AOA**
No	56 (38%)	38 (80%)	**No**	49 (33%)	31 (56%)	**No**	65 (44%)	44 (83%)
Yes	93 (62%)	15 (20%)	**Yes**	101 (67%)	24 (44%)	**Yes**	83 (56%)	9 (17%)
p-value	<0.001			0.003			0.017	

These data suggest that the frequency of deletions of 1p, 19q or both would be higher if the prior Phase III RTOG and EORTC studies had been restricted to 'pure' AO, and likely would have impacted OS. However, patients with single deletions appear to have more variable (usually shorter) survivals. Thus, in discussions held at the ASCO meeting in 2006 mentioned earlier, the decision was mutually made to not include patients with single deletions in this study (they will instead be included in the proposed EORTC anaplastic glioma trial , EORTC 26053).

For this study, 1p/19q LOH status will be ascertained prior to treatment, to determine eligibility for inclusion in the trial.

- In the US, this process will take place at Mayo Clinic utilizing Dr. Robert Jenkins' laboratory, who also performed the analyses for RTOG 9402, and central pathology review will take place by NCCTG neuropathologists (Scheithauer, Giannini) and potentially assisted by RTOG neuropathologists (Aldape).
- For the EORTC institutions, this testing will be done similar to the procedure for the CATNON study using either a local approach or a central approach. In the local approach, patients are included based on the local histological and 1p/19q diagnosis, with central review of 1p/19q status and histology. In the central approach, if patients are deemed eligible, the histological and 1p/19q status is determined prior to registration/randomization and patients are entered if they are eligible based on the central diagnosis. Central review will be done for all cases by the Department of Pathology of the Erasmus University Rotterdam (Dr. M. Van den Bent). Only centers that fulfill minimum quality requirements for 1p/19q testing and that are cleared by the EORTC Headquarters (HQ) will be allowed to register/randomize patients based on local diagnosis and it will be centrally confirmed subsequent to registration/randomization. The dual analyses on the European patients will allow a subsequent analysis of variability of assay results between central and community institutions, which may be helpful in planning future trials (as the case with IHC and FISH testing for HER-2 status in breast cancer within NCCTG 9831).

Since MGMT gene promoter hypermethylation status may also be an important prognostic variable in these patients, tumor tissue will be collected for this analysis, as well as for 1p; 10 and 19q:10 translocation status, and other relevant signaling markers. It has been proposed that a single translational correlative science committee be established for this trial and EORTC 26053, with appropriate representation by experts from each of the groups involved. This committee will be charged with decision making regarding the most efficient and best utilization of the tissue and blood samples, and prioritization of any additional proposals for translational research.

Since toxicity may vary significantly between treatment arms, both ongoing QOL and neurocognitive analyses using validated instruments will be included in the trial design. This will be of key interest since there is the potential for differences between patient arms, in particular with inclusion of a non-radiotherapy arm. For this study, a joint QOL/neurocognitive committee will be established that will oversee both for this trial and for EORTC 26053, with appropriate representation by experts from each of the groups involved, who will be charged with design and implementation of the most appropriate test instruments and review of the related data.

1.2 Preclinical and Translational Correlative Marker Studies in Anaplastic Oligodendroglioma

There is an expanding body of knowledge related to molecular events in AO, which has generated considerable excitement. Recent investigations have identified several genetic markers of potential prognostic or predictive significance in oligodendrogliomas, including 1p/19q, p53, and PTEN mutations; EGFR and PDGFR amplification, MIB-1, methylguanine-methyltransferase (MGMT) expression and gene promoter methylation status, 1p/19q translocation, and other signaling events and candidate gene investigations.

1.21 The Relationship of Loss of Heterozygosity for Chromosomes 1, 19q, and 10 to Anaplasia and Outcome in AO patients

Over one-half of oligodendrogliomas exhibit loss of heterozygosity (LOH) of chromosomes 1p and 19q (Bigner, 1999; Van den Bent, 2003). This strongly suggests that mutation of as yet unidentified tumor suppressor genes located on these chromosomes contribute to the pathogenesis of oligodendrogliomas. In comparative genomic hybridization studies utilizing bacterial artificial chromosomes (BACS), 1p and 19q losses in all cases were found to be due to physical hemizygous deletions of the whole chromosome (Cowell, 2004).

In early studies, LOH of the chromosome 1p was associated with increased sensitivity of tumors to standard chemotherapeutic agents (Nayak, 2004; Johnson, 2003). Combined 1p and 19q LOH has been observed in up to 83% of oligodendrogliomas, 63% of AO, 56% of mixed low grade oligoastrocytoma, and 52% of anaplastic mixed oligoastrocytoma. Combined loss of 1p and 19q was a univariate predictor of overall survival in an uncontrolled study of patients with pure oligodendroglioma ($p=0.03$), and remained significant after adjusting for age (Smith 2000). In another study of AO pts treated with RT and/or chemo, the presence or absence of 1p+19q LOH associated with an overall survival (OS) of 91 vs. 46 months, a median time to progression of 86 vs. 39 months, and 5-year survival of 80% and 36%, respectively (Felsberg, 2004). Ino and colleagues went as far as to divide patients with AO into four groups, based on clinical and genetic features. Patients with combined 1p and 19q loss often showed response to treatment and improved overall survival, with or without postoperative RT. Patients with only 1p loss also responded to chemotherapy, but had shorter survival. In patients lacking 1p loss, the presence of TP53 mutations often predicted response to chemotherapy, but these patients experienced early tumor relapse. Patients with tumors that did not have TP53 mutations were poorly responsive and demonstrated aggressive behavior (Ino 2001). The relationship of 1p/19q mutations to outcome has also been explored in patients with recurrent oligodendroglioma. In a retrospective analysis of 55 patients with Grade 2-3 oligodendroglioma who had received prior radiotherapy and either neoadjuvant chemotherapy, or chemotherapy after progression following initial RT, LOH for chromosome 1p was identified in 36 (65%) of those tumors tested. The overall median PFS following RT in this group was 40.4 months; however, the median PFS was 55 months in those with 1p loss versus 6.2 months for those without 1p

loss ($p<0.004$). The 1p loss remained significant for PFS in the multivariate analysis for both Grade 2 and 3 tumors. Furthermore, the addition of chemotherapy to RT prolonged radiographic tumor control for those patients with 1p loss ($p=0.004$) (Bauman, 2001).

In correlative analyses performed in conjunction with RTOG 94-02, 92/201 (46%) of AO specimens available for analysis had 1p or 19q deletions (Cairncross, 2004).1p LOH was seen in 108 specimens (53%), 19q LOH in 125 (62.2%), and both were deleted in 92 (45.8%). The proportion of 1p, 19q, both, and non-deleted cases ended up approximately balanced between the two arms (although not a stratification variable). The median overall survival of patients with 1p and 19q deletions (N=92) was not reached at the time of presentation of the preliminary results in June 2004, whereas the median OS in patients with one or neither deletion was only 2.8 yr (HR=0.31, $p<0.001$). By multivariate analysis, LOH for either marker was a significant independent prognostic variable correlating with outcome (1p: HR=0.45, 95% CI 0.27-0.75, $p=0.002$; 19q: HR=0.53, 95% CI 0.33-0.86, $p=0.01$).

Chromosome 10q has also received attention in oligodendroglioma. In an analysis of 72 oligodendrogliomas, 10q loss was identified in 14/67 (21%), including the PTEN and DMBT1 regions in all, but sparing the chromosome 10q ERCC6 locus in 2. No mutations were identified in the ERCC6 exon 2, which is also on chromosome 10. In a multivariable analysis, after adjustment for both 10q and 1p loss, PTEN gene alterations were predictive of a poor survival, even in patients with chemosensitive tumors (Sasaki, 2001). In another study of 22 patients (AO-10, oligodendroglioma -6, and or mixed glioma -7), seven (30%) had LOH for 10q. There were 7 pts from the total group that showed clinical response to chemotherapy, all of whom showed 1p LOH ($p=0.02$); however, 10 q deletions portended a poorer prognosis. Median PFS was only 31 months for patients with 10q LOH, as compared with 118 months for patients whose tumors had intact 10q. Median PFS was only 31 months for patients with tumors lacking 1p deletions, but was 118 mo for patients with 1p LOH pts ($p=0.14$) (Thiessen, 2003). Other markers (MIB-1, pRbLI, p27 LI) have been found to correlate significantly with higher grade (Grade 3) of oligodendroglioma and mixed glioma (Kamiya, 2002).

1.22 Growth Factor Receptors, Signaling Events and Gene Hypermethylation Status in Anaplastic Oligodendroglioma

Increases in p53 expression have been used to evaluate the malignant potential of these tumors. By immunohistochemistry, p53 can be demonstrated in 28% of oligodendroglial tumors (Nayak, 2004). Although p53 may be overexpressed in a proportion of oligodendrogliomas, expression is often exceeded by signaling events which drive cellular division and proliferation (Miettinene 2001). Amplification of the PDGFR-A gene has been reported in 4/41 (9.8%) of AOs, and 1/29 (3.4%) of anaplastic mixed gliomas, but not in Grade 3 or 4 anaplastic astrocytomas (N=167) (Smith. 2000).

Investigations have identified concurrent inactivation of both RB1 and TP53 pathways in AOs. In tumors showing disruption of the RB1 pathway, 69% have disruption of regulation of the TP53 pathway; these combined alterations appear more common with the anaplastic phenotype (Watanabe, 2001). Alteration of RB1/CDK4/p16INK4a/p15INK4b signaling, which normally regulates G1 to S transition, has been demonstrated in 65% of AO, and appears related to alterations of RB1, CDK4 amplification, p16/p15 homozygous deletions, and / or promoter hypermethylation. In addition, 50% of AO tumors showed abnormalities of the TP53 pathway, including promoter hypermethylation or homozygous deletion of the p14/ARF gene, or less frequently, TP53 mutation or MDM2 amplification (Watanabe, 2004).Gene and gene promoter status has been of intense interest in gliomas, including oligodendrogliomas. The methylation status of 11 genes was evaluated in 43 oligodendrogliomas and mixed gliomas of different grades (Dong, 2001). Nearly 75% of the tumors were hypermethylated for at least one gene studied (O6MGMT-60%; RB1-34%; estrogen receptor - 30%; p53 - 16%; p16INK4a - 12%; death-associated protein kinase - 10%; p15INK4b - 7%; and p14ARF - 2%). There was some correlation of gene hypermethylation with grade of the oligodendroglioma; hypermethylation of CpG islands of p16INK4a and p15INK4b correlated in a positive and significant manner with anaplastic histology. Hypermethylation of O6MGMT was also significantly associated with loss of chromosome 19q or combined 1p19q loss (Dong, 2001). Hypermethylation of CDKN2A, p14ARF, and CDKN2B may also be important epigenetic mechanisms by which oligodendroglial tumors escape from p53- and pRb- dependent growth control (Wolter 2001).

The INK4a/ARF locus on chromosome 9p21 encodes two cell cycle regulator proteins; pINK4a, which inhibits CDK4 - mediated RB phosphorylation, and p14 ARF, which binds to MDM2, producing p53 stabilization. Additional investigations have found that the INK4a/ARF locus is deleted in up to 25% of oligodendrogliomas and 50% of AOs. Promotor hypermethylation of the p14 ARF gene has been detected in 6/29 (21%) oligodendrogliomas and 3/20 (15%) of AOs; in this study, no p16INK4a hypermethylation was found in the low grade oligodendrogliomas, and hypermethylation was identified in only 1/20 (5%) AOs. These authors concluded that aberrant p14ARF expression from hypermethylation was an early INK4a/ARF change in the evolution of oligodendrogliomas, and that deletions of p14ARF and p16INK4a correlated with anaplastic progression (Watanabe, 2001).

There has been ongoing interest in the O-6 methylguanine methyltransferase (MGMT) gene and protein expression status as predictors of outcome or response following treatment of human malignant gliomas. Several studies have shown variable correlation of MGMT protein expression status with outcome. A correlative analysis to a prospective South West Oncology Group (SWOG) Phase III prospective trial (SWOG 9218) in patients with malignant astrocytomas showed that by multivariable analysis, MGMT expression in malignant astrocytoma tissue was an independent predictor of outcome following nitrosourea chemotherapy (Jaeckle, 1998).

More recently, promoter hypermethylation/silencing status in malignant gliomas has been of intense interest, sparked further by the recent presentation of a companion analysis to the EORTC Phase III trial that showed a positive correlation of MGMT gene silencing by promoter hypermethylation with survival outcome measures in patients with newly diagnosed glioblastoma (Hegi, 2004). Promoter hypermethylation appears to be an early event in the development of astrocytic neoplasms, but this gene silencing mechanism may also be a late event for certain loci (Gonzalez-Gomez, 2003). In one study, promoter hypermethylation was identified in 19/42 (45.2%) of AA patients and 33/74 (44.6%) of GBM patients. In contrast to the EORTC correlative analysis, this study indicated that promoter hypermethylation of the MGMT gene was associated with longer survival time in newly diagnosed patients with anaplastic astrocytoma but not glioblastoma, although the studies differed in that these patients had received nitrosourea chemotherapy in addition to their surgery and radiation instead of temozolomide. (Kamiryo, 2004) More recent studies (Paz, 2004) have shown that the methylation of the MGMT promoter positively correlated with the clinical response to initial therapy of newly diagnosed glioma patients receiving temozolomide as first line therapy; 8/12 (67%) patients with MGMT methylated tumors had a complete or partial response, compared with 7/28 patients with unmethylated MGMT (25%, p=0.03).

A positive correlation of response with MGMT hypermethylation status was also noted for patients treated initially with either BCNU (p=0.041) or procarbazine (p=0.043). This implies that response may relate intrinsically to hypermethylation status, rather than the specific treatment employed. One common denominator between these groups (temozolomide, BCNU, procarbazine) is that all patients received radiotherapy. It is important to note that these investigators did not find a correlation of MGMT promoter hypermethylation with clinical response in a cohort of patients with recurrent gliomas (who did not, by nature, receive radiotherapy). One wonders, in light of the EORTC GBM data that showed a positive survival effect of combined chemoradiotherapy with temozolomide and RT (which some investigators have interpreted as indirectly suggesting that a large portion of the survival benefit is due to the concomitant administration of temozolomide during radiation), whether this phenomena relates to a peculiar chemo-radiosensitivity of patients with hypermethylated MGMT, rather than the specific chemotherapeutic agent employed.

MGMT promoter hypermethylation appears to be an even more common event in oligodendroglial neoplasms than in those of astrocytic lineage. In a study of 52 oligodendrogliomas, 46 (88%) had MGMT promoter hypermethylation as defined by methylation of more than 50% of the sequenced CpG sites. Reduced MGMT mRNA levels and protein expression, relative to that in non-neoplastic brain tissue, was demonstrated by RT-PCR and immunohistochemistry in most tumors found to have MGMT promoter hypermethylation. Most interestingly, MGMT promoter hypermethylation was significantly more frequent, as was percentage of methylated CpG sites, in tumors with 1p/19q LOH (Molleman, 2005). This latter finding had also been reported in an earlier study of AO tumors, in which the hypermethylation of MGMT was significantly associated with loss of chromosome 19q and with combined loss of chromosomes 1p and 19q (Dong, 2001). Collectively, these findings imply that the hypermethylation

status of the MGMT promoter may correlate with 1p/19q status, survival, and possibly response to therapy in oligodendroglioma patients. This hypothesis clearly needs to be tested as a correlative analysis within the context of a prospective clinical trial, in which the 1p/19q deletion status of tumors will also be assessed.

1.3 Clinical studies in Oligodendroglioma and Anaplastic Oligodendroglioma/Mixed Glioma

1.31 Retrospective Descriptive Correlations

Clinicians have generally considered oligodendroglioma a relatively less aggressive tumor, but some studies suggest that survival may be more compromised than is generally recognized. In one study of oligodendroglioma patients (N=100), survival at 2, 5 and 10 years was only 43, 16 and 15%, respectively (Lebrun 2004). Despite this concern, longer survivals were reported in another contemporaneous study of patients with AO + or mixed AOA treated with radiotherapy and PCV chemotherapy. Median survival was 9.9 years; 5- and 10- yr survival rates were 57 and 47%, respectively (Jeremic, 2004). In yet another retrospective analysis, the overall median survival of patients with AO (N=106) was 7.3 years, and the 5-year survival rate was 62%, and the median time to progression was 48 months. Univariate analysis showed that age ($p<0.0001$) and KPS ($p=0.04$) correlated significantly with survival. Many patients (50/106, 47%) progressed despite initial therapy (Puduvalli 2003).

1.32 Uncontrolled and Phase II Clinical Trials

1.321 Newly Diagnosed Oligodendroglioma

In chemotherapy-naïve patients with grade 2 or 3 oligodendrogliomas, response (CR or PR) to pre-RT PCV chemotherapy has been observed in 45% (Streffer J 2000). In fact, up to 70% of patients with AO may respond to neoadjuvant PCV chemotherapy, but 30% of these patients progress early on, or are intolerant of chemotherapy, and subsequently receive radiotherapy (Paleologos 1999). In a retrospective review of 53 patients with newly diagnosed oligodendroglioma (albeit a mixture of low grade , anaplastic and mixed glioma) treated with adjuvant or subsequent PCV chemotherapy, there was an overall median survival of 123 months, with 5- and 10- year survivals of 73 and 53% respectively (Fortin 2001). In a Phase II prospective study of 23 patients with newly diagnosed anaplastic oligodendroglioma who received PCV chemotherapy following surgery and radiotherapy, 5-year survival was observed in 52%; grade 4 hematologic toxicity was observed in 13% of these patients (Jeremic 1999). Finally, in a Phase II chemoradiation study of 21 patients with newly diagnosed AO or AOA who received accelerated fractionation RT and concomitant carboplatin, followed by PCV chemotherapy, the mean overall survival was 40.8 months (Levin 2002).

Temozolomide has been utilized with increasing frequency as initial treatment for AO in the community, although not approved by FDA specifically for this indication. As with PCV, the response of AO to temozolomide chemotherapy is also quite high (> 70% of newly diagnosed AO patients), with less toxicity. Response to temozolomide appears more frequent when 1p/19q gene LOH is present in tumor (Chalavi, 2003). A Phase II study (RTOG 0131) recently evaluated the outcome of 40 AO patients treated with pre-RT temozolomide. Of the 29 evaluable patients, pre-RT response rate (CR + PR) to temozolomide was 33%, which is lower than observed with PCV in prior trials (45-70%), but sample sizes were small. Ten of the 29 (34%) withdrew from study prior to reaching the study primary outcome endpoint of 6-mo progression free survival (progression -2; toxicity-4; other -4); this was similar to the 30% withdrawal rate of patients during pre-RT PCV (Paleologos 1999). The authors reported an overall 6 month progression rate of 3/29 (10.3%). The rate of progression on PCV prior to RT (RTOG 9402) was higher, 20% (Vogelbaum, 2005). A recent update (Vogelbaum, personal communication, Nov 2006) of response data on 60 patients indicated a CR rate of 3% (both AO with 1p deletions), stable disease in 62%, and progressive disease in 35%. PFS had not been reached in those patients with 1p or 19q deletion, whereas the median PFS was 27 months in the undeleted anaplastic glioma patients.

1.322 Recurrent Oligodendroglioma

Temozolomide appears to have activity in recurrent oligodendroglioma and mixed glioma. In a retrospective review of 30 patients with recurrent AO treated with temozolomide at 150-200mg/M2 D 1-5 q 28 d, responses were seen in 9 (30%); 27% of these were patients who had failed prior PCV chemotherapy. Median time to progression was 13 months (van den Bent, 2001). A follow-up study of 24 patients with oligodendroglioma or mixed glioma confirmed the observation that initially responding patients may re-respond to a re-challenge with chemotherapy. Among the 12(50%) patients who had initially responded to PCV chemotherapy, subsequent challenge with temozolomide at progression produced a second response in 3 (25%) of these patients. The MTP for such responding patients was 8 months, and at 12 months, 11% of these responders remained free of progression (van den Bent, 2003).

In another Phase II study, which tested treatment with temozolomide plus cis-retinoic acid for patients with recurrent glioma, in the subgroup with AO or mixed AO (N=20), the CR + PR rate was 15% (Jaeckle 2003). Another study reported slightly better response rates; in 48 patients with recurrent AO or anaplastic mixed glioma who had failed prior PCV and were treated with conventional temozolomide dosing (over 5 days every 28 days), 16.7% achieved CR and 27.1% PR (CR+PR of 43.8%), with a median PFS of 6.7 months, and a median overall survival of 10 months (Chinot, 2001). In yet another phase II study of temozolomide administered to 47 relapsed oligodendroglioma patients, a reasonable response rate was observed (15% CR) with an overall median progression-free survival of 6 months, and 34% survival at 12 months. There was an overall median survival of 26 months for complete

responders and 11 months for partial responders. Toxicity of this regimen was acceptable, with grade 3-4 thrombocytopenia in 14% of patients (Chinot, 2001). Finally, in a prospective multicenter Phase II trial of 38 patients with recurrent oligodendroglioma or mixed glioma who had failed prior surgery and RT, temozolomide produced a CR +PR rate of 62.6%, with median TTP of 10.4 mo.; 40% of patients were progression free at 1 yr. It should be noted that in this latter study, patients with large tumors or new clinical deficits were excluded (van den Bent, 2003).

1.323 Randomized Phase III trials

Cairncross provided preliminary analysis data from the Phase III RTOG 94-02 at the 2004 ASCO meeting (Cairncross, 2004) and additional follow-up data at the 2004 meeting of the Society for Neuro-Oncology (Cairncross, 2004) and in the fully published analysis (Cairncross, 2006). This trial randomized 299 newly diagnosed eligible AO and mixed oligoastrocytoma patients to one of two arms: pre-RT "intensive" PCV given every 6 weeks for 4 cycles, followed by RT; or, RT alone (standard arm). The primary endpoint was overall survival, and secondary endpoints included progression-free survival, time to progression, toxicity and quality of life. The study also included an important translational component, specifically an analysis of the relationship of 1p and/or 19q chromosomal deletions to outcome. These correlative analyses were performed on tissue samples that were available from 209 patients (preliminary details are discussed in Section 1.14), 201 of whom were informative for the chromosomal analysis.

Demographic features were presented on 291 of the randomized, eligible patients. The analysis showed that 60% of patients were male; 68% were of age <50 years; 88% had undergone a subtotal or gross total resection; 90% had a KPS ≥80; and 70% had a tissue diagnosis of pure AO. 148 patients received PCV plus RT and 143 received RT alone. The study arms were stratified for age <50 vs >50, KPS 60-70 vs >80, and histologic evidence of moderate versus highly anaplastic tumors. In addition, the treatment arms were subsequently shown to be balanced for known prognostic factors in AO.

The preliminary results show that there was no superiority of PCV + RT over RT alone in treatment of these newly diagnosed AO/ mixed anaplastic glioma patients. The median overall survival was similar for both groups; 4.9 years for PCV plus RT, and 4.7 years for RT alone (HR .90, 95% CI .66-1.24, one-sided p=0.26). There was a statistically significant difference favoring combined PCV+RT over RT for progression-free survival (2.6 vs 1.7 years; HR= 0.69, 95% CI 0.52-0.91, one-sided p=0.008) and time to progression (3.0 vs 2.2 years, p=0.013, HR not stated). However, this benefit appeared to be at the expense of increased toxicity. In patients receiving RT+PCV, 34% experienced Grade 3, and 32% Grade 4 toxicities, one patient died. In the RT only arm, Grade ≥3 toxicities were rare. It should be noted that 79% of patients randomized to RT alone eventually received chemotherapy (generally PCV or temozolomide) after progression, and only 73% of

patients in the PCV arm actually received chemotherapy per protocol, with 46% receiving all 4 cycles. Furthermore, second surgery following relapse was significantly more common in the RT alone group (43% vs. 20%), which may have influenced OS.

Combined 1p and 19q LOH was identified in 46% of patients in whom specimens were evaluable (71%), and these patients had significantly longer survival than those with one or no deletions (median OS not reached vs. 2.8 years; HR 0.31; 95% CI - 0.21, 0.47, $p < 0.001$). Patients with 19q deletions alone had intermediate survival, but patients with 1p deletions alone did not differ significantly from those without deletions, in contrast to prior reports. There was no apparent effect of 1p /19 genotype on OS by treatment arm; however, for patients with 1p/19q loss, the median PFS was significantly longer as compared with undeleted patients (median PFS not reached vs. 2.6 years; HR, 0.42; 95% CI - 0.24, 0.75, p=0.001. Finally, comparison between 1p/19q co-deleted and not–codeleted patients showed that PFS with RT alone was 31 and 12 months respectively, and with RT+PCV, PFS was not reached in co-deleted patients but was 17 months in not-codeleted patients.

The second Phase III trial of newly-diagnosed oligodendroglioma and mixed glioma (EORTC 26951) involved 368 patients who were randomized to RT (59.4 Gy) followed by 6 cycles of PCV chemotherapy (CCNU 110 Day I, PCZ 60/M2 Day 8-21, and vincristine 1.4 mg/M2 Day 8 and 29, every 6 weeks) versus RT (59.4 Gy) alone. The median age was 50, and treatment arms were balanced for age, sex, histology, and 1p/19q deletion status. Most patients had subtotal or gross total tumor resection and good performance status. There were 13% of patients randomized to RT/PCV that did not actually receive PCV, 32% completed at least 5 cycles, and 82% of RT only patients (N=131) received salvage chemotherapy at relapse (65% PCV, 37% temozolomide, 47% other) whereas 55% of RT/PCV patients received subsequent salvage chemotherapy (temozolomide 43%, PCV 11%, other 51 %). The median OS for patients receiving RT vs. RT+ PCV was not significantly different (30.6 and 40.3 months, respectively; HR 0.85; 95% CI - 0.65, 1.11; p=0.2257). Two- and 5-year survival for RT versus RT + PCV were 55% versus 62%, and 37% vs. 44 %, respectively. There was a difference in median PFS favoring RT + PCV over RT alone (23 versus 13 months, HR 0.68; 95% CI - 0.53-0.87, p= 0.0018). There was a significant difference (p=0.003) in survival for patients with 1p/19q loss as compared with those with no deletions. However, there were no significant differences in overall survival as a function of treatment arm when analyzed for either genotype (1p-/19q-, or no deletions) (van den Bent, 2003; 2005; 2006). A comparison between the 1p/19q co-deleted patients and the not-codeleted patients showed PFS with RT alone of 62 and 9 months, respectively, and with RT+ PCV, not reached vs 15 months, respectively.

The results of these two Phase III studies are summarized in Table 1.

TABLE 1

Randomized Phase III Clinical Trials for Treatment of Newly Diagnosed Anaplastic Oligodendroglioma / Mixed Glioma

Trial	N	Treatment	Patient Cohort	Med Surv (yrs)	p value	PFS (yrs)	p value
RTOG 9402	289	NeoPCV→RT	All	4.9	0.26	2.6	0.008
		RT		4.7		1.7	
		NeoPCV→RT	1p-/19q-	NR	<0.001	NR	0.001
		RT	1p- or 19q- or no loss	2.8		2.6	
EORTC 26951	368	RT + adjuv PCV	All	3.4	0.23	1.9	0.002
		RT		2.6		1.1	
		RT + adjuv PCV	1p-/19-	NR	0.0001	NR	0.0001
		RT + adjuv PCV	No Loss	2.1		1.3	
		RT	1p-/19-	NR		NR	
		RT	No Loss	1.8		0.7	

N= number of patients; Med Surv= median survival; PFS= progression free survival; neo= neoadjuvant (prior to RT); PCV= procarbazine, CCNU and vincristine; adjuv = adjuvant; RT= radiation therapy; (-) = loss of heterozygosity for a portion of this chromosome; NR = not yet reached; references 24-28

1.4 Translational Studies

1.41 Correlative studies of 1p and 19q deletions with survival and time-to-progression: RTOG 94-02

As described above, single institutional, retrospective studies have suggested that patients with AO and 1p and 19q deletions may have a prolonged survival, and a higher response rate (CR+PR) following treatment with PCV. Table 2 summarizes the overall prevalence of 1p and/or 19q deletion in the tumors entered on RTOG 9402 and EORTC 26951.

TABLE 2

LOH for 1p and 19q* in Anaplastic Oligodendroglioma and Anaplastic Oligoastrocytoma Specimens in Prospective Phase III Trials: RTOG 9402 and EORTC 26951

Study	Number of Tumor specimens	1p and 19q deleted	1p deleted	19q deleted	Neither deleted
RTOG 9402	201	92 (46%)	16 (8%)	33 (16%)	60 (30%)
EORTC 26951	311	78 (25%)	47 (15%)	39 (12.5%)	147 (47.5%)

- By FISH analysis performed on informative tumor specimens received

Table 3 summarizes the preliminary correlations of tumor histology (AO, AOA) with 1p/19q status in patients entered on RTOG 94-02 whose tumors were available for LOH studies.

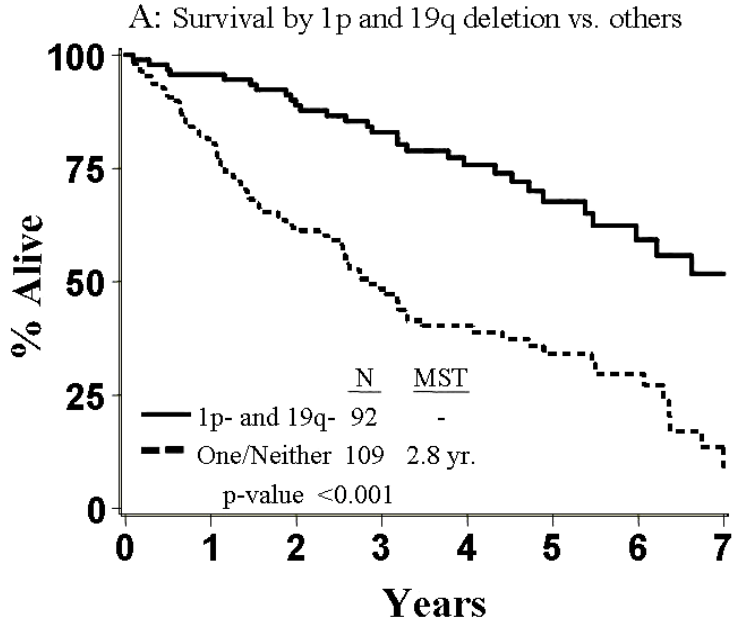
TABLE 3

Association of Morphology Type with 1p and/or 19q Deletions:

Anaplastic Oligodendrogliomas + Mixed Oligoastrocytoma

1p del	Pure AO	Mixed OA	19q del	Pure AO	Mixed OA	1p and 19q del	Pure AO	Mixed OA
No	18 (38%)	12 (80%)	**No**	15 (31%)	8 (53%)	**No**	20 (43%)	12 (80%)
Yes	29 (62%)	3 (20%)	**Yes**	33 (69%)	7 (47%)	**Yes**	27 (57%)	3 (20%)
p-value	0.007			0.14			0.017	

As expected, 1p, 19q and both 1p and 19q loss were associated with tumors of oligodendroglial lineage. 47% of all gliomas entered on the trial had combined 1p and 19q loss. Irrespective of treatment, patients whose tumors had both 1p and 19q deletions lived longer than other patients – median survival at the time of analysis was not reached in the patients with both 1p and 19q deletions, *versus* 2.8 years for those with either one deletion or no deletions (HR 0.31, 95% CI 0.20-0.48; $p < 0.001$) (Figure 1a).



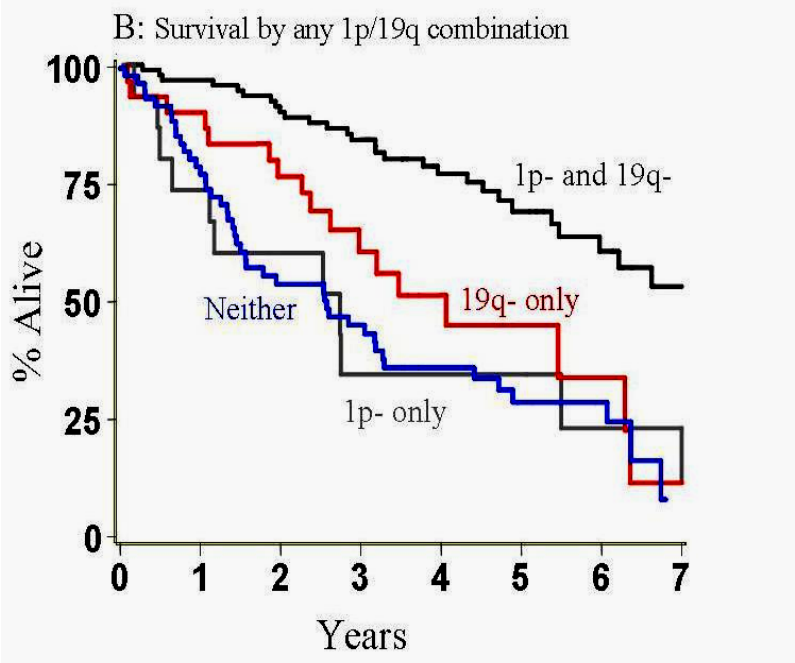


Figure 1 A and B: Overall survival of patients with anaplastic oligodendroglioma and mixed oligoastrocytoma enrolled on RTOG trial 94-02. **Figure 1A:** Comparison of patients whose tumor had 1p and 19q deletion versus those with one or neither deletion. **Figure 1B:** Comparison of patients whose tumor had both 1p and neither deletion. .

MST = Median Survival Time.

Patients whose tumors were found to have 19q deletions also lived longer than those without deletions (median overall survival 6.2 *versus* 2.6 years; HR 0.36, 95% CI 0.24-0.54; $p < 0.001$). Patients whose tumors had 1p deletion lived longer than those without deletions (median survival 6.2 *versus* 3.0 years, HR 0.39, 95% CI 0.26-0.59; $p < 0.001$). Interestingly, patients with 1p deletions alone did not have a difference in survival as compared to those patients without any deletions. Patients with 19q deletions alone had intermediate overall survival (Figure 1b).

Multivariable analysis indicated that both 19q and 1p deletion independently predicted survival (Table 4). In addition, in the 1p/19q deleted patients, OS was significantly longer after combined treatment; 2.5 years for PCV plus RT *versus* 1.9 years for RT alone (HR 0.73, 95% CI 0.53-0.98; p=0.034). Patients with 1p and 19q deletions also had longer progression-free survival (not yet reached for PCV plus RT, *versus* 3.6 years for RT alone, HR 0.55, 95% CI 0.30-0.99; p=0.044). Multivariable analysis indicated that both 19q and 1p deletion independently predicted PFS (data not shown).

Table 4

Cox Multivariate Regression Modeling:
Effect of Variables on Risk of Death[a]

Variable	HR (95%CI)	p-value
Age (increase of 10 years)	1.57 (1.31 - 1.87)	<0.001
KPS (increase of 1 level)	0.71 (0.58 - 0.87)	<0.001
1p- (loss vs. no loss)	0.45 (0.27 - 0.75)	0.002
19q- (loss vs. no loss)	0.53 (0.33 - 0.86)	0.010
Grade (mod. vs. high)	0.60 (0.39 - 0.90)	0.014

[a] Other variables in model: treatment; extent of surgery; history of low grade glioma; tumor histology

Recently, Dr. Robert Jenkins reported (Jenkins, 2006) that a translocation t(1;19) may be the relevant event in oligodendrogliomas. In this study, an unbalanced centromeric 45,XX, t(1;19)(q10;p10) translocation was identified in metaphases from an oligodendroglioma cultured using stem cell techniques. Cells from this tumor were then analyzed for t(1;19) by measuring interphase fusion of a CEP1 probe and a 19p12 probe. Fusion of the CEP1 and 19p12 probes was observed in all abnormal metaphases as well as 74% of interphase nuclei. Among 21 paraffin-embedded retrospective oligodendrogliomas, the prevalence of CEP1/19q12 fusion was 81% and the presence of fusion was significantly correlated with combined 1p/19q deletion (90% concordance; $p<0.001$). Paraffin-embedded tissues from 98 pts prospectively enrolled in 2 NCCTG trials for newly-diagnosed low-grade glioma were then evaluated for CEP1/19p12 fusion. Among the NCCTG patients tested, CEP1/19p12 fusion prevalence was 55%, 47% and 0% among the oligodendrogliomas, mixed oligoastrocytomas, and astrocytomas, respectively. 91% of NCCTG gliomas with and 12% without 1p/19q deletion had CEP1/19p12 fusion ($p<0.001$, Chi-square test). The median OS for all pts was 8.1 years (yrs) without and 11.9 yrs with fusion ($p=0.003$). The median OS for pts with low grade oligodendroglioma was 9.1 yrs without and 13.0 yrs with fusion ($p=0.01$). Similar significant median OS differences were observed for patients with combined 1p and 19q deletions. The absence of CEP1/19p12 fusion or combined 1p and 19q deletion was associated with a significantly shorter OS and PFS for patients who received higher doses of radiotherapy. These results suggested that a t(1;19)(q10;p10) mediates the combined deletion of 1p and 19q in human gliomas. Like combined 1p and 19q deletion, the 1;19 translocation is associated with superior OS and PFS in low-grade glioma patients (Jenkins, 2006; 2006).

It is likely that these findings may have relevance to AO as well. As a result, studies for the fusion of the CEP1 and 19p12 probes and the t(1; 19) will be included in the current study on available specimens, and a descriptive correlative translational analysis will be performed which correlates these parameters with outcome (OS, PFS, response).

1.5 Neurocognitive and QOL Assessments

Neurotoxicity after radiotherapy is a concern for high-grade glioma (HGG) patients, and this is especially pertinent for AO and oligoastrocytoma patients with median survivals of several years (Jeremic, 2004). However, analyses of neurocognitive data prospectively collected on two cooperative group trials found the vast majority of HGG patients maintained a stable neurocognitive status after focal radiotherapy as measured by the Folstein Mini-Mental State Examination (MMSE) (Taylor, 1998). Although these results suggest stable cognitive function after radiotherapy, more discriminating neurocognitive assessment tools may have identified cognitive decline not apparent through the use of the MMSE (Meyers, 2003).

Ideally, a neurocognitive screening tool would be quick and brief (being cognizant of the busy community oncology practice), but sensitive to different cognitive changes or deficits. The following test battery was selected due to its brevity (approximately 20 minutes) and its widely used standardized psychometric instruments for assessing specific neurocognitive impairment known to be affected by brain tumors and treatment:

- Hopkins Verbal Learning Test (HVLT-R) (Revised): Memory (4.5 minutes)
- Controlled Oral Word Association test from the Multilingual Aphasia Examination (COWA): Fluency (3.5 minutes)
- Trail Making Test A: Visual scanning speed
- Trail Making Test B: Divided attention (5 minutes to complete both Trials)
- HVLT-R: Delayed memory, recall and recognition of word list encoded from the HVLT-R (1.5 minutes)

Add 1

This test battery has been used in a large number of other clinical trials including RTOG 0525, RTOG 0534, RTOG 0614, RTOG 0834, RTOG 0825, ACOSOG Z0300, and NCCTG N0574. This battery has also been utilized in international studies and translated in several different languages.

Although there are prospectively collected QOL data for HGG patients, there is very little testing of QOL specifically in AO and oligoastrocytoma patients. It is important to measure QOL particularly when patients may receive different treatments based on genetic testing. By collecting QOL data, one may infer the impact that different modalities (i.e. radiotherapy with or without temozolomide) may have on this population. In addition, since mood disturbances may influence cognitive function, it is important to have QOL data in conjunction with cognitive tests. Two methods of HRQOL assessment selected for the trial are the EORTC QOL questionnaire core-30 (QOL-C30, version 3) and EORTC QOL questionnaire – brain module (QOL-BN20). Both tools have robust psychometric properties as a result of rigorous testing and development from their use in several international clinical trials of cancer and are highly consistent across different language-cultural groups. The EORTC QOL-C30 comprises five function scales: physical, role (related to interference of disease with family life or social activities), emotional, cognitive, and social; six single-item scales including dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial effect of tumor and treatment; and overall QOL. EORTC QOL-BN20 is designed for use with patients with brain tumors undergoing chemotherapy or radiotherapy and has 20 items that assesses visual disorders, motor dysfunction, communication deficit, various disease symptoms (e.g., headaches and seizures), toxic effects of treatment (e.g. hair loss), and future uncertainty.

Items on both questionnaires are scaled and scored by use of recommended EORTC procedures. Raw scores are transformed to a linear scale ranging from 0 to 100, and the higher the score, the higher the level of functioning or the higher the level of symptoms. Differences of at least 10 points will be classified as the minimum clinically meaningful change in an HRQOL measure. For example, an increase of 10 points or more on a functional scale would mean a clinically significant improvement, whereas a decrease of 10 points or more would be interpreted as clinically significant worsening. Furthermore, a rise in a symptom score means deterioration, whereas a reduced score means improvement of the specific symptom. Changes of less than 10 points were regarded as no change, or as clinically irrelevant.

2.0 Goals

2.1 Primary

2.11 Determine whether there is a survival advantage for those who receive concomitant temozolomide and RT followed by adjuvant temozolomide (Stupp regimen) over that observed in patients treated with RT alone (control).

2.2 Secondary

2.21 Determine whether there is a neurocognitive advantage for those who receive temozolomide alone (Arm C) or temozolomide with concomitant RT (Arm B) over that observed in patients treated with radiotherapy alone (Arm A).

2.22 Determine whether there is a difference in survival based on t(1;19)(q10,p10) translocation status and MGMT promoter hypermethylation status.

2.23 Perform descriptive comparisons of additional secondary outcome endpoints, including time to progression, progression free survival, and the proportion of patients free of progression at 6, 12, and 24 months (PFS6, PFS12, PFS24).

2.24 Determine the toxicity of the treatment with RT and concomitant/adjuvant temozolomide in the patient cohorts described in this study.

2.25 Determine descriptively whether it is reasonable to delay RT in this patient cohort by documenting the time to progression and progression free survival of patients receiving temozolomide alone.

2.26 Determine the QOL and neurocognitive effects in patients treated on this protocol and correlate these results with outcome endpoints.

2.27 To bank blood products (i.e., plasma, DNA, and buffy coat) and tumor tissue for future scientific investigations.

3.0 Patient Eligibility

NCCTG and CTSU institutions EXCEPT NCIC CTG: ***One-Time Submission - Study Agent Shipment Form*** has been emailed to Clinicaltrials@biologicstoday.com (see Section 15.14 for complete instructions) prior to registration of the first patient to allow enough time (7-10 days) for Biologics, Inc. to process the form for drug shipment. Biologics, Inc. will confirm receipt of the SASF by email to the site.

3.1 Pre-registration – Inclusion Criteria

3.11 Willing to submit tissue samples for mandatory central pathology review submission (see Section 17.2) and deletion status determination (see Section 17.51). It should be initiated as soon after surgery as possible.

3.2 Registration – Inclusion Criteria

3.21 ≥18 years of age.

3.22 Newly diagnosed and ≤3 months from surgical diagnosis.

3.23 Histological confirmation of anaplastic glioma (oligodendroglioma, mixed, or astrocytoma [WHO grade III]), as determined by pre-registration central pathology review, and tumor is also co-deleted for 1p and 19q. NOTE: Mixed gliomas are eligible, regardless of the degree of astrocytic or oligodendrocytic predominance, as long as the tumor is also co-deleted for 1p and 19q.

3.24 Surgery ≥2 weeks prior to registration must have recovered from the effects of surgery.

3.25 The following laboratory values obtained ≤21 days prior to registration.
- ANC ≥1500
- PLT ≥100,000
- Hgb>9.0 g/dL
- Total bilirubin ≤1.5 x UNL
- SGOT (AST) ≤3 x UNL
- Creatinine ≤1.5 x ULN

3.26 Negative pregnancy test done ≤7 days prior to registration, for women of childbearing potential only.

3.27 Willing and able to complete neurocognitive examination without assistance and the QOL by themselves or with assistance (see Section 4.4).

3.28 ECOG performance status (PS) of 0, 1 or 2 (Appendix II).

3.29a Provide informed written consent.

Add 1

3.29b Patient willing to provide tissue samples for translational research purposes (see Sections 6.14, 17.3, and 17.52-17.53).

3.3 Registration – Exclusion Criteria

3.31 Any of the following because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.32 Received any prior surgery, radiotherapy or chemotherapy for any CNS neoplasm (hormones, vitamins and growth factors are not considered chemotherapy for the purposes of this study).

3.33 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.34 Concomitant serious immuno-compromised status (other than that related to concomitant steroids).

3.35 Active uncontrolled systemic infection or HIV.

3.36 Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

3.37 Active other malignancy, excepting non-melanotic skin cancer or carcinoma-in-situ of the cervix. NOTE: If there is a history of prior malignancy, they must not be receiving other specific treatment (other than hormonal therapy) for their cancer.

3.38 History of myocardial infarction ≤6 months, or congestive heart failure requiring use of ongoing maintenance therapy for life-threatening ventricular arrhythmias.

3.39 Recent history of hepatitis infection or treating physician determined that the patient would be at significant risk of reactivation of hepatitis.

4.0 Test Schedule

4.1 Arm A (RT only)

	Active-Monitoring Phase				
			During Radiation		Observation
Tests and procedures	Pre-Registration	≤21 days prior to registration	Every other week during RT	4-6 weeks post RT	Every 8 weeks for 18 months from start of treatment and then every 12 weeks until PD
Pathology review and determination of deletion status (see Section 17.2)	X[1]				
Radiation Oncology consult (see Section 6.15)	X				
History and exam, weight, performance status		X		X	X
Height		X			
Neuro history and exam		X		X	X
Pregnancy test		X[2]			
Hematology group; ANC, PLT, Hgb		X	X[6]	X	As clinically indicated
Chemistry group: SGOT [AST}, alk phos, T. bili, creatinine, CA, phos, glucose, sodium, potassium		X	X[6]	X	As clinically indicated
Head MRI with contrast or CT with contrast		X[3]		X	X
Adverse event assessment		X		X	X
Recording of steroid dose		X			X
Optional research blood draw (see Section 14.0)[R]		X[4]			
Mandatory research tissue (see Section 17.0)[R]		X[7]			
Neurocognitive/QOL Questionnaire Booklets – mandatory (See Section 4.4)		X		X	X[5]

1. If materials have been previously submitted to Mayo Clinic Rochester Neuropathology for a consult review, fax a copy of this review to the NCCTG pathology coordinator (507-284-9628) to verify diagnosis eligibility for this study. If materials have been previously submitted to the Mayo Clinic Rochester Cytogenetics Laboratory for 1p/19q deletion status, fax a copy of this review to the NCCTG pathology coordinator (507-284-9628). Then follow the pathology material procedures found in Section 17.0 so the process can be completed. Please allow 10 business days from the time NCCTG receives ALL pathology materials and usable tissue (see Section 17.23) to obtain the deletion status and get it communicated to the site.
2. For women of childbearing potential only. Must be done ≤7 days prior to registration.
3. MRI preferred; however, patients who have medical contraindications are still eligible for study by substituting contrast-enhanced CT.
4. Blood draw should be collected after registration but before any treatment. Kits are required for this collection. See Section 14.0.

Add 1 5. Every 6 months or as close as possible to the 6-month corresponding cycle number, including at time of PD. ***If at time of PD, please administer prior to informing the patient that they have PD.***

6. Weekly determinations optional as determined by the treating physician.

Add 1 7. Must be submitted <30 days following registration.

R Research funded (see Section 19.0).

4.2 Arm B (RT + TMZ → TMZ)

	Active-Monitoring Phase				
			During Radiation	**During Adjuvant Temozolomide**	**Observation**
Tests and procedures	Pre-Registration	≤21 days prior to registration	Every other week during RT	≤7 days before each cycle (cycle = 4 weeks)	After adjuvant temozolomide,[9] every 8 weeks for 18 months from start of treatment and then every 12 weeks until PD
Pathology review and determination of deletion status (see Section 17.2)	X[1]				
Radiation Oncology consult (see Section 6.15)	X				
History and exam, weight, performance status		X		X	X
Height		X			
Neuro history and exam		X		X	X
Pregnancy test		X[2]			
Hematology group: ANC, PLT, Hgb		X	X[8]	X	As clinically indicated
Chemistry group: SGOT [AST}, alk phos, T. bili, creatinine, CA, phos, glucose, NA, K		X	X[8]	X	As clinically indicated
Head MRI with contrast or CT with contrast		X[3]		X[4]	X
Adverse event assessment		X		X	X
Recording of steroid dose		X		X	X
Patient Medication Diary (Appendix IX)			X[7]	X[7]	
Optional research blood draw (see Section 14.0)		X[5,R]			
Mandatory research tissue (see Section 17.0)		X[10,R]			
Neurocognitive/QOL Questionnaire Booklets – mandatory (See Section 4.4)		X		X[6]	X[6]

1. If materials have been previously submitted to Mayo Clinic Rochester Neuropathology for a consult review, fax a copy of this review to the NCCTG pathology coordinator (507-284-9628) to verify diagnosis eligibility for this study. If materials have been previously submitted to the Mayo Clinic Rochester Cytogenetics Laboratory for 1p/19q deletion status, fax a copy of this review to the NCCTG pathology coordinator (507-284-9628). Then follow the pathology material procedures found in Section 17.0 so the process can be completed. Please allow 10 business days from the time NCCTG receives ALL pathology materials and usable tissue (see Section 17.23) to obtain the deletion status and get it communicated to the site.
2. For women of childbearing potential only. Must be done ≤7 days prior to registration.
3. MRI preferred; however, patients who have medical contraindications are still eligible for study by substituting contrast-enhanced CT.
4. ≤7 days before 1st cycle, then at 10 weeks, and then every other subsequent chemotherapy cycle.
5. Blood draw should be collected after registration but before any treatment. Kits are required for this collection. See Section 14.0.
6. Add 1 At 10 weeks, then every 6 months or as close as possible to the 6-month corresponding cycle number, including at time of PD. ***If at time of PD, please administer prior to informing the patient that they have PD.***
7. Must begin the date patient starts taking temozolomide and be completed on a daily basis as long as the paitnet is taking temozolomide and returns at next visit **OR** compliance should be documented in the medical record.
8. Weekly determinations optional as determined by the treating physician.
9. Patients receiving adjuvant treatment beyond 6 cycles should continue follow-up every other cycle, if cycles are delayed during chemotherapy, then resume every 8 weeks until completion of therapy then every 12 weeks until progressive disease.
10. Add 1 Must be submitted <30 days following registration.

R Research funded (see Section 19.0).

4.3 Arm C (TMZ only)

	Active-Monitoring Phase			
			During Temozolomide	**Observation**
Tests and procedures	Pre-Registration	≤21 days prior to registration	≤7 days before each cycle (cycle=4 weeks)	After temozolomide treatment every 8 weeks until 18 months from start of treatment then every 12 weeks until PD
Pathology review and determination of deletion status (see Section 17.2)	X[1]			
Radiation Oncology consult (see Section 6.15)	X			
History and exam, weight, performance status		X	X	X
Height		X		
Neuro history and exam		X	X	X
Pregnancy test		X[2]		
Hematology group; ANC, PLT, Hgb		X	X	As clinically indicated
Chemistry group: SGOT [AST}, alk phos, T. bili, creatinine, CA, phos, glucose, NA, K		X	X	As clinically indicated
Head MRI with contrast or CT with contrast		X[3]	X[8]	X
Adverse event assessment		X	X	X
Recording of steroid dose		X	X	X
Patient Medication Diary (Appendix IX)			X[6]	
Optional research blood draw (see Section 14.0)[R]		X[4]		
Mandatory research tissue (see Section 17.0)[R]		X[7]		
Neurocognitive/QOL Questionnaire Booklets – mandatory (See Section 4.4)		X[9]	X[5]	X[5]

1. If materials have been previously submitted to Mayo Clinic Rochester Neuropathology for a consult review, fax a copy of this review to the NCCTG pathology coordinator (507-284-9628) to verify diagnosis eligibility for this study. If materials have been previously submitted to the Mayo Clinic Rochester Cytogenetics Laboratory for 1p/19q deletion status, fax a copy of this review to the NCCTG pathology coordinator (507-284-9628). Then follow the pathology material procedures found in Section 17.0 so the process can be completed. Please allow 10 business days from the time NCCTG receives ALL pathology materials and usable tissue (see Section 17.23) to obtain the deletion status and get it communicated to the site.
2. For women of childbearing potential only. Must be done ≤7 days prior to registration.
3. MRI preferred; however, patients who have medical contraindications are still eligible for study by substituting contrast-enhanced CT
4. Blood draw should be collected after registration but before any treatment. Kits are required for this collection. See Section 14.0.

Add 1

5. At time of Cycle 3 then every 6 months or as close as possible to the 6-month corresponding cycle number, including at time of PD. ***If at time of PD, please administer prior to informing the patient that they have PD.***
6. Must begin the day patient starts taking temozolomide and be completed on a daily basis as long as the patient is taking temozolomide and returns at next visit **OR** compliance should be documented in the medical record.
7. Must be submitted <30 days following registration.
8. Every other cycle.
9. For all patients accrued to this arm.

R Research funded (see Section 19.0).

Add 1 4.4 Neurocognitive/QOL Studies – Mandatory

Add 1 **EORTC institutions:** Refer to the EORTC Group Specific instructions.

4.41 Neurocognitive

Add 1 4.411 Neurocognitive Certification [North American (NCCTG and CTSU) sites ONLY] – **Must be completed prior to registering a patient**

4.4111 The healthcare professional (e.g., nurse, psychologist, etc.) who is responsible for test administration in this study requires certification by Dr. Jane H. Cerhan, Mayo Clinic Rochester, in order to participate in this protocol. ***Each person*** who will be administering the neuropsychological assessments needs to be certified.

Test Administrator's Packet needs to be ordered upfront as the site prepares for IRB submission so the certification is in place prior to registering a patient. See the Forms Packet for the order form.

4.4112 ***Previously Certified:***

Add 1
- Individuals previously certified for RTOG 0525, RTOG 0534, RTOG 0614, RTOG 0834, RTOG 0825, ACOSOG Z0300, NCCTG N0574, or the two phase III randomized motexafin gadolinium studies (e.g., the SMART trial for lung cancer) do not need to be re-certified for this study if they have been **fully certified** (see Section 4.4113 for certification guidelines) within the last 6 months **from the time of requesting certification on N0577.**

Add 1
- Certification worksheet or email approval from the original protocol for that individual must be faxed (507-284-5280 ATTN: RPS III for N0577) or emailed to (N0577credentialing@mayo.edu) for documentation purposes (reviewing the training video is highly recommended – Access to the video can be found on the CTSU website).

Add 1 4.4113 ***Need Certification:***

- Procedures are outlined in detail in the document labeled Administration Procedures for the Neurocognitive Test Battery found in the Test Administrator's packet.
- Prior to the enrollment of any patient into the study, the healthcare professional responsible for test administration in this study ***is required to*** view a video of test administration and data collection methods. Access to the video can be found on the CTSU website. Please allow enough time for the video to download. If you have trouble accessing the

Add 1

video, please check with your programming staff ***first*** before contacting the NCCTG Operations Office at 507-538-1424 or 507-284-8670.

- Prior to the enrollment of any patient into the study, the healthcare professional responsible for test administration in this study must complete a "practice" assessment (found in the Test Administrator's packet) with another colleague (NOT a patient).
  - Complete test forms/score sheets
  - Complete and sign the Certification Worksheet for Test Administrator found in the Test Administrator's packet.
  - Mail the tests, score sheet, and signed Certification Worksheet for Test Administration to the NCCTG Operations Office, ATTN: RPS III for N0577, Plummer 4, 200 First St SW, Rochester, MN 55905.
  - Once this material is received, Dr. Cerhan will be contacted by the NCCTG Operations Office. Dr. Cerhan will then call the healthcare professional responsible for test administration to discuss the test administration and scoring issues (15-20 minutes).
- Dr. Cerhan will notify the NCCTG Operations Office regarding certification approval by faxing the Certification Worksheet for Test Administration to (507) 284-5280. The NCCTG Operations Office will then forward this information to the site and the CTSU Central Regulatory Office (CCRO) at ctsuregoffice@ecogchair.org. The CTSU CCRO will enter this information in the CTSU Regulatory Support System (RSS) so that the status of your site's credentialing review will be reflected in the RSS Site Registration Status screen at http://members.ctsu.org/rss/.

Add 1

4.4114 ***Recertification:*** Persons previously fully certified who have not administered the test battery on any of the studies noted above in Section 4.4112 within the past year from the time they were considered certified for N0577 should email N0577credentialing@mayo.edu to arrange a brief telephone review.

4.4115 Throughout the study, Dr. Cerhan will review test forms and summary sheets for cases from each site. For quality control purposes, procedural deviations (if any) will be identified, and institutions will be notified of the results of the review. If significant procedural variations are noted, re-training ('re-certification') of the test administrator will be requested.

4.4116 Completed test forms must be signed by the certified test administrator. If questions arise about testing procedures, email N0577credentialing@mayo.edu.

4.4117 **Originals of the test booklets** should be mailed to the NCCTG Operations Office, ATTN: RPS III for N0577, Plummer 4, 200 First St SW, Rochester, MN 55905. Copies of the test booklets **must** also be kept on file at the institution.

4.412 Timing of Assessments

Baseline evaluations will be performed following the surgical procedure but before beginning treatment, and thereafter as outlined in Sections 4.1, 4.2, 4.3 except in the case of disease progression at which point patients will be re-tested for the final time.

4.413 Tests and Battery Format

The tests and battery format that will be done includes the following and will take approximately 20 minutes to complete:

- Memory (4.5 minutes): Hopkins Verbal Learning Test – Revised (HVLT-R)
- Fluency (3.5 minutes): Controlled Oral Word Association test from the Multilingual Aphasia Examination (COWA)
- General Mental Ability (5 minutes): Trail Making Test A and B
- Delayed Memory (1.5 minutes): Recall and Recognition of Word List encoded from the HVLT-R

4.414 **Ordering of Material:** The clinical site should obtain all necessary booklets before pre-registering patients. Two start-up packets will be sent. When a packet is started for a new patient, order another packet right away so that you always have a supply on hand for two patients. See the Forms Packet for the Booklet Packet order form.

Add 1

4.415 If examiners have questions or are unsure about a patient's ability to complete the tests, they should contact Dr. Cerhan at N0577credentialing@mayo.edu.

4.42 Quality of Life (QOL)

4.421 QOL Assessments

Two methods of QOL assessment selected for the trial are the EORTC QOL questionnaire core-30 (QOL-C30, version 3) (Appendix V) and EORTC QOL questionnaire-brain cancer module (QOL-BN20) (Appendix VI). The average time to complete these questionnaires is approximately 10-15 minutes.

4.422 QOL Timing

Prior to randomization (baseline) and thereafter as outlined in Section 4.0 except in the case of disease progression at which point patients will complete the forms for the final time.

4.423 QOL Form Completion

QOL questionnaires must be filled out by the patient in the clinic when the patient comes for a scheduled visit. The questionnaire will be handed out to the patients by the investigator or a study nurse prior to seeing the doctor for clinical evaluations. Patients will be asked to fill out the questionnaires as completely and accurately as possible. Since the patient may experience cognitive deterioration during treatment, a 'significant other' (e.g., a spouse) may help the patient complete the questionnaires, if the patient is unable to complete the form. The responder, identified in consultation with the patient and his/her physician will be recorded on the forms.

Add 1

5.0 Stratification Factors

5.1 Cooperative groups: EORTC vs. North American groups (NCCTG, RTOG, CTSU, and NCIC CTG)

5.2 Age: ≤50 vs. >50

5.3 ECOG Performance Score: 0 and 1 vs. 2.

6.0 Registration/Randomization Procedures

ALL INSTITUTIONS:

Neurocognitive Credentialing

Completion of the below Credentialing is required **Prior** to the Pre-registration/Randomization of patients:

Add 1

EORTC institutions: Refer to the EORTC Group Specific instructions.

Examiners must complete the Neurocognitive Testing training online as outlined in Section 4.411 and as outlined in the document labeled Administration Procedures for the Neurocognitive Test Battery found in the Test Administrator's packet.

Notes:

- **An individual certification does not certify an entire institution. If more than one individual wants to administer the neurocognitive test, each individual must be certified.**

- **The individual registering the patient does not have to complete the neurocognitive credentialing component unless they intend to be an examiner HOWEVER patients cannot be registered to the study until, at minimum, one person from the institution is approved for credentialing.**

IMRT Credentialing

Add 1

EORTC institutions: Refer to the EORTC Group Specific instructions.

For institutions using IMRT: Credentialing is required **PRIOR** to the Pre-registration of patients (see Section 7.11). Review Appendix III then go to the Radiological Physical Center (RPC) web page at http://rpc.mdanderson.org/rpc to review the procedures for becoming credentialed or to determine if your institution has already met the requirements for this protocol.

RPC will notify the NCCTG Operations Office of your approved credentialing by e-mailing N0577credentialing@mayo.edu. The NCCTG Operations Office will then forward this information to the NCCTG Registration Office and to the CTSU Central Regulatory Office (CCRO) at ctsuregoffice@ecogchair.org. The CTSU CCRO will enter this information in the CTSU Regulatory Support System (RSS) so that the status of your site's credentialing review will be reflected in the RSS Site Registration Status screen at http://members.ctsu.org/rss/.

Study Agent Shipment Form (SASF)

NCCTG and CTSU institutions EXCEPT NCIC CTG: ***One-Time Submission - Study Agent Shipment Form*** (SASF) **MUST** be emailed to Clinicaltrials@biologicstoday.com (see Section 15.14 for complete instructions) prior to registration of the first patient to allow enough time (7-10 days) for Biologics, Inc. to process the form for drug shipment. Biologics, Inc. will confirm receipt of the SASF by email to the site.

6.1 Pre-Registration (Step 1)

CTSU institutions (including NCCTG institutions): Refer to the CTSU Appendix VII for site registration instructions and patient pre-registration/randomization instructions.

Add 1

EORTC institutions: Refer to the EORTC Group Specific instructions for site registration and patient pre-registration/randomization.

Add 1

6.11 To pre-register a patient, see CTSU (including NCCTG institutions) Appendix VII or EORTC Group Specific instructions.

Add 1

6.12 IRB approval(s) is required for each treating site. See CTSU (including NCCTG institutions) Appendix VII or EORTC Group Specific instructions.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the CTSU Regulatory Office (fax 215-569-0206). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the CTSU is no longer necessary.

6.13 Prior to accepting the pre-registration, the Registration Application will verify the following:

- IRB approval at the registering institution
- Patient pre-registration eligibility

- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information (*USA institutions only*).

6.14 The site has reviewed and understands the process listed in Section 17.0 and must account for sufficient time to complete pre-registration and registration steps.

6.15 An approved radiation oncologist and medical oncologist have seen the patient and confirmed the patient is a suitable candidate for this study.

6.2 Registration (Step 2)

6.21 **CTSU and NCCTG institutions**: Upon completion of the patient's submitted tissue evaluation status (see Sections17.2 and 17.51), NCCTG Pathology Coordinator will contact by fax the person provided on the samples submission form. If based upon the sample evaluations the subject is approved for registration, the pre-registering institution must register the subject to the protocol.

Add 1 **EORTC institutions**: See EORTC Group Specific instructions.

6.22 To register a patient, see CTSU (including NCCTG institutions) Appendix VII or EORTC Group Specific instructions.

6.23 At the time of registration, the following will also be recorded:

Add 1
- Patient has/has not given permission to keep left over tissue sample(s) for use in future research to learn about, prevent, or treat cancer
- Patient has/has not given permission to collect and keep blood sample(s) for use in future research to learn about, prevent, or treat cancer (see Section 14.0).

Add 1
- Patient has/has not given permission to keep left over tissue sample(s) for use in future research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission to collect and keep blood sample(s) for use in future research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Add 1
- Patient has/has not given permission for their left over tissue sample to be used for future genetic research.
- Patient has/has not given permission to collect and keep their blood sample for use in future genetic research.

Add 1
- Patient has/has not given NCCTG/EORTC permission to give their left over tissue sample(s) to outside researchers.

Add 1
- Patient has/has not given NCCTG/EORTC permission to collect and give their blood sample(s) to outside researchers.
- Patient has/has not given permission to be contacted in the future to take part in more research.

Add 1 6.24 A mandatory translational research component is part of this study; the patient will be automatically registered onto this component (Sections 3.29b, 17.3 and 17.52-53).

6.25 Treatment on this protocol must commence at the accruing membership under the supervision of a CTSU, NCCTG, or EORTC member physician.

6.26 Treatment cannot begin prior to registration and must begin ≤14 days after registration.

6.27 ***NCCTG and CTSU institutions except NCIC CTG:*** ***One-Time Submission - Study Agent Shipment Form*** has been emailed to Clinicaltrials@biologicstoday.com (see form in Forms Packet and see Section 15.14 for complete instructions) prior to registration of the first patient to allow enough time (7-10 days) for Biologics, Inc. to process the form for drug shipment. Biologics, Inc. will confirm receipt of the SASF by email to the site.

6.28 Body Surface Area has been determined. Value:_____

Add 1

6.29a Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

Add 1

6.29b All required baseline symptoms (see Section 10.3) must be documented and graded.

Add 1

6.29c **North American (NCCTG and CTSU) sites ONLY**: Blood draw kit is available on site.

Add 1

6.29d Neurocognitive/QOL questionnaire booklets are available on site; copies are not acceptable for this submission.

Add 1

6.29e NCCTG institutions only: N0392 must be open at site and offered to patient. At time of registration, the following will be recorded:

- Patient has/has not agreed to be enrolled on N0392.

6.3 Randomization Procedures:

Treatment assignment will be calculated using a dynamic allocation procedure that balances the marginal distributions of the stratification factors between the treatment arms (Pocock-Simon 1975). The factors defined in Section 5.0 will be used as stratification factors:

- Arm A – RT alone
- Arm B – RT + concomitant temozolomide → temozolomide
- Arm C – temozolomide alone

7.0 Protocol Treatment

Add 1

After registration, the following treatments must not be used (surgical procedures for tumor debulking, other types of chemotherapy, immunotherapy or biologic therapy, additional stereotactic boost radiotherapy) (see Section 13.5).

7.1 Radiotherapy – Radiotherapy will be the same in Arms A and B

7.11 Certification: Standard and conformal techniques will be allowed in this study along with IMRT. To utilize IMRT on this study, the institution must have met

specific technology requirements and have provided baseline physics information. See Section 6.0 for additional instructions. Instructions for completing these requirements or determining if they already have been met are available on the Radiological Physics Center (RPC) web site at http://rpc.mdanderson.org/rpc. An IMRT phantom study with the RPC must be successfully completed (if the institution has not previously met this credentialing requirement on another IMRT protocol). Instructions for requesting and irradiating the phantom are available on the RPC web site; select "Credentialing" and "NCCTG." To determine if some or all of the requirements have already been met, select "Credentialing Status Inquiry."

If planning to utilize IMRT, please also refer to Appendix III (ACT Guidelines for the Use of IMRT [including Intra-Thoracic Treatments]).

7.12 Radiation Energy: Minimum photon energy of 4MV with multiple ports designed and verified by simulation. If IMRT is utilized, 6 MV is preferred. Minimum SSD or SAD of 80 cm.

7.13 Treatment Volumes

7.131 Gross Tumor Volumes (GTV)

A postoperative MRI must be used for tumor localization, with the exception of 1) patient in whom MRI is contraindicated (e.g., pacemaker, claustrophobia, etc.) in which case a CT scan can be used, and 2) patients who underwent biopsy only; in which case the preoperative MRI scan can be used.

For purposes of the protocol, the GTV1 will be the so-called "edema volume" which is best visualized on the FLAIR or T2-weighted MR images. The GTV1 should also include the surgical resection cavity and any FLAIR or T2 abnormalities beyond the edges of the cavity. In the case of a gross total resection without any residual FLAIR/T2 abnormalities, then the surgical cavity will be considered the GTV1.

In cases where a partial or complete lobectomy has been performed, the region anterior to the edge of the resection (i.e., where no brain tissue is present) does not need to be included in the GTV1 (or the CTV1). For example, if a patient has an anterior temporal lobectomy, the anterior middle cranial fossa dose not need to be included in the tumor volume. In this situation, the GTV1 should encompass the resection margin and any FLAIR to T2-weighted abnormalities and areas of tumor enhancement.

If tumor enhancement is present, then a GTV boost volume should be created by contouring the area of tumor enhancement (for more details please see below) along with the resection margin. CTV boost and PTV boost are described below.

7.132 Clinical Target Volume (CTV)

The CTV1 is the GTV1 plus a margin of 1.0 cm in all directions. However, the CTV1 must not extend outside the brain. The CTV1 may also be modified to meet critical dose constraints (e.g., optic nerves) but should never be less than the GTV1.

In cases where a partial or complete lobectomy has been performed, the region anterior to the edge of the resection (i.e., where no brain tissue is present) does not need to be included in the CTV1. For example, if a patient has an anterior temporal lobectomy, the anterior middle cranial fossa does not need to be included in the tumor volume. In this situation, the CTV1 should be an expansion of the GTV1 in all directions, but not into the resection cavity.

7.133 Planning Target Volume (PTV)

The PTV1 is the CTV1 plus a 5 mm margin in all directions to account for daily setup variation and patient movement, but not beam penumbra or buildup. Generally another 5-7 mm is added to block edge in 3D planning to account for penumbra.

7.134 CTV boost is identical to the GTV boost if drawn. If there is no GTV boost then the CTV boost is identical to the GTV1.

7.135 PTV boost is the CTV boost plus a 5 mm margin in all directions to account for daily setup variation and patient movement, but not beam penumbra or buildup. Generally another 5-7 mm is added to block edge in 3D planning to account for penumbra.

7.136 Internal Margin (IM), Set-Up Margin (SM): There will be no IM or SM.

7.14 Prescription Isodose

The prescription isodose (i.e. the isodose that is 100% of the prescription dose) shall be the isodose surface (i.e. curve) that encompasses 95% of the PTV. In addition, the goal of the treatment plan is to encompass the entire PTV within the 95% isodose surface. The dose uniformity guidelines below must be met for both the PTV and the PTV boost. If IMRT is used, the PTV and the PTV boost will be treated concomitantly.

7.15 Tissue Heterogeneity

Calculations are required for IMRT and strongly recommended for 3D treatment planning to take into account the effect of tissue heterogeneities whenever CT-based planning is used. See Appendix III for the ATC Guidelines for IMRT.

7.16 Total Dose

7.161 3D Total Dose

The dose to the prescription isodose for the PTV1 (derived from the GTV1 – see above) will be 5040 cGy in 28 daily fractions of 180 cGy each. The dose will be delivered to the treatment volumes as previously described.

The dose to the prescription isodose for the PTV boost (derived from the GTV boost or GTV1 – see above) will be 900 cGy in 5 daily fractions of 180 cGy each. The dose will be delivered to the treatment volumes as previously described.

Therefore, the total dose will be 5940 cGy in 33 daily fractions of 180 cGy each.

7.162 IMRT Total Dose

The dose to the prescription isodose for the PTV1 (derived from the GTV1 – see above) will be 5445 cGy in 33 daily fractions of 165 cGy each. The dose to the prescription isodose for the PTV boost (derived from the GTV boost or GTV1 – see above) will be 5940 cGy in 33 daily fractions of 180 cGy each. The dose will be delivered concurrently to the treatment volumes as previously described.

NOTE: The BED calculations for 5445 cGy in 33 daily fractions of 165 cGy are 84.4 Gy3 and 42.1 Gy10 compared to 80.6 Gy3 and 41.4 Gy10 for 5040 cGy in 28 daily fractions of 180 cGy.

7.17 Dose Uniformity

The entire PTV shall be encompassed within the 95% isodose surface as evaluated by dose volume histogram. Please note it is preferable that 95% or more of the PTV receives the prescribed dose. The uniformity guidelines shall be met for both the PTV 1 and the PTV boost. In addition, none of the PTV boost should receive more than 110% of the prescription dose.

7.18 Time Considerations

Patients will receive one treatment per day, five days per week (Monday through Friday). All fields will be treated each day. At least two fractions must be given during the first week of treatment.

7.181 Interruptions

No special considerations need to be made for treatment delays of 1 week or less. Treatment may be given on weekends to make up for treatment interruptions. If treatment is delayed more than 1 week, notify the study chair.

7.19a Simulation

Simulation will be performed using either a conventional CT or MRI simulator.

7.19a1 Patient Position and Immobilization

The patient shall be treated in the supine or other appropriate position, depending on the location of the lesion. A head-holding device that is transparent to x-rays (thermoplast masks, bit-block, etc) must be used to ensure adequate immobilization during therapy of reproducible treatment setups.

7.19b Organs at Risk (OAR)

When possible, without shielding GTV/CTV/PTV, no more than 1% of the volume or 1 cc of each of the following OAR should receive more than the following doses: brainstem 5500 cGy, optic nerves and optic chiasm 5400 cGy, retina 4500 cGy, cervical spinal cord 5000 cGy, and lens 1000 cGy. These constraints should have a higher priority than the target volumes.

If possible, no more than 1% or 1 cc of the contralateral uninvolved brain should receive more than 3000 cGy. Also, no more than 1% or 1 cc of unspecified tissue outside of the PTV to receive >110% of the prescribed dose.

Planning organ at risk volumes (PRVs) are recommended such that the spinal cord should have 3-dimensional expansion by 5 mm while the optic nerves, optic chiasm, and brainstem should have a 3 dimensional expansion by at least 1 mm. The dose constraints to the PRVs will be the same as for their respective OARs as outlined above.

Lower priority (lower priority than PTV coverage) include: Parotids (entire volume) ≤10 Gy, oral cavity/lips/nasal cavity mean dose 20 Gy and <1% >40 Gy; inner/middle ear mean dose 30 Gy and <1% >50 Gy; lens as low as reasonable possible. Typically 100% of the parotids should receive <10 Gy, but tumor coverage is of higher priority in cases where this dose will exceed 10 Gy.

7.19c Dose Calculation and Reporting

Isodose distributions must be submitted for the treatment plan. IMRT plans must be submitted electronically to the Image-guided Therapy QA Center (ITC). 3D CRT plans should be submitted to the ITC but may be submitted in hard copy if digital submission is not possible. See the RPC web page (http://rpc.mdanderson.org/rpc) for instructions for establishing an account with the ITC and submitting data. The prescription isodose and the outlines of the planning target volume and critical organs must be shown. Isodose values must be clearly labeled. Isodose distributions in the axial, sagittal and coronal planes, which includes the isocenter of the planning target volume (PTV), must be submitted. For 3D/IMRT treatment plans in which the sagittal and coronal planes are not available, then a minimum of five axial distributions must be submitted (central axis, two superior, and two inferior planes).

7.19d Dose Volume Histograms

Dose volume histograms must include GTVs, CTVs, PTVs, and OARs as noted above. A DVH in absolute dose must also be submitted for so called "unspecified tissue," i.e., tissue contained within the skin, but not included with the GTV, CTV, PTV, or OAR.

7.19e IMRT Plan Verification

If IMRT is used, the monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the plan's fluence distribution can be re-computed for a phantom geometry.

7.19f Quality Control and Definitions of Deviations will be done according to the guidelines in Appendix IV. All plans and associated materials as per NCCTG standard will be reviewed by 2 radiation oncologists and the RPC.

7.19g Verification of treatment set-up

Port films of each field will be obtained and compared with initial simulation films at least weekly. Alternatively, after initial ports are taken of all fields (excluding vertex), an orthogonal pair of reference ports may be taken on a weekly basis. For IMRT, orthogonal pair of reference films is sufficient for the initial and subsequent ports.

Questions regarding the radiotherapy section of this protocol should be directed to:

Paul Brown, M.D.
Department of Radiation Oncology
Mayo Clinic
Rochester, MN 55905
Phone: (507) 284-2949
Email: brown.paul@mayo.edu

7.2 Treatment Schedule

Add 1

After registration, the following treatments must not be used (surgical procedures for tumor debulking, other types of chemotherapy, immunotherapy or biologic therapy, additional stereotactic boost radiotherapy) (see Section 13.5).

7.21 Arm A - Radiation therapy alone

Agent	Dose Level	Day	ReRx†
RT	5940 cGy/33 fx	1 through 5	Weekly x 6*

* May be longer based on timing of intervening weekends.

Cycle = 10-12 weeks (depends on whether or not the patient takes the full 6-week rest period)

7.22 Arm B – RT + TMZ ⟶ TMZ

Agent	Dose Level	Route	Day	ReRx†
Pretreatment medication Prophylaxis for Pneumocystis carinii pneumonia (PCP) is required (see Sections 7.25-7.254)				
RT	5940 cGy/33 fx		1 through 5	Weekly x 6*
TMZ	75 mg /m^2	Oral	Daily	Weekly x 6
Followed by a 4-week (+/- 3 days) rest period then adjuvant treatment with TMZ for 6 cycles (28 days = 1 cycle)				
TMZ	150 or 200 mg/m^{2***}	Oral	Week 1 days 1 through 5	Every 28 days x 6 cycles**

* May be longer based on timing of intervening weekends.

** May extend to 12 cycles at physician discretion.

*** The first cycle of adjuvant temozolomide is administered at the dose of 150 mg/m^2. The dose is escalated to 200 mg/m^2 as of subsequent cycles in the absence of toxicity (see Section 8.0).

† If there is radiological evidence of progression only (without clinical neurologic progression) before the first cycle of adjuvant treatment, the decision to stop radiotherapy can be made, but adjuvant chemotherapy should be initiated/continued, if in the judgment of the treating physician, the radiologic progression may represent pseudo-progression, and/or the patient is clinically stable or deriving clinical benefit.

7.23 Arm C – TMZ alone

Dose Level	Route	Day	ReRx†
Pretreatment medication Prophylaxis for Pneumocystis carinii pneumonia (PCP) is required (see Sections 7.25-7.254)			
150 or 200 mg/m^{2*}	Oral	Week 1 days 1 through 5	Every 28 days x 12 cycles

* The first cycle of temozolomide is administered at the dose of 150 mg/m^2. The dose is escalated to 200 mg/m^2 as of Cycle 2 in the absence of toxicity (see Section 8.0).

† If there is radiological evidence of progression only (without clinical neurologic progression) before the first cycle of adjuvant treatment, the decision to stop radiotherapy can be made, but adjuvant chemotherapy should be initiated/continued, if in the judgment of the treating physician, the radiologic progression may represent pseudo-progression, and/or the patient is clinically stable or deriving clinical benefit.

7.24 Temozolomide dosing will be based on body surface area (BSA) calculated by using the subject's height and actual body weight. The smallest temozolomide capsules are 5 mg. Therefore, patient doses of temozolomide will be rounded to the nearest interval of 5 mg. Temozolomide capsules should be taken preferably in the morning with up to 200 mL of water on an empty stomach one hour before or one hour after food. Since temozolomide may cause nausea, an appropriate anti-emetic (e.g., 1 mg dose of granisetron or 4-8 mg of ondansetron) should be given once a day before the temozolomide. On days when patients do not have radiation, they should take temozolomide in the morning on an empty stomach.

7.25 Temozolomide with or without steroids can result in significant immunosuppression and places patients at increased risk for opportunistic infections such as Pneumocystis carinii pneumonia (PCP) and gram-negative organisms. Therefore, **antibiotic prophylaxis is absolutely required** for patients treated on this protocol. There are 3 acceptable prophylaxis regimens. Prophylaxis should start with the first day of cycle 1 and continue for at least 1 month following completion of drug therapy.

7.251 Prophylaxis with trimethoprim/sulfamethoxazole is the highly preferred method and should be used unless there is a documented severe allergy to sulfa medications. Initial therapy should be trimethoprim/sulfamethoxazole (SS or DS) PO, 1 tablet daily. If this is not tolerated well, trimethoprim/sulfamethoxazole may be reduced to 1 tablet three times a week.

7.252 If patients have a history of mild to moderate sensitivity to sulfa drugs, then they should undergo sulfa desensitization. This is routinely performed for patients undergoing organ transplantation. A consultation with an allergist familiar with trimethoprim/sulfamethoxazole desensitization should be considered prior to desensitization. A recommended desensitization protocol is attached as Appendix X. Patients with prior history of sulfa-induced anaphylaxis, Stevens Johnson's syndrome, erythema multiforme or airway compromise are not appropriate candidates for desensitization and should be treated with pentamidine or dapsone.

7.253 If patients have a severe allergy to sulfa, are intolerant of trimethoprim/sulfamethoxazole once they start therapy, or cannot be successfully desensitized, then they must be treated with intravenous pentamidine (4 mg/kg infused over 60 to 90 minutes once per month). Pentamidine can also be administered via inhalation (300 mg via aerosol) if preferred. If a patient is not able to take either trimethoprim/sulfamethoxazole or pentamidine, dapsone (100 mg po each day [except in patients with G6PD deficiency]) can be given. These agents should be given according to institutional guidelines.

7.254 Prophylaxis for PCP with either trimethoprim/sulfamethoxazole or pentamidine or dapsone must be maintained continuously during therapy with temozolomide, regardless of the lymphocyte count (ALC). After completion of the temozolomide, patients with an ALC $<500/mm^3$ should have CD4 quantification. If the ALC or CD4 is <200, then prophylaxis is recommended to continue and the CD4 should be quantified on a monthly basis. If the ALC is ≥500 or the CD4 is >200, then prophylaxis can be stopped. Trimethoprim/sulfamethoxazole or pentamidine or dapsone therapy should continue for at least 1 month following discontinuation of drug therapy with temozolomide.

7.26 Following registration, surgical procedures for tumor debulking, other types of chemotherapy, and immunotherapy or biologic therapy must not be used; if medically necessary, the patient will be considered off study. Further, additional stereotactic boost radiotherapy is not allowed. If any of these treatments are required, the patient will not receive further therapy with temozolomide according to this protocol. All further therapy is at the treating physician's discretion, but should be recorded in the CRF.

8.0 Dosage Modification Based on Adverse Events - Strictly follow the modifications in this table until individual treatment tolerance can be ascertained. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed.

8.1 Radiotherapy

With the type and site of radiotherapy foreseen in this protocol, interruption due to acute radiation toxicity is unlikely. Individual reasons, such as major worsening of neurological or mental status or any other medical condition that would preclude the continuation of radiotherapy and conversely the decision to resume radiation therapy after interruption will be taken on an individual basis by the treating physician.

For example, cranial irradiation can be withheld for CNS toxicity or ototoxicity ≥grade 3 attributable to radiotherapy. The overall time of interruption and over all time of radiotherapy must be recorded. Radiotherapy should not be interrupted due to hematologic toxicity or other temozolomide-related toxicities. If radiotherapy is interrupted, actions regarding dosing on concomitant temozolomide are described below:

- If the administration of temozolomide is interrupted, the radiotherapy will proceed normally and no catch up days of temozolomide will be given after the end of radiotherapy.
- Concomitant temozolomide treatment will last until the end of radiotherapy, but in the event of delays in radiotherapy which are unforeseen or clearly related to radiotherapy, the temozolomide should be continued daily up to a total not to exceed 49 days (e.g., may be continued up to a maximum of 7 weeks/49days in event of such radiotherapy delays).
- If radiotherapy definitely stopped, treatment with daily temozolomide should stop. Temozolomide can resume with the initiation of the adjuvant phase of treatment.

8.2 Temozolomide

8.21 Concomitant Treatment (RT+TMZ)

8.211 No dose reduction will be made, but delay or discontinuation of temozolomide will be decided according to hematologic and non-hematologic adverse events (AEs).

8.212 If temozolomide is delayed, the RT will proceed normally. Missed doses of temozolomide will not be made up at the end of radiotherapy.

8.213 If the dose was reduced or delayed for adverse events, there will be no dose escalation.

ALERT: *ADR reporting may be required for some adverse events (See Section 10)*

→ → *Use Common Toxicity Criteria (CTC) Version 3.0 unless otherwise specified* ←←		
CTC CATEGORY	ADVERSE EVENT	DOSAGE CHANGE
Blood/Bone Marrow	ANC <1500 – 1000 **OR** PLTS <50,000-25,000	Continue RT but hold temozolomide until ANC ≥1500 and PLTS ≥100,000. If unresolved after 2 weeks, discontinue and go to event monitoring.
	ANC <1000 – 500 **OR** PLTS <50,000 – 25,000 x 10^9/L (≥ grade 2)	Continue RT but hold temozolomide until ANC ≥1500 and PLTS ≥100,000. A complete blood count (CBC) should be done at least twice weekly. If unresolved after 3 weeks, discontinue and go to event monitoring.
	ANC <500 **OR** PLTS <25,000(grade 4)	Hold RT. Resume RT when ANC ≥500 and PLTS ≥50,000. Discontinue temozolomide.
Non hematologic	Grade 3 (except fatigue, nausea and vomiting if on maximal antiemetic therapy, and alopecia)	Omit temozolomide until ≤grade 1 (or ≤grade 2 if present at baseline) then resume temozolomide at the same dose as used initially. Relevant laboratory tests should be done at least weekly. If unresolved after 3 weeks, discontinue and go to event monitoring.
	Grade 4 (except fatigue, nausea and vomiting if on maximal antiemetic therapy, and alopecia)	Discontinue temozolomide.

8.22 Adjuvant Treatment (TMZ alone)

8.221 If the dose was reduced or delayed for adverse events, there will be no dose escalation.

8.222 Delay or discontinuation of temozolomide will be decided according to hematologic and non-hematologic adverse events (AEs).

ALERT: *ADR reporting may be required for some adverse events (See Section 10)*

→ → *Use Common Toxicity Criteria (CTC) Version 3.0 unless otherwise specified* ←←		
CTC CATEGORY	ADVERSE EVENT	DOSAGE CHANGE*†
Blood/Bone Marrow	ANC & PLT Grade 2	Delay temozolomide up to 3 weeks until ≤grade 1. If unresolved after 3 weeks, discontinue and go to event monitoring.
	Grade 3-4	Delay temozolomide up to 3 weeks until ≤grade 1 then reduce by 1 dose level. If unresolved after 3 weeks, discontinue and go to event monitoring.
Non hematologic	Grade 3 (except fatigue, nausea and vomiting if on maximal antiemetic therapy, and alopecia)	Delay temozolomide up to 3 weeks until ≤grade 1 (or ≤grade 2 if present at baseline) then reduce by 1 dose level. If unresolved after 3 weeks, discontinue and go to event monitoring.
	Grade 4 (except fatigue, nausea and vomiting if on maximal antiemetic therapy, and alopecia)	Discontinue and go to event monitoring.

* **Dose Escalation:** If, during the first cycle, all non-hematologic AEs observed were ≤grade 2 (except alopecia, nausea and vomiting) and platelets ≥100 x 10^9/L and ANC ≥1.5 x 10^9/L then the temozolomide dose should be escalated to dose level 1 and this dose should be used as the starting dose for subsequent cycles. If treatment after cycle 1 has to be delayed because of ongoing non-hematologic AEs of ≥grade 2, then no escalation is possible. If the dose was not escalated at cycle 2, then the dose should not be escalated in further cycles.

† **Dose Reduction:** 1) No more than 2 dose reductions will be allowed. 2) If any of the same non-hematologic grade 3 AE recurs (except alopecia, nausea and vomiting while on maximal antiemetic therapy and alopecia) after reduction for that AE, then temozolomide will be stopped.

8.223 TMZ Dose Reduction/Escalation Table

Dose Level	Dose mg/m^2/day (1-5)	Dosage Change
-2	100	Reduction if prior toxicity as defined in Section 8.22 table
-1	125	Reduction if prior toxicity as defined in Section 8.22 table
0	150	Starting dose Cycle 1
+1	200	Escalated dose as of Cycle 2 in absence of toxicity

9.0 Ancillary Treatment

9.1 Corticosteroid treatment.

9.11 Dosages of steroids must be recorded on the Concurrent Steroid and Anticonvulsant Treatment Form.

9.12 Corticosteroids should be used in as low a dose as possible.

9.13 At progression of disease, corticosteroid choice and dosages are at the discretion of the patient's physician.

9.2 Growth factors are not permitted to induce elevations in neutrophil count for the purposes of (1) administration of temozolomide on the scheduled dosing interval, or (2) allowing treatment with temozolomide at a higher dose, or (3) avoiding interruption of the treatment during concomitant radiotherapy.

9.3 Antiemetics – Since TMZ may cause nausea, it is suggested that an appropriate anti-emetic (e.g., 1 mg dose of granisetron, or 4 mg of ondansetron, or other) be given one hour before the TMZ. As an alternative procedure, the antiemetic may be provided the first 3 days of concomitant RT/TMZ and the first 3 days of adjuvant TMZ, with any further need determined by the treating physician based on perception of clinical need. Additional symptoms will be managed as per standard antiemetic guidelines.

9.3 Anticonvulsants - Dosages must be recorded on Concurrent Steroid and Anticonvulsant Treatment Form. Anticonvulsant levels will be maintained in the therapeutic range and doses adjusted for maximal therapeutic efficacy, at the discretion of the patient's physician. Where medically appropriate, the use of a non-enzyme-inducing anticonvulsant will be encouraged.

9.4 Temozolomide and pneumocystis carinii pneumonia

9.41 Pneumocystis carinii pneumonia has developed in patients when taking concomitant temozolomide and steroids. This is of concern especially for lymphopenic patients. See Sections 7.25-7.254.

10.0 Adverse Event (AE) Reporting and Monitoring

CTSU institutions: Refer to the CTSU Appendix VII for additional information

Add 1 **EORTC institutions:** Refer to the EORTC Group Specific instructions for additional information

10.1 This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 for adverse event monitoring and reporting. The CTCAE v3.0 can be accessed from the CTEP home page http://ctep.cancer.gov. All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE. Next, determine whether the event is expected or unexpected (refer to Section 10.12) and if the adverse event is related to the medical treatment or procedure (see Section 10.13). With this information, determine whether an adverse event should be reported as an expedited report (see Section 10.2). Important: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Section 10.3 and 18.0).

Expedited adverse event reporting requires submission of an Adverse Event Expedited Reporting System (AdEERS) report(s). Other expedited reporting requirements and systems may also apply. Expedited and/or routine reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.2 and 10.3. All expedited AE reports must also be sent to the local Institutional Review Board (IRB) according to local IRB's policies and procedures.

10.12 Expected vs. Unexpected

- The determination of whether an AE is expected is based on the agent-specific information provided in Section 15.0 of this protocol.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of this protocol.

10.13 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

10.2 Expedited Adverse Event Reporting Requirements

10.21 Requirements for Expedited Reporting via AdEERS for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

	Grade 1	**Grade 2**	**Grade 3**		**Grade 3**		**Grades 4 & 5**
			Unexpected		**Expected**		
	Unexpected and Expected	**Unexpected and Expected**	**with Hospitalization**	**without Hospitalization**	**with Hospitalization**	**without Hospitalization**	**Unexpected and Expected**
Unrelated Unlikely	Not Required	Not Required	Not **Required**[2]	Not **Required**	Not Required[2]	Not Required	Not Required[2]
Possible Probable Definite	Not Required	Not Required	7 Calendar Days	Not Required	7 Calendar Days	Not Required	24-Hour; 3 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under an IND require reporting as follows:**
AdEERS 24-hour notification followed by complete report within 3 calendar days for:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 4 unexpected events
- Grade 5 expected events and unexpected events

[2] Although expedited reporting via AdEERS is not required for hospitalizations or Grade 4 or 5 events with attribution of unlikely or unrelated, other expedited <u>and</u> routine reporting requirements must be adhered to. Please refer to the sections below for related instructions.

Please see additional instructions and/or exceptions below under section entitled "Additional Instructions or Exceptions."

- Expedited AE reporting timelines defined:
  - "24 hours; 3 calendar days" – The investigator must initially report the AE via AdEERS within <u>24 hours</u> of learning of the event followed by a complete AdEERS report within <u>3 calendar days</u> of the initial 24-hour report.

- "7 calendar days" - A complete AdEERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any event that results in persistent or significant disability/incapacity, congenital anomaly, or birth defect must be reported via AdEERS if the event occurs following treatment with an agent under an IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all expedited reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements

The NCCTG SAE Coordinator will forward a copy of all AdEERS reports to:

- The NCCTG IND Coordinator who will notify the FDA as warranted by the event and stipulated in the U.S. Code of Federal Regulations.
- Schering Plough Drug Safety Surveillance (DSS) using the DSS SAE Cover Sheet WITHIN 24 HOURS of NCCTG becoming aware of the event by faxing (973) 921-7422 or 7424
- Add 1 In the rare event when Internet connectivity is disrupted, a report may be prepared using the Adverse Event Expedited Report – Single Agent or Multiple Agents paper template (available on the CTEP Home Page at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adeers.htm under AdEERS Templates) and faxed to the NCCTG Operations Office at 507-284-9628. A 24-hour notification may be made to NCCTG by telephone at 507-266-3028, only when Internet connectivity is disrupted. Once Internet connectivity is restored, an AE report submitted on a paper template or a 24-hour notification phoned in must be entered electronically into AdEERS by the original submitter at the site. Contact the NCCTG SAE Coordinator (as identified on the NCCTG Protocol Resources page) for additional back-up submission instructions.

10.22 Other Required Expedited Reporting

EVENT TYPE	REPORTING PROCEDURE
Secondary AML/MDS	Reporting for this event required during and after completion of study treatment. Submit the NCI/CTEP Secondary AML/MDS Report form within 15 days via fax or mail to the NCCTG SAE Coordinator, NCCTG Operations Office, 200 First Street SW, Rochester, MN 55905, Fax (507)284-9628. The Operations Office will submit to NCI.

For NCCTG institutions only: Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report	Complete a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form within 5 working days of the date the clinical research associate (CRA) is aware of the event(s) necessitating the form. If an AdEERS report has been submitted, this form does not need to be submitted. Submit the Non-AER form electronically via the NCCTG Remote Data Entry System within 5 working days of the date the CRA is aware of the event(s) necessitating the form.
Pregnancy	If a female patient becomes pregnant during the study, the site should complete the Pregnancy Monitoring Form found in the Forms Packet and **fax within 24 hours to** Schering Plough: (973) 921-7425.

Add 1

10.3 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 grading unless otherwise stated:

Category	Adverse Event/Symptoms	Baseline	Each evaluation
Pulmonary/Upper Respiratory	Cough	X	X
	Dyspnea (shortness of breath)	X	X
Dermatology/Skin	Rash/desquamation	X	X
Ocular/Visual	Keratitis (corneal inflammation/corneal ulceration)	X	X
Gastrointestinal	# stools per day	X	
	Diarrhea		X
	Nausea	X	X
Neurology*	CNS necrosis/cystic progression		X*
	Cognitive disturbance		X*
	Memory impairment		X*

*Late effects of RT – evaluate after completion of RT (Arms A and B).

10.31 Submit to the NCCTG Research Base via the Nadir/AE Log the following AEs experienced by a patient and not specified in Section 10.3

10.311 Grade 1 and 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.312 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.313 Grade 5 AEs (Deaths)

10.3131 Any death within 30 days of the patient's last study treatment or procedure.

10.3132 Any death more than 30 days from the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.32 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation

11.1 Response criteria: The neurologic examination and the MRI and/or CT at each evaluation will be scored as follows:

11.11

NEURO EXAM STATUS (compared to pre-Rx exam)	
Better:	must be on stable or decreasing dose of steroids.
Same:	failure to qualify for better or worse.
Worse: *	includes patients requiring increasing steroid dose to remain stable.

* In the case of predominately non-enhancing tumors: an increase of 25% in bi-dimensional perpendicular product of signal hyperintensity area on MRI T2 weighted images or FLAIR images, or area with hypodensity on CT scan.

11.12 MRI AND/OR CT ASSESSMENT (compared to pretreatment scan for bidimensionally measurable disease:

CR =	Total disappearance of all tumor. CR requires that patients be on no corticosteroids or on only adrenal replacement maintenance.
PR =	≥50% reduction in product of perpendicular diameters of contrast enhancement or mass with no new lesions. PR requires stable or decreasing steroid dosing.
SD =	failure to qualify for CR, PR, or PD.
PD =	>25% increase in product of perpendicular diameters of contrast enhancement or mass or appearance of new lesions.

11.13 MRI AND/OR CT ASSESSMENT (compared to pretreatment scan) for evaluable disease (i.e., contrast enhancing mass on MRI and/or CT which is not bidimensionally measurable but clearly evaluable for response to therapy.

NED	Patients who have had a gross total resection and thus have no measurable residual tumor will be assessed for NED versus PROG only. Use only if appropriate
CR =	Total disappearance of all tumor. CR requires that patients be on no corticosteroids or on only adrenal replacement maintenance.
REGR =	unequivocal reduction in extent of contrast-enhancement or a decrease in mass effect as agreed upon independently by primary physician and quality control physicians; no new lesions.
SD =	failure to qualify for CR, REGR, or PD.
PD* =	unequivocal increase in size of contrast enhancement or increase in mass effect as agreed upon independently by primary physician and quality control physicians: appearance of new lesions.

* In the case of predominately non-enhancing tumors: an increase of 25% in bi-dimensional perpendicular product of signal hyper-intensity area on MRI T2 weighted images or FLAIR images, or area with hypo-density on CT scan.

11.14 Objective Status: Scored as follows for cycles with MRI and/or CT.

<table>
<tr><td>NEURO STATUS</td><td colspan="6">MRI and/or CT Status</td></tr>
<tr><td></td><td>NED</td><td>CR</td><td>PR</td><td>REGR</td><td>SD</td><td>PD</td></tr>
<tr><td>Better</td><td rowspan="2">NED</td><td rowspan="2">CR</td><td rowspan="2">PR</td><td rowspan="2">REGR</td><td rowspan="2">SD</td><td>UNKN*</td></tr>
<tr><td>Same</td><td rowspan="2">PD</td></tr>
<tr><td>Worse</td><td colspan="5">UNKN*</td></tr>
</table>

* Set the Objective Status equal to unknown. Treat one more cycle and evaluate according to the table below:

<table>
<tr><td>NEURO STATUS</td><td colspan="6">MRI and/or CT Status</td></tr>
<tr><td></td><td>NED</td><td>CR</td><td>PR</td><td>REGR</td><td>SD</td><td>PD</td></tr>
<tr><td>Better

Same</td><td>NED</td><td>CR</td><td>PR</td><td>REGR</td><td>SD</td><td>PD</td></tr>
<tr><td>Worse</td><td colspan="5"></td></tr>
</table>

11.15 Comments regarding definitions of progression

Special attention should be given so as to avoid labeling progressive enhancement or edema which develops immediately after the end of radiotherapy as tumor progression. Pseudo-progression within the first three months from completion of radiotherapy is recognized to occur. Such pseudo-progression may continue for months and may be accompanied by clinical signs and symptoms. Therefore, only in exceptional cases should the adjuvant treatment be discontinued or canceled within 3 months of radiotherapy. In

addition, surgery may cause increased contrast update, which should be differentiated from tumor progression. The clinical follow-up must dictate how the initial progression of the lesion should be labeled. If the course of events shows that true progression indeed occurred, the date of the first increase is to be considered as the date of progression. The study chair may be contacted for further discussions on a case-by-case basis. At all times, in case of clinical/neurological progression, radiological confirmation of the progression is recommended. If no clear progression is visible on neuro-imaging, other explanations for the deterioration must be sought (e.g. anticonvulsant medication, metabolic disturbances).

12.0 Descriptive Factors

12.1 Location of lesion: Frontal vs. temporal vs. parietal vs. occipital.

12.2 Side of lesion: Right vs. left vs. midline vs. bilateral.

12.3 Other tumor sites: Thalamus vs. basal ganglia vs. hypothalamus vs. 3rd ventricle vs. 4th ventricle vs. optic chiasm vs. brain stem vs. other.

12.4 Maximum diameter in cm on a preoperative scan of:
a) Contrast enhancement.
b) Abnormal T_2 signal on MRI (specify) or low attenuation on CT.

12.5 Extent of resection (by treating physicians' opinion): Biopsy vs. subtotal vs. gross total.

12.6 Family history of brain tumor: Yes vs. no.

If yes, check all that apply
_____Father
_____Mother
_____Brother or sister
_____Child
_____Other (list:_____)

12.7 Contrast enhancement on preoperative scans: Yes vs. no vs. uncertain.

12.8 Corticosteroid therapy at study entry: Yes vs. no.

12.9 Anticonvulsant use: Yes vs. no.

13.0 Treatment/Follow-up Decision at Evaluation of Patient

13.1 A patient is deemed *ineligible* if at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient will go directly to the event-monitoring phase of the study.
- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

The patient may continue non-protocol treatment at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.2 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. Event monitoring will be required per Section 18.0 of the protocol. The patient may continue non-protocol treatment at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.3 A patient is deemed a *cancel* if he/she is removed from study for any reason after pre-registration but prior to randomization. The Pre-Registration Screening Failure Form must be submitted. No further data submission is necessary.

13.4 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. The patient will go directly to the event-monitoring phase of the study per Section 18.0.

13.5 After registration, the following treatments must not be used (surgical procedures for tumor debulking, other types of chemotherapy, immunotherapy or biologic therapy, additional stereotactic boost radiotherapy). If medically necessary, the patient will be considered off study and will go directly to the event-monitoring phase per Section 18.0. All further therapy is at the treating physician's discretion.

13.6 Patient will continue treatment as stated in Section 7.0 or until PD, unacceptable toxicity, investigator's decision to remove patient from the study, patient refusal to continue or alternate treatment. Treatment will be discontinued. The patient will go to event monitoring per Section 18.0.

Add 1

13.7 Patients may continue on treatment as stated in Section 7.0 if they refuse to do any further neurocognitive testing and/or QOL testing.

13.8 All other patients will enter Observation after completion of RT and/or TMZ treatment until PD when the patient will go to event monitoring:

- Arm A patients: every 8 weeks for 18 months from start of treatment, then every 12 weeks until PD
- Arm B patients: every 8 weeks for 18 months from start of treatment, then every 12 weeks thereafter until PD
- Arm C patients: every 8 weeks for 18 months from start of treatment, then every 12 weeks until PD.

13.9 If there is radiological evidence of progression only (without clinical neurologic progression) before the first cycle of adjuvant treatment, the decision to stop radiotherapy can be made, but adjuvant chemotherapy should be initiated/continued, if in the judgment of the treating physician, the radiologic progression may represent pseudo-progression, and/or the patient is clinically stable or deriving clinical benefit.

14.0 Body Fluid Biospecimens

14.1 Body Fluid Biospecimen Submission – **Optional - For North American institutions only (NCCTG and CTSU)**

14.11 Summary Table of Body Fluid Biospecimens for This Protocol

Type of Biospecimen to submit	Mandatory or optional	When to submit	Reason for submission (background/methodology section)	Where to find specific details for specimen submission
Blood/blood products (EDTA and Na heparin blood and EDTA plasma)	Optional	After registration but before any treatment	Banking (Section 14.4)	Section 14.2

14.2 Blood/Blood Products

14.21 **Kits are required for this study.**

14.211 The kit contains supplies and instructions for collecting, processing, and shipping specimens.

14.212 Participating institutions may obtain kits by faxing the Supply Order Form (found in the Forms Packet) to the number listed on the form. Because we are now being charged for all outgoing kits, a small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry.

14.213 Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. **Allow at least two weeks to receive the kits.**

14.214 Kits will not be sent via rush delivery service unless the participating institution provides their own FedEx® account number or alternate billing number for express mail. **NCCTG will <u>not</u> cover the cost for rush delivery of kits.**

14.22 All samples must be collected **Monday-Thursday ONLY.**

14.23 Label specimen tubes with protocol number, NCCTG patient ID number, and time and date blood drawn.

14.24 Collect and process all blood/blood products according to specific kit instructions and table below.

14.241 Summary Table of Research Blood/Blood Products to be Collected for this Protocol

Indicate if specimen is mandatory or optional	Collection tube description and/or additive (color of tube top)	Volume to collect per tube (number of tubes to be collected)	Blood product being processed	After registration but before any treatment	Process at site?	Storage/ shipping conditions[1]
Optional	EDTA (purple)	10 mL (1)	Whole Blood	X	No	Refrigerate/ cold pack (DO NOT FREEZE)
Optional	EDTA (purple)	10 mL (1)	Plasma	X	Yes	Frozen/dry ice
Optional	Na heparin (green)	10 mL (2)	Whole Blood	X	No	Refrigerate/ cold pack (DO NOT FREEZE)

[1] After all samples have been processed according to kit instructions, ship all specimens according to shipping instructions (see Section 14.25 for detailed shipping instructions).

14.25 Shipping

14.251 Verify ALL sections of the Blood Specimen Submission Form (see Forms Packet), MML Requisition Form (provided in kit), and specimen collection labels are completed and filled in correctly.

NCCTG institutions: Enter information from the Blood Specimen Submission Form into the remote data entry system ≤14 days of specimen collection (see Forms Packet).

CTSU institutions: See Appendix VII for instructions.

14.252 Specimens must be shipped the same day they are drawn.

Add 1

14.253 The MML kits will include a smart shipper label (white-barcoded label) affixed to the berry-colored shipping boxes. The smart shipper label is pre-addressed and replaces the need for the FedEx airbill. Shipping costs will be covered by NCCTG if this berry-colored box is used for shipping the specimens to MML.

14.254 Specimens will be shipped in a dual-temperature shipping container. Place the refrigerated EDTA and sodium heparin whole blood tubes with a properly prepared cold pack in one compartment. See kit instructions for specific details for cold pack preparation (i.e., frozen or refrigerated) and proper packing of blood and cold pack to avoid freezing of specimen. Place the frozen plasma samples with dry ice in the other compartment of the dual-temperature shipping container.

14.255 Ship specimens via Priority Overnight service, **Monday – Thursday ONLY,** to Mayo Medical Laboratories (MML). **Do not send samples on weekends or holidays.**

Add 1

14.256 MML will receive the samples and immediately forward specimens within two hours of accessioning to the NCCTG Research Base Biospecimens Accessioning and Processing (BAP) Shared Resource, Stabile 13-10A, Attention: BAP Supervisor.

14.257 BAP will process specimens according to Appendix XII instructions.

14.3 Other Body Fluids: None.

14.4 Background/Methodology Information

14.41 Peripheral blood mononuclear cells (PBMCs) will be isolated from 2 x 10 mL Na heparin whole blood at baseline. PBMCs will be stored frozen in liquid nitrogen at the NCCTG Research Base BAP Shared Resource for future research according to patient consent information (see Section 6.23). As specific analyses are identified and protocols are developed, they will be presented for NCCTG and IRB review and approval.

14.42 DNA and buffy coat will be extracted at baseline from whole blood collected in one 10 mL EDTA tube. DNA and buffy coat will be stored frozen at -80ºC in the BAP Shared Resource, for future pharmacogenetic research according to patient consent information (see Section 6.23). As specific analyses are identified and protocols are developed, they will be presented for NCCTG and IRB review and approval. (This collection is part of a general strategy of investigation for the majority of NCCTG studies.)

14.43 Plasma will be processed and frozen at the participating institutions from one 10 mL EDTA tube and stored frozen at -80ºC in the NCCTG Research Base BAP Shared Resource for future research depending on the patient consent permission (see Section 6.23). As protocols are developed and specific analyses are identified, they will be presented for NCCTG and IRB review and approval. (This collection is part of a general strategy of investigation for the majority of NCCTG studies.)

14.44 Return of Genetic Testing Research Results

For this study, DNA specimens are only being banked and no specific genetic testing is being performed. If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Drug Information

15.1 Temozolomide (Temodar®, Temodal®)

IND exempt (#105196)

15.11 Formulation: Other Names: - methazolastone; Temozolomide is supplied in preservative-free, two-piece, hard gelatin capsules of the following p.o. dosage strengths: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg. Each capsule contains drug substance in combination with lactose, anhydrous NF, colloidal silicon dioxide NF, sodium starch glycolate NF, tartaric acid NF, and stearic acid NF. The capsule shells contain gelatin NF, titanium dioxide USP, and sodium lauryl sulfate NF.

15.12 Mode of Action: Alkylating agent of imidazotetrazinone class.

15.13 Storage and Stability: See product label for storage and stability information.

15.14 Supply: Temozolomide will be supplied, free of charge, by Schering-Plough, for all patients entered into this study.

Add 1

EORTC institutions: See EORTC Group Specific instructions for ordering information.

NCIC CTG institutions: See NCIC specific instructions

NCCTG and CTSU institutions except NCIC CTG: The drug will be distributed by a vendor, Biologics, Inc., under contract to NCCTG. Shipments will be patient-specific. Please refer to the product's complete prescribing information for additional information and the following:

15.141 The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all drugs received using the Drug Accountability Record form. The Study Agent Shipment Form (SASF) (found in the Forms Packet) must be submitted electronically to **Biologics, Inc at Clinicaltrials@biologicstoday.com** as soon as the individual responsible for the study agent has been identified. The SASF is only required to be submitted one time per institution. The SASF **must be** processed before the institution can be approved to receive drug. Institutions should allow adequate time (7-10 days) for form processing before registering the first case. Biologics, Inc. will confirm receipt of the SASF by email to the site.

15.142 The temozolomide supply will not be shipped by Biologics, Inc. until the patient has been registered and Biologics, Inc. has received the Study Agent Shipment Form (SASF) (see Section 15.141).

- Biologics generally ships drug Mondays through Fridays.
- Biologics, Inc. does not ship drug prior to weekends or holidays.
- Biologics, Inc. will ship orders "same day" for all orders received before 4 p.m. E.T. Monday through Friday. U.S. shipments will be sent via Federal Express for *Second day delivery.*
- Orders received after 4 p.m. E.T. Monday through Friday will be processed and shipped the next business morning.
- NCCTG registration system will notify Biologics, Inc. by email that a patient has been officially registered in order to initiate each of these shipments. The shipments will be sent to the site according to the information provided on the SASF. **Patient registration**, not submission of the SASF, **triggers the patient's initial drug shipment.** Each institution is responsible for notifying Biologics, Inc. at Clinicaltrials@biologicstoday.com if the drug does not arrive on the expected date. The drug will be shipped per patient. The vials will be manufacturer stock vials with no specific patient identifier on them. It will be important to store the vials per patient for inventory purposes.

Arm B

- Once official notification is received (via email notification from NCCTG registration system to Biologics, Inc.) that a new patient is randomized to Arm B of the study, Biologics, Inc. will prepare and ship a 49-day supply of temozolomide. Quantity shipped is based on the patient's BSA and prescribed dose (75 mg/m2 - see Section 7.22). Biologics, Inc. will call the site contact who will receive the agent to provide the date and time of anticipated delivery to the site.
- Biologics, Inc. will contact the site study coordinator at the conclusion of the patient's radiation therapy (about 6.5 weeks) to confirm that the patient will begin adjuvant temozolomide treatment and obtain the patient's most current BSA. Biologics, Inc. prepares and ships temozolomide for cycles 2-7. Quantity shipped is based on the patient's BSA and prescribed dose as outlined in Section 7.22.
- Two weeks prior to the 7^{th} cycle, Biologics, Inc. will contact the site study coordinator to confirm that the patient is still on study while confirming their current dose. If the patient is still on study, Biologics, Inc. will prepare temozolomide for cycles 8-13.

Arm C

- Once official notification is received (via email notification from NCCTG registration system to Biologics, Inc.) that a new patient is randomized to Arm C of the study, Biologics, Inc. will prepare and ship temozolomide for cycles 1-6. Quantity shipped is based on the patient's BSA and prescribed dose as outlined in Section 7.23. Biologics, Inc. will call the site contact who will receive the agent to provide the date and time of anticipated delivery to the site.
- Two weeks prior to the patient's 7th cycle, Biologics, Inc. will contact the site study coordinator to confirm that the patient is still enrolled in the study, while confirming their current dose. If the patient is still on study, Biologics, Inc. prepares temozolomide for cycles 7-12.

Add 1

15.143 Drug request form if patient experiences a dose change (see Forms Packet): If an enrolled patient experiences a dose change for whatever reason and requires additional temozolomide to complete treatment cycles prior to the next scheduled shipment at cycle 7, complete this form and fax it as indicated on the form.

Add 1

15.144 Drug transfer form (see Forms Packet): This form can be used to transfer drug between patients. Once an enrolled patient has been taken off study, the remaining supply of temozolomide that has **NOT been** dispensed to the patient, has **NOT been** opened or has **NOT** expired may be transferred to new and/or currently enrolled patients. Complete this form and fax as indicated on the form. This needs to be documented on the Drug Accountability Form. Any temozolomide that has been dispensed to the patient, has been opened, or has expired should be destroyed on site via the institution's policies and documents on the Drug Accountability Form.

15.145 At the close of the study, unused, unopened, non-expired drug marked can be destroyed or disposed of at the site according to institutional policy. This needs to be documented on the Drug Accountability Form. In a case where drug expires and requires replacing, the drug can be destroyed on site and reordered through the normal reorder procedure noting the re-supply is to replace the destroyed expired drug.

15.146 Additional questions about supply and delivery should be directed to:
Clinical Trials Department
Biologics, Inc.
Phone (800) 840-4306 Fax (919) 256-0794
Clinicaltrials@biologicstoday.com

15.15 Pharmacokinetics: Temozolomide is rapidly and completely absorbed after oral administration; peak plasma concentrations occur in 1 hour. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and Tmax increased 2-fold (from 1.1 to 2.25 hours) when temozolomide was administered after a modified high-fat breakfast. Temozolomide is rapidly eliminated with a mean elimination half-life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range. Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%.

15.16 Metabolism and Elimination: Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC) and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), which is known to be an intermediate in purine and nucleic acid biosynthesis and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. Relative to the AUC of temozolomide, the exposure to MTIC and ACI is 2.4% and 23%, respectively. About 38% of the administered temozolomide total radioactive dose is recovered over 7 days; 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is as unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolites(s) (17%). Overall clearance of temozolomide is about 5.5 L/hr/m^2.

15.17 Special Populations

15.171 Creatinine Clearance: Population pharmacokinetic analysis indicates that creatinine clearance over the range of 36-130 mL/min/m^2 has no effect on the clearance of temozolomide after oral administration. The pharmacokinetics of temozolomide have not been studied in patients with severely impaired renal function (CLcr < 36 mL/min/m^2). Caution should be exercised when temozolomide is administered to patients with severe renal impairment. Temozolomide has not been studied in patients on dialysis.

15.172 Hepatically Impaired Patients: In a pharmacokinetic study, the pharmacokinetics of temozolomide in patients with mild to moderate hepatic impairment (Child's-Pugh Class I-II) were similar to those observed in patients with normal hepatic function. Caution should be exercised when temozolomide is administered to patients with severe hepatic impairment.

15.173 Gender: Population pharmacokinetic analysis indicates that women have an approximately 5% lower clearance (adjusted for body surface area) for temozolomide than men. Women have higher incidences of Grade 4 neutropenia and thrombocytopenia in the first cycle of therapy than men.

15.174 Age: Population pharmacokinetic analysis indicates that age (range 19-78 years) has no influence on the pharmacokinetics of temozolomide. In the anaplastic astrocytoma study population, patients 70 years of age or older had a higher incidence of Grade 4 neutropenia and Grade 4 thrombocytopenia in the first cycle of therapy than patients under 70 years of age. In the entire safety database, however, there did not appear to be a higher incidence in patients 70 years of age or older.

15.18 Drug-Drug Interactions: In a multiple dose study, administration of temozolomide with ranitidine did not change the Cmax or AUC values for temozolomide or MTIC. Population Analysis indicates that administration of valproic acid decreases the clearance of temozolomide by about 5%. The clinical implication of this effect is not known. Population analysis failed to

demonstrate any influence of co-administered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H2-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

15.19a Known Potential Adverse Events (Please see the temozolomide package insert for a comprehensive list of adverse events)

Add 1

- Hematological: Thrombocytopenia, leukopenia, lymphopenia, myelodysplastic syndrome, aplastic anemia.
- Gastrointestinal: Nausea, vomiting, anorexia, pain in the abdomen.
- Hepatic: Elevated liver enzymes (reversible)
- Skin: Rash, itchiness, severe skin reaction
- Other: Constipation, diarrhea, stomatitis, fatigue, decreased performance status, headache, fever, weakness, dizziness, anxiety, depression, memory loss, muscle or joint pain, tingling or burning in your arms or legs, shortness of breath, cough, swelling in your arms or legs, increased need to pass urine, convulsions, weakness on one side of your body, abnormal coordination, paralysis, allergic reaction, re-activation of hepatitis infection, pneumonitis, change in kidney function tests

Add 1

15.19b Temozolomide is potentially mutagenic and should be handled with appropriate precautions by both staff and patients. Capsules should not be opened. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes. Procedures for proper handling and disposal of anticancer drugs should be considered**.**

15.19c Contraindications: Temozolomide is contraindicated in patients who have a history of a hypersensitivity reaction to any of its components or to DTIC.

15.19d Pregnancy Category D: Temozolomide may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Women of childbearing potential should be advised to avoid becoming pregnant during therapy with temozolomide.

Treatment of a man with temozolomide may increase the risk of birth defects if he causes a woman to become pregnant while he is taking temozolomide. Men treated with temozolomide may have difficulty causing a woman to become pregnant after their treatment is completed. Men receiving temozolomide should be directed to use effective contraception while they are being treated. There is insufficient data to know what the risk of subsequent problems with fertility will be. Similarly, women who are treated with temozolomide may have difficulty becoming pregnant in the future and may at be at increased risk of having children with birth defects. There is insufficient evidence to determine what the risk of these complications will be.

15.19e Nursing guidelines

15.19e1 Myelosuppression has been found to be the dose-limiting toxicity. Grade 3 thrombocytopenia occurred in 6% of patients and Grade 4 in 1%. Grade 3 lymphopenia occurred in 36% of patients tested and Grade 4 in 28%. Leukopenia, lymphopenia, thrombocytopenia and anemia usually occur 2-8 weeks after initiation of treatment. Monitor CBC carefully and report any significant changes to MD. Instruct patient to report signs/symptoms of infection, unusual bruising and bleeding to health care team.

15.19e2 In a previous study, 2/15 patients developed pneumocystis carinii pneumonia (PCP) when taking concomitant temozolomide and steroids. Instruct patient to report any fever, cough, chest pain, of other signs of infection to the health care team.

15.19e3 Advise patient that a mild-moderate rash may be experienced.

15.19e4 Fatigue may be experienced. Work with patient in energy conserving lifestyle.

15.19e5 Remind patient that drug needs to be taken on an empty stomach with a full glass of water. Work with patient in establishing a schedule in which the patient takes drug one hour before radiation. Follow up to assure compliance. Drug should not be crushed, chewed, opened, or dissolved.

15.19e6 Nausea and vomiting are common. Teach patient to self-medicate with anti-emetics one hour prior to dose. Assess for effectiveness.

15.19e7 Temozolomide may interact with valproic acid by reducing the clearance of temozolomide by 5%. Assess concomitant medication use.

15.19e8 Constipation is common. Encourage patient to increase fluid intake. Administer stool softeners or laxatives as ordered and monitor for their effectiveness.

16.0 Statistical Considerations and Methodology

16.1 Study overview: This study will be a randomized phase III trial for patients with newly diagnosed anaplastic glioma. The trial will only enroll patients with 1p/19q co-deletion. This study includes three arms: Arm A – RT alone (the control arm); Arm B – temozolomide concomitant with RT followed by adjuvant temozolomide; Arm C – temozolomide alone. A dynamic allocation procedure will be used to allocate an equal number of patients to different arms (Arms A:B:C = 1:1:1 in the first 2 years and Arms A:B = 1:1 in the remaining 4.5 years). This procedure will balance the marginal distributions of the stratification factors between arms. The stratification factors that will be used are: cooperative groups (EORTC vs. all other North American groups), age (≤50 vs. >50), performance score (ECOG 0-1 vs. 2).

16.2 Goals

16.21 The primary goal of the study is the comparison of Arm A vs. Arm B, which will be used to address whether patients who receive temozolomide with concomitant RT have a significantly better overall survival than patients who receive RT alone.

Add 1

16.22 The secondary goals of the study are the comparison of Arm A vs. Arm B and Arm A vs. Arm C, which will be used to address whether patients who receive temozolomide alone or temozolomide with concomitant RT will have 1) a significantly longer time to neurocognitive progression or 2) a significantly longer time to progression as compared to patients who receive RT alone.

16.3 Definition and documentation of efficacy endpoints

16.31 For the primary goal of the study: Overall survival is the primary endpoint and is defined as the time from study registration to time of death due to any cause. Patients who are lost to follow-up will be censored at the date of their last follow-up. Patients still alive at the time of analysis will be censored.

16.32 For the secondary goals of the study:

Add 1

- Time to progression is defined as the time from study registration to the earliest evidence of 1) clinical progression or 2) radiographic progression. Clinical progression is defined in Section 11.11 and radiographic progression is defined in Section 11.12 and 11.3.

Add 1

- Time to neurocognitive progression is defined as the time from study registration to the first cognitive failure on any of the following tests: the HVLT-R for Free Recall, Delayed Recall, and Delayed Recognition; the COWAT; and the Trail Making Test Part A or B. Cognitive failure for each test is defined as a change in a score that meets or exceeds the Reliable Change Index (RCI) value for each test indicating a performance that is worse than the patient's personal baseline score.

16.4 Accrual time and study duration: The total number of eligible patients to be accrued is 488 (219 per arm for Arm A and Arm B and 50 for Arm C). Based on the accrual in a recently completed RTOG Phase III trial (RTOG 94-02) and with additional cooperative groups (EORTC and NCIC – CTG) committed to participating in this trial, we anticipate that 166 newly diagnosed AO-AOA patients will be screened each year. Data from RTOG 94-02 suggests approximately 46% of newly diagnosed AO-AOA patients have tumors with 1p/19q co-deletion. Thus, we estimate the accrual rate for this trial will be approximately 75 eligible patients per year. The accrual period will be approximately 6.5 years for Arm A and B and 2 years for Arm C. We anticipate pre-registering 585 patients to register/randomize a total of 488 patients necessary for the study design. The above detail regarding sample size should not be seen as binding and enrollment decisions could be made to preserve the ability of the trial to detect the prospectively hypothesized differences.

16.5 Sample size derivation for the primary goal: The primary goal of this trial is to address whether patients who receive temozolomide with concomitant RT have significantly longer overall survival than patients who receive RT alone. The comparison will be performed at an alpha level of 0.05 with two planned interim looks for efficacy and one planned interim look for futility. In the RTOG randomized Phase III trial for newly diagnosed AO/AOA patients (RTOG 94-02), those with tumors that had 1p/19q co-deletions and were treated with RT had a median survival time of 7.2 years. It is assumed that the following holds true: 1) approximately 75 eligible patients per year over 6.5 years, 2) the minimal follow-up period after accrual terminates will be 3.5 years, 3) the distributions of overall survival for Arm A and B follow an exponential distribution and 4) the hazard rates are proportional, then a sample size of 219 eligible patients per treatment arm will yield a 80% power to detect a 33% decrease in the hazard rate using a one-sided alpha=0.05 logrank test. This is equivalent to a 50% increase in the median survival time from 7.2 years to 10.8 years. The expected number of deaths is 178.

16.6 Analysis plan for the primary goal: Efficacy analysis will be based on the intention-to-treat principle with all eligible patients belonging to the treatment arm to which they were randomized. The Cox proportional hazards model will be used to assess whether the distributions of overall survival times differ with respect to treatment regimen having adjusted for all stratification factors (cooperative groups, age, and Performance Score). The corresponding p-value associated with the treatment covariate will be compared to the nominal p-value to make the conclusion regarding the primary goal. The distribution of overall survival for Arm A and B will be estimated using the Kaplan-Meier method. The hazard ratios and median survivals will be estimated with their 95% confidence intervals.

16.7 Interim analysis for the primary goal: For the primary goal, both rejection of H_0 and rejection of H_1 will be considered.

16.71 Interim futility analysis for the primary goal: one futility interim look will be applied when 25% (45 deaths) events have occurred (approximately 4.3 years after the start of the trial). The study is designed to spend 37.5% of type II error (β spending function = 7.5%) at the only futility interim look. If the nominal p-value associated with the treatment covariate in the Cox proportional hazards model (adjusted for all stratification factors) is $\geq$0.55, the alternative hypothesis will be rejected in favor of concluding that there is little chance of demonstrating the experimental arm (TMZ/RT arm) is superior to the control arm (RT alone arm) and we may recommend terminating the study.

Interim efficacy for the primary goal: Three efficacy looks designed to provide information relevant to the primary goal will be applied: formal comparisons of overall survival will be made when 50% (89 deaths), 75% (133 deaths), and all of the expected number of events (178 deaths) have occurred (approximately 6.2, 8, and 9.5 years after the start of the trial, respectively). For efficacy interim looks, the Lan-Demets methods for computing discrete sequential one-sided boundaries with an alpha spending function yielding O'Brien-Fleming type boundaries will be used to account for sequential testing and to maintain the overall preset type I error rate. For a comparison with type I error rate of 0.05, the alpha levels for the interim analyses and final analysis are 0.006, 0.022, and 0.043 respectively. If the p-value associated with the treatment

covariate in the Cox proportional hazards model (adjusted for all stratification factors) is less than corresponding alpha level, we will conclude that the experimental arm (TMZ/RT arm) is superior to the control arm (RT alone arm) and may recommend terminating the study. Power simulations were performed with EAST v 5.0 and the results are presented in the table below based on 10000 simulations.

	Prob. Of Rejection of H1	Prob. Of Rejection of H0			Overall Power
Scenario	Futility Interim Analysis	1st Interim Analysis	2nd Interim Analysis	Final Analysis	
HR=0.67	7.64%	22%	35%	23%	80%
HR=0.63	5.03%	30%	37%	23%	90%
HR=0.775	16.7%	6%	18%	27%	51%

16.8 Sample size derivation for the secondary goal: The secondary goal of this trial is to address whether patients who receive TMZ alone or TMZ with concomitant RT have a significantly longer time-to-progression (clinical and/or radiographic per section 16.32) than patients who receive RT alone. For each comparison, the test will be performed at an alpha level of 0.05 without any interim look. In the RTOG randomized Phase III trial for newly diagnosed AO/AOA patients (RTOG94-02), those with tumors that had 1p/19q co-deletions and were treated with RT had a median progression free survival of 2.8 years. It is assumed that the following holds true: 1) accrue approximately 75 eligible patients per year over 2 years (Arms A: B: C = 50: 50: 50), 2) the minimal follow-up period after accrual terminates will be 4.5 years, 3) the distributions of time-to -progression for Arm A, B, and C follow an exponential distribution, and 4) the hazard rates are proportional, then a sample size of 50 eligible patients per treatment arm will yield an 80% power to detect a 44% decrease in the hazard rate using a one-sided alpha=0.05 logrank test. This is equivalent to a 81% increase in the median progression time from 2 years to 3.6 years. For each comparison (Arm A vs. C or Arm A vs. B), the expected number of events is 75. As neurocognitive progression usually predicts tumor progression and can occur many months before tumor progression, the power in detecting the hazard ratio in time to neurocognitive progression will be at least the same as estimated above.

Add 1

16.9a Analysis plan for the secondary goal: The following test battery is selected due to its brevity (approximately 20 minutes) and its widely-used standardized psychometric instruments for assessing specific neurocognitive impairment known to be affected by brain tumors and treatment:

- Hopkins Verbal Learning Test – Revised (HVLT-R): Memory (4.5 minutes)
- Controlled Oral Word Association Test from the Multilingual Aphasia Examination (COWA): Fluency (3.5 minutes)

- Trail Making Test A: Visual scanning speed
- Trail Making Test B: Divided attention (5 minutes to complete both Trails)
- HVLT-R: Delayed memory, recall and recognition of word list encoded from the HVLT-R (1.5 minutes)

Add 1

The patients in each of the three arms will be given this battery of standardized neurocognitive tests administered by trained and certified nurses or clinical research associates as indicated in Sections 4.1, 4.2, 4.3 until there are 50 evaluable patients in each of the three arms. Evaluable is determined as having completed baseline and four additional test booklets. The 50 evaluable patients will be given this battery of standardized neurocognitive tests until progression. For each test in the battery, a standard error of measurement will be used to derive the Reliable Change Index (RCI) which will be used to represent the 90% confidence interval for the difference in raw scores from baseline to follow-up assessment will be coded as 1 (deterioration), 2 (no change), and 3 (improved) according to the RCI. Percentage of patients in each treatment arm who show meaningful losses or gains in the various tests or test domains over the course of the study will be provided by frequency tables. Treatment group differences will be compared using chi-squared analysis. Time-to-neurocognitive progressions will be estimated by Kaplan-Meier method and analyzed by Cox regression model adjusting all stratification factors. Correlations among baseline neurocognitive test scores and overall survival will be analyzed using Cox proportional hazards model.

Add 1

In addition, neurocognitive tests will be grouped into three domains: three memory domain tests are the HVLT for immediate recall; delayed recall and recognition; and two executive function tests are COWA and Trail Making B. Visual-motor scanning speed will be measured by Trail Making Test A. Time-to-neurocognitive progression in each domain will be estimated by Kaplan-Meier method and analyzed by Cox regression model adjusting all stratification factors.

16.9b Secondary endpoint and analysis: For Arm A and B, secondary endpoints include progression-free survival, objective tumor response, toxicity, prognostic factor analysis, and quality of life.

16.9b1 Progression-free survival (PFS): is defined as the time from study registration to the date of first observation of disease progression or death due to any cause (whichever comes first). If a patient has not progressed or died, progression-free survival is censored at the time of last follow-up.

16.9b2 Objective tumor response: An objective tumor response is defined as a CR, PR, or REGR that is maintained for at least 4 weeks. The tumor response rate will be summarized for each arm and compared between the arms using the Chi-square test.

16.9b3 Treatment related adverse events: As per NCI CTCAE version 3.0, the phrase "treatment-related adverse event" is defined as an adverse event that is classified as either "possibly," "probably," or "definitely related" to study treatment. The maximum grade for each type of treatment-related adverse event will be recorded for each patient, and frequency tables for each arm will be reviewed to determine patterns. In addition, we will review all adverse event data that is graded as 3, 4, or 5 and classified as either "unrelated" or "unlikely to be

related" to study treatment in the event of an actual relationship developing. Adverse events and treatment-related adverse events will be evaluated using all patients who have received any study treatment as well as summarizing those who have been included in the efficacy analyses. Treatment-related adverse events will be tabulated for each arm and will be compared among arms.

16.9c Translational endpoints: These will be more exploratory and descriptive in nature rather than confirmatory. Specifically, FISH method will be utilized to detect Interphase fusion of the CEP1 probe and a 19p12 probe to detect the t (1:19) in paraffin-embedded tumor sections. Kaplan-Meier distributions of overall survival (OS) and progression-free survival (PFS) for patients whose tumors did or did not exhibit CEP1/19p12 fusion will be compared using the Log-rank test. Associations will be explored between clinical outcomes (survival, progression-free survival, and objective response) and MGMT methylation status.

In addition, tumor tissue will be studied for additional known prognostic markers, including but not limited to PTEN, EGFR, EGFRvIII, p53, and any additional markers which are known or are identified during the course of this study that are considered relevant by the study investigators. Associations will be explored between clinical outcomes and those prognostic markers; associations between time-to-event endpoints (OS, PFS) and prognostic markers will be assessed using Cox Proportional Hazard models. Association between categorical endpoint (objective response) and prognostic markers will be assessed using logistic regression.

16.9d Prognostic factor analysis: Cox modeling with the Cox partial likelihood score test will be used to examine the strength of association between the overall survival distributions and additional prognostic factors, such as age, gender, ECOG performance scores, extent of resection (biopsy vs resection), tumor location, pure vs mixed histology, MGMT promoter methylation status.

Summary statistics for patient and tumor characteristics, eligibility rates and length of follow-up will be calculated by assigned treatment arm.

Add 1

16.9e Quality of life: QOL assessments will be administered to all patients enrolled on all three arms and the two methods of HRQOL assessment selected for this trial are the EORTC quality of life questionnaire core-30 (QLQ-C30, version 3), EORTC quality of life questionnaire – brain cancer module (QLQ-BN20). Specifically, these measures will be made at baseline and as indicated in Sections 4.1, 4.2, 4.3 and at the time of PD. The measurements will be compared at each time point across all the arms. In addition, changes from baseline and each follow-up endpoint will be compared across the arms. The QOL measures will also be evaluated for their association with survival, PFS, and best objective tumor response. A Cox regression model with the QOL measures treated as time-dependent covariates will be used for the assessment of association with time-to-event data (survival and PFS). The level of agreement among the two methods will also be determined. The QOL evaluations will be administered to all patients enrolled on all three arms. Hence, the target sample size and anticipated accrual are similar to what is expected for the primary goal of the study (found in the statistical design section above). From past experience with QOL studies in glioma patients, we anticipate we will obtain these measures from 85% to 95% of the patients who are still on-study at each time point. Missing data will be handled in a number of ways. First, all analyses will be run using only the data available. Second, imputation will be carried out by use of last-value-carried forward (LVCF), average-value-carried forward (AVCF), and nearest neighbor. Collectively, these four approaches have been demonstrated to be useful for identifying the impact of missing data on results as long as the amount of missing data is no more than 20%.

16.9f Adverse Event Stopping Rule for Arm B

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event that at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment combination under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to Arm B of this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy the following:

- if 5 or more patients in the first 20 treated Arm B patients (or 25% of all Arm B patients after 20 are accrued) experience a grade 4 or higher non-hematologic adverse event.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.9g Monitoring:

16.9g1 This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. An abbreviated report containing cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

16.9g2 This study will be monitored by the NCCTG External Data Monitoring Committee (DMC), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DMC every six months as per NCI guidelines.

16.9h Inclusion of Women and Minorities

This study will be available to all eligible patients regardless of race, gender, or ethnic group.

There is no information currently available regarding differential agent effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analyses will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for such subset analyses. A total of 488 patients may be enrolled.

Based on prior studies involving similar disease sites, we expect about 7% of patients will be classified as minorities by race and about 40% of patients to be women. Expected sizes of racial by gender subsets are shown in the following table:

Ethnic Category	**Sex/Gender**			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	14	21	0	35
Not Hispanic or Latino	181	272	0	453
Ethnic Category: Total of all subjects*	195	293	0	488
Racial Category				
American Indian or Alaskan Native	1	2	0	3
Asian	0	1	0	1
Black or African American	1	0	0	1
Native Hawaiian or other Pacific Islander	0	1	0	1
White	193	289	0	482
Racial Category: Total of all subjects*	195	293	0	488

These totals must agree. Enter actual estimates (not percentages**)*

Ethnic Categories:	**Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino." **Not Hispanic or Latino**
Racial Categories:	**American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment. **Asian –** a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.) **Black or African American –** a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American." **Native Hawaiian or other Pacific Islander –** a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. **White –** a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Tissue Biospecimen Submission

Add 1 **EORTC institutions:** Refer to the EORTC Group Specific instructions.

Type of tissue to submit	Mandatory or optional	When to submit	Reason for submission	Where to find specific details for submission
All diagnostic slides	Mandatory	As soon as possible after surgery, prior to enrollment	Pre-registration requirement, confirmation of diagnosis through central review	Section 17.2
Formalin-fixed paraffin-embedded (FFPE) tissue blocks with corresponding H&E (**OR** five unstained slides with one corresponding H&E)*	Mandatory	As soon as possible after surgery, prior to enrollment	Pre-registration requirement for determination of deletion status (Section 17.51)	Section 17.2
Add 1 15 unstained slides with 2 corresponding H&E*	Mandatory unless the specimens are exhausted or unavailable after a reasonable attempt has been made by the site to retrieve them. This will not make the patient ineligible for the study.	≤30 days after registration	Correlative studies (Sections 17.52-17.53) Add 1 Future research studies (Sections 17.54-17.55)	Section 17.3

* If the FFPE tissue block was previously submitted for pre-registration requirement for determination of deletion status, no additional tissue slides are required. These slides are required if unstained slides (instead of a tissue block) were originally submitted for the pre-registration requirement for determination of deletion status.

17.2 All diagnostic slides from material obtained at the time of initial diagnosis must be submitted AND paraffin embedded tissue blocks or slides for pre-registration requirement for determination of deletion status. NOTE: Intra-operative tissue blocks previously frozen are not acceptable, unless it is the only diagnostic tissue block available.

17.21 Diagnostic Slides

Clearly labeled original diagnostic slides used to make the diagnosis of anaplastic glioma (WHO grade III) cancer should be forwarded ***as soon as possible after surgery for pre-registration*** according to shipping instructions below.

If diagnostic slides and accompanying materials have been previously submitted to Dr. Caterina Giannini and associates, Mayo Clinic Rochester, for a consult review, fax a copy of this review to the NCCTG Pathology Coordinator (507-284-9628) to verify diagnosis. Clearly labeled original and diagnostic slides will still need to be forwarded according to shipping instructions below (see Sections 17.22-17.26).

If a patient's surgery was at Mayo Clinic Rochester, you may call the Pathology Coordinator listed on the protocol Resource Page. The Pathology Coordinator will request a copy of the Surgical Pathology Report and determine patient block availability.

17.22 Paraffin Embedded Tissue Block OR Unstained Slides for Pre-registration Requirement

As soon as possible after surgery and prior to enrollment, submit one formalin fixed paraffin-embedded (FFPE) tumor tissue block with representative tumor from surgery. Biopsy material obtained at the time of initial diagnosis of anaplastic glioma should be submitted. **A corresponding H&E slide for the submitted block must be provided** to permit quality assessment (QA) of the tissue block for determination of deletion status.

The FFPE tissue block is preferred; however, **if an institution is unable to provide a tissue block**, cut 6 five micron sections using RNAse-free techniques and mount sections on charged glass slides. **Label the slides with NCCTG patient ID number, accession number, and order of sections (i.e., 1-6).** H&E stain the first cut slide (i.e., slide labeled #1). This slide will be reviewed centrally under the research base's quality assessment protocol. The remaining 5 unstained slides will be processed as described in 17.51. For samples containing less than 7 square millimeters of tumor tissue, multiple sections should be mounted onto each slide to ensure that the appropriate amount of tumor tissue is available. Ideally, each slide must have a minimum of 75% tumor tissue on the slide to be deemed adequate for study. **Do not bake or place covers slips on the slides.**

17.23 The following materials below are mandatory (unless indicated otherwise) and required for shipment:

- All diagnostic slides from **surgery** at the time of initial diagnosis of anaplastic glioma should be submitted.

- Paraffin Embedded Tissue block with Corresponding H&E Slide **OR** 5 Unstained Slides with Corresponding H&E Slide
- Pathology Reporting Form
- Pathology Submission Form
- Surgical Pathology Report
- Operative Report *(optional)*

NOTE: Please include the NCCTG patient ID number on all materials listed above.

17.24 The block and/or slide must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, NCCTG patient ID number, and patient initials.

Add 1

17.25 Verify that Section 1 of the Pathology Reporting Form is completed and filled in correctly. Verify that the appropriate sections of the Pathology Submission Form are completed and filled in correctly.

17.26 **In order to assure prompt handling, please call the NCCTG Pathology Coordinator at (507) 266-0724 or (507) 266-8919 to alert of the time/date sent and courier contracted.**

17.27 Review is being performed at the NCCTG Research Base at Mayo Clinic Rochester. Ship all diagnostic slides and accompanying materials as follows:

17.271 Mayo Clinic Rochester (MCR) patients only: please forward pathology material to Dr. Caterina Giannini, Hilton 11, for review. The Pathology Coordinator will determine block availability for the determination of deletion status.

17.272 For all memberships, including MCJ and MCA, ship all specimens and accompanying materials to the NCCTG Research Base:

NCCTG Operations Office
Attn: PC Office (Study N0577)
RO_FF_03_24-CC/NW Clinic
200 First Street SW
Rochester, MN 55905

17.28 The NCCTG Operations Office will forward the pathology materials to Dr. Caterina Giannini and/or associates, Hilton 11. The diagnostic slides will be used for central review to confirm diagnosis of anaplastic glioma. If FFPE tissue block is submitted, the pathology area will request 5 five micron slides (charged) to be cut for 1p/19q deletion results to the NCCTG Operations Office Attn: Pathology Coordinator Office. FISH slides will be retained in Dr. Jenkins' laboratory.

17.29a Dr. Giannini and/or associates will mark the H&E slide for FISH analysis and the marked H&E and 5 unstained slides will be forwarded to Dr. Robert Jenkins' laboratory for 1p/19q deletion analysis. Upon completion of FISH

Add 1

analysis, Dr. Jenkins' laboratory will return the H&E slide and 1p/19q deletion results will be electronically communicated to the NCCTG Operations Office Attn: Pathology Coordinator Office. FISH slides will be retained in Dr. Jenkins' laboratory.

17.29b After the pathology materials have been reviewed for confirmation of diagnosis for eligibility, the pathologist will return all pathology materials to the NCCTG Operations Office, Attn: PC Office (Study N0577), RO_FF_03_24-CC/NW Clinic.

17.29c The Pathology Coordinator will notify the submitting institution of Dr. Giannini's and/or associates' review and the results of the 1p/19q deletion analysis. The eligibility status of the patient will be entered into the pre-registration database. This will enable the Registration Office to verify eligibility when the institution proceeds to step 2 of the registration. Eligible patients can now be registered.

17.29d If both 1p and 19q are deleted and the patient is eligible for this study, one or two slides will be identified by the reviewing pathologist for inclusion in the pathology files for this study. These slides are being stored at NCCTG for quality assurance purposes only and no future research will be conducted on them. All remaining diagnostic slides will be returned to the submitting institution.

17.29e If the patient is eligible for this study, but does not enter the study, please notify the Pathology Coordinator listed on the Protocol Resource page and then all blocks, slides, and forms will be returned to the submitting institution, unless otherwise indicated.

17.3 Paraffin Embedded Tissue Blocks (OR Unstained Slides) for Correlative Studies

17.31 If the FFPE tissue block was previously submitted for pre-registration requirement for determination of deletion status, no additional tissue specimen submission is required. The original block that was submitted will be used for the correlative studies as outlined in Sections 17.52-17.55.

17.32 If unstained slides were submitted for the pre-registration requirement for determination of deletion status, submit one FFPE tumor tissue block with representative tumor from surgery. Biopsy material obtained at the time of initial diagnosis of anaplastic glioma should be submitted. **A corresponding H&E slide for the submitted block must be provided** to permit quality assessment (QA) of the tissue block for correlative studies.

17.33 The FFPE tissue block is preferred for correlative studies; however, **if an institution is unable to provide a tissue block,** cut 17 five micron sections and mount sections on charged glass slides. **Label the slides with NCCTG patient ID number, accession number, and order of sections (i.e., 1-17).** H&E stain the first and eleventh cut slide (i.e., slide labeled #1, #11). These slides will be reviewed centrally under the research base's quality assessment protocol. The remaining slides will be processed as described in Sections 17.52-17.55. For samples containing less than 7 square millimeters of tumor tissue, multiple

sections should be mounted onto each slide to ensure that the appropriate amount of tumor tissue is available. Ideally, each slide must have a minimum of 75% tumor tissue on the slide to be deemed adequate for study. **Do not bake or place covers slips on the slides.**

Add 1

17.34 The following materials below are mandatory (unless the tissue has been exhausted or is unavailable, after a reasonable attempt has been made by the site to retrieve them. This will not make the patient ineligible for the study) and required for shipment:

- Paraffin Embedded Tissue Blocks with Corresponding H&E Slide (**OR** 15 Unstained Slides with 2 Corresponding H&E Slides)
- Tissue Specimen Submission Form
- Surgical Pathology Report

17.35 The block/slides must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, NCCTG patient ID number, and patient initials.

17.36 Tissue specimens must be shipped before or ≤30 days following registration.

17.37 Verify that the appropriate sections of the Tissue Specimen Submission Form are completed and filled in correctly.

NCCTG institutions: Enter information from the Tissue Specimen Submission Form into the remote data entry system the same day the specimen is submitted (see Forms Packet).

CTSU and EORTC institutions: See Appendices VII and VIII for instructions, respectively.

17.38 Ship all tissue specimens and accompanying materials to the NCCTG Research Base:

NCCTG Operations Office
Attn: PC Office (Study N0577)
RO_FF_03_24-CC/NW Clinic
200 First Street SW
Rochester, MN 55905

17.39a If corresponding H&E slide was not submitted with the tissue specimen, the NCCTG Operations Office will request an H&E slide to be processed from the tumor tissue block. Processing will be performed in the NCCTG Research Base TACMA Shared Resource, Mayo Clinic Rochester.

17.39b The NCCTG Operations Office will forward the block and H&E slide to Dr. Giannini and/or associates to be reviewed under the research base's protocol for assessing tissue quality for the proposed correlative studies.

17.39c After the pathologist assess the tissue quality, the block and appropriate paperwork will be returned to the NCCTG Operations Office.

17.39d When an appropriate request is submitted, the NCCTG Operations Office will forward the block/slides to the NCCTG Research Base TACMA Shared Resource, Stabile 13-10B, Mayo Clinic Rochester (Attn: TACMA Supervisor) for processing as outlined in Sections 17.52-17.55.

17.4 Frozen Tumor Tissue: None.

17.5 Study Methodology and Storage Information

17.51 Predictive value of 1p/19q deletion status

In RTOG 94-02, correlative biomarker studies were performed to determine if 1p and/or 19q deletions were associated with response to PCV and overall survival. Patients were not stratified nor were their treatments modified if their tumors contained 1p and/or 19q deletion. We propose to extend and expand the findings, and in tandem with the proposed EORTC undeleted anaplastic glioma trial, to determine whether prospective determination of 1p and/or 19q status allows identification of populations of patients that are more or less likely to have improved outcome following specific treatments. Since 1p/19q status must be determined prior to treatment, the 1p/19q FISH studies described are an essential component of this trial.

17.511 FISH Methods

FISH of paraffin sections for determination of 1p and 19q gene deletion status will be performed as previously described. (Smith JS, 2000) in the laboratory of Dr. Robert Jenkins, who also performed the studies for RTOG 94-02 using similar methodology. A similar reference laboratory will be utilized in Europe, which includes scientists who have previously collaborated with Dr. Jenkins and was the laboratory utilized for conduct of 1p/19q studies in EORTC 26951.

Briefly, dual-probe FISH analyses are performed on paraffin-embedded sections, with locus-specific probes for 1p36 and 19q13.3 (labeled with Spectrum Orange) paired with control locus-specific probes for 1q24 and 19p13.1 (labeled with SpectrumGreen), respectively (Vysis, Downers Grove, IL). The FISH probes mapping to 1p36 and 19q13.3 were developed based on previous reports that they map to regions of common allelic loss in gliomas. All FISH probes used for these analyses were previously developed by the Jenkins group and the capacities of these probes to detect alterations of chromosomes 1 and 19 have been validated by comparison with loss of heterozygosity (LOH) and comparative genomic hybridization (CGH) analyses. Vysis, Inc. used this information to develop clinical research reagents for the NeuroOncology community.

For each case, a paraffin-embedded tumor block is selected by Dr. Giannini and/or associates based on tumor content, including the highest grade component and representation of the predominant morphology of the individual case. Approximately six 5-µm sections are required for FISH analysis. The first section is hematoxylin and eosin (H&E) stained and regions representing tumor and normal tissue are delineated. These are regions enumerated by the technologist performing the FISH analysis.

Based on prior experience with this assay at the Mayo Clinic, Dr. Jenkins has indicated that in the absence of extenuating circumstances, the typical turnaround time for the FISH assay (required prior to registration on study) will be 10 business days after receipt of usable specimens.

Finally, FISH will also be utilized to detect interphase fusion of the CEP1 probe and a 19p12 probe to detect the t(1;19) in paraffin-embedded tumor sections. Kaplan-Meier distributions of overall survival (OS) and progression-free survival (PFS) for patients whose tumors did or did not exhibit CEP1/19p12 fusion will be compared using the Log-rank test.

17.52 Predictive value of MGMT gene promoter hypermethylation status

An additional 11 (10 unstained and 1 H&E) 5-µm sections will be requested for other marker analyses (e.g., MGMT methylation, see Sections 17.53-17.54). As mentioned above, recent studies (Paz, 2004) have shown that the methylation of the MGMT promoter positively correlated with the clinical response in newly diagnosed glioma patients receiving TMZ as first line therapy, with 67% patients with tumor MGMT hypermethylated having a complete or partial response, versus 25% of patients with unmethylated tumor MGMT ($p=0.03$). The recent presentation of a companion analysis to the EORTC Phase III trial involving a larger patient cohort also showed a positive correlation of MGMT gene promoter hypermethylation with survival in glioblastoma patients (Hegi, 2004). It is not definitively known whether inactivation of MGMT protein expression in tumors from these patients is the primary mechanism responsible for apparent observations of chemo-radiosensitivity of gliomas and the improved survival of patients treated with RT+TMZ on the EORTC study. In addition, the predictive value of MGMT promoter hypermethylation in 1p/19q co-deleted tumors is not clearly defined at this time.

MGMT promoter hypermethylation appears to be an even more common event in oligodendroglial neoplasms than in glioblastoma. In a reported study of 52 oligodendrogliomas, 46 (88%) had MGMT promoter hypermethylation as defined by methylation of more than 50% of the sequenced CpG sites. Reduced MGMT mRNA levels and protein expression, relative to that in non-neoplastic brain tissue, was demonstrated by RT-PCR and immunohistochemistry in most tumors found to have MGMT promoter hypermethylation. We are most interested in the observation that MGMT promoter hypermethylation was significantly more frequent, as was percentage of methylated CpG sites, in tumors with 1p/19q LOH (Molleman, 2005).

The data reported by Molleman et al, supported findings described in an earlier study, in which hypermethylation of MGMT in AO significantly associated with loss of 19q or combined 1p/19q loss. Collectively, these findings promote a hypothesis that the hypermethylation status of the MGMT promoter may correlate with 1p/19q status, survival, and possibly even response to RT + TMZ therapy in AO patients. This hypothesis clearly needs to be evaluated in a Phase III trial.

Add 1

After submission of tumor specimens to the NCCTG Operations Office, the Pathology Coordinators will forward blocks to TACMA (Stabile 13-10B) for cutting of slides. The slide specimens will be banked until logistics regarding data and samples are in place between NCCTG and EORTC.

17.53 Other Tissue Markers

In addition to the above, tumor tissue will be studied for additional known prognostic markers, including but not limited to PTEN, EGFR, EGFRvIII, p53, and any additional markers which are known or are identified during the course of this study that are considered relevant by the study investigators.

17.54 Other candidate gene studies

Add 1

In addition to the use of tissue specified in this study, portions of these materials will be catalogued and stored at the NCCTG Operations Office for potential future analysis according to the patient consent permission (see Section 6.23). We selected 1p/19q deletion analysis and MGMT methylation as the primary correlative studies for this proposed trial, because there is very strong evidence that these markers will be clinically relevant. However we are aware that these specimens may prove critical for future studies both within and outside of NCCTG investigators that potentially will evaluate the importance of other known gene deletions of interest in anaplastic co-deleted oligodendrogliomas, including but not limited to, 9p and 10q and any as yet unidentified candidate genes of interest. These additional studies may define molecular markers that also associate with improved survival or glioma predisposition. During and following conduct of the trial, the PIs and Co-PIs will carefully review any potential additional marker studies on an ongoing basis, so that the precious resource being developed is not depleted and is utilized to greatest benefit.

17.55 At the completion of the study, any unused/remaining material will be stored in the NCCTG Operations Office (Attn: Pathology Coordinator) for future research according to the patient consent permission (see Section 6.23). Potential future research may include immunohistochemistry (IHC) analyses, DNA extraction, and/or tissue microarray (TMA) construction to analyze predictive biomarkers, changes in expression pattern with therapy, and correlation with response and/or adverse events. When a protocol is developed, it will be presented for IRB review and approval.

17.6 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

18.0 Records and Data Collection Procedures

Add 1 **Note:** NCCTG members will enter data into the NCCTG RDC system. Institutions participating through EORTC see EORTC Group Specific instructions and for CTSU see Appendix VII for instructions.

Forms	Active-Monitoring Phase (Compliance with Test Schedule)				Event-Monitoring (Completion of Active-Monitoring Phase)		At Each Occurrence			
		Initial Material	Follow-up material							
	Pre-Reg	≤2 weeks after registration	At each evaluation	At end of treatment	After PD every 6 months until death	Death	ADR/ AER	New Primary	Grade 4 or 5 Non-AER Reportable Events/ Hospitalization	Late Adverse Event
On-Study Form		X								
Baseline Adverse Events Form		X								
OP and Path Reports	X									
Measurement Form		X	X	X						
Tissue Specimen Submission Form (Section 17.3)		X[11]								
Pathology Material (see Section 17.2)	X									
RT material				X[10]						
Pre-Reg Screening Failure Form	X[2]									
Evaluation Treatment Form			X							
Blood Specimen Submission Form (Section 14.0)		X[7]								
Event Monitoring Form				X	X	X		X		X
End of Active Treatment/Cancel Notification Form	X[1]			X						
Evaluation/Observation Form			X[3]	X						
Nadir/Adverse Event Form			X	X						
Concurrent Treatment Form		X	X	X						
Concurrent Steroid and Anticonvulsant Treatment Form		X	X	X						
Patient QOL Questionnaire Booklet		X[4]	X[4,5]	X						
Patient QOL Questionnaire Booklet Compliance Form			X[6]	X						
Add 1 Neurocognitive Examiner's Booklet		X	X	X						
Neurocognitive Testing Booklet Compliance Form			X[6]	X						
ADR/AER (see Section 10.0)							X			
NCI/CTEP Secondary AML/MDS Report Form (see Section 10.0)								X[8]		
Notification Form[9]									X	
Late Effects of Radiation Therapy			X	X						
Add 1 Schering Plough Pregnancy Form							X			

Footnotes are on the next page

1. Submit this form only if withdrawal/refusal prior to beginning protocol therapy occurs.
2. Complete only if patient is NOT registered after he/she is pre-registered.
3 Complete at each evaluation during Observation (see Section 4.0).
4 Patient questionnaire booklets **must** be used; copies are not acceptable for this submission.
5 Every other cycle.
6 This form must be completed **only** if the quality of life questionnaires contain absolutely **NO** patient provided assessment information.
7 After registration but before any treatment.
8 Only applicable to new AML/MDS primaries, not for all new primaries.
9 NCCTG institutions only.
10 **Both NCCTG and CTSU Institutions submit the following to NCCTG Operations Office. EORTC institutions should see EORTC Group Specific instructions:**

Add 1

For patients who do not receive any scheduled radiation therapy, submit the radiation therapy reporting form with the reason radiation was not given. For patients who receive partial or complete radiation therapy, submit the following materials ≤14 days after the last day of radiation:

a. RT reporting form.
b. If IMRT – IMRT Plan Verification Reports (e.g. Phantom measurements)
c. Daily treatment records.
d. Dosimetry calculations, monitor unit calculations, and color copies of the required isodose curves.
e. Color copies of required DVH's.
f. Copies of representative simulation films of all treated fields.
g. Copies of representative port films of all treated fields.
h. Copies of CT/MRI scans used for treatment planning (indicate whether pre-op or post-op)
Note: Images submitted on CD(s) **must** include a viewing tool.

NOTE: All materials will be forwarded to the NCCTG Operations Office, RT Coordinator, NW Clinic 3-24, 200 First Street SW, Rochester, MN 55905

11 Submit ≤30 days after registration.

19.0 Budget

19.1 Costs charged to patient: Routine clinical care

19.2 Tests to be research funded: 1p/19q deletion status; translocation status, MGMT gene promoter methylation status; other translational correlative analyses.

19.3 Temozolomide will be provided to patients free of charge by Schering-Plough.

20.0 Reference

Abrey LE, Childs BH, Paleologos N, Kaminer L, Rosenfeld S, Salzman D, Finlay JL,Gardner S, Peterson K, Hu W, Swinnen L, Bayer R, Forsyth P, Stewart D, Smith AM, Macdonald DR, Weaver S, Ramsey DA, Nimer SD, DeAngelis LM, Cairncross JG. High-dose chemotherapy with stem cell rescue as initial therapy for anaplastic oligodendroglioma. J Neurooncol 2003 65:127-34.

Armstrong TS, Mendoza T, Gning I, Coco C, Cohen MZ, Eriksen L, Hsu MA, Gilbert MR, Cleeland C. Validation of the M.D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT). J of Neuro-Onc, 80(1):27-35, 2006 Oct.

Bauman GS, Ino Y, Ueki K, Zlatescu MC, Fisher BJ, Macdonald DR, Stitt L, Louis DN, Cairncross JG. Allelic loss of chromosome 1p and radiotherapy plus chemotherapy in patients. with oligodendrogliomas. Int J Radiat Oncol Biol Phys. 2000 48:825-30.

Bigner SH, Rasheed BK, Wiltshire R, McLendon RE. Morphologic and molecular genetic aspects of oligodendroglial neoplasms. Neuro-oncol. 1999 Jan;1(1):52-60.

Buckner, Jan C. M.D.; Scheithauer, Brend W. M.D.; Dinapoli, Robert P. M.D.; Votava, Henry J. M.D.; Giannini, C M.D.; Iturria, Nancy M.D.; O'Fallon, Judith R., Comparison of mixed anaplastic oligoastrocytoma and high-grade astrocytoma in NCCTG clinical trials of high-grade glioma, Proc Am Soc Clin Oncol 21:77a, 2002

Cairncross G, Seiferheld W, Shaw E, Jenkins R, Scheithauer B, Brachmna D, Buckner J, Fink K, Souhami L, Curran W: An intergroup randomized controlled clinical trial (RCT) of chemotherapy plus radiation (RT) versus RT alone for pure and mixed anaplastic oligodendrogliomas: Initial report of RTOG 94-02. Proc Am Soc Clin Oncol 2004 23:107 (Abstr. 500).

Cairncross G, Seiferheld W, Shaw E, Jenkins R, Scheithauer B, Brachman D, Buckner J, Fink K, Souhami L, Curran W: An Intergroup randomized controlled clinical trial (RCT) of chemotherapy plus radiotherapy (RT) versus RT alone for pure and mixed anaplastici oligodendroglioma: initial report of RTOG 94-02. Neuro-oncology 2004 6:371, (Abstr TA-09).

Cairncross G, Berkey B, Shaw E, Jenkins R, Scheithauer B, Brachman D, Buckner J, Fink K, Souhami L, Laperierre n, Mehta M, Curran W: Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Oncology Group Trial 9402. J Clin Oncol 24: 2707-2714, 2006.

Cella DF: Quality of life outcomes: measurement and validation. Oncology (Huntington) 1996 10:233-46.

Chahlavi A, Kanner A, Peereboom D et al: Impact of chromosome 1p status in response of oligodendroglioma to temozolomide: preliminary results. J Neurooncol 2003:61, 267-273.

Chinot O. Chemotherapy for the treatment of oligodendroglial tumors. Semin Oncol. 2001 Aug;28(4 Suppl 13):13-8.

Chinot OL, Honore S, Dufour H, Barrie M, Figarella-Branger D, Muracciole X, Braguer D, Martin PM, Grisoli F: Safety and efficacy of temozolomide in patients with recurrent anaplastic oligodendrogliomas after standard radiotherapy and chemotherapy. J Clin Oncol. 2001 May 1;19(9):2449-55.

Cowell JK, Barnett GH, Nowak NJ: Characterization of the 1p/19q chromosomal loss in oligodendrogliomas using comparativegenomic hybridization arrays (CGHa). J Neuropathol Exp Neurol. 2004 Feb;63(2):151-8.

Dong SM, Pang JC, Poon WS, Hu J, To KF, Chang AR, Ng HK Concurrent hypermethylation of multiple genes is associated with grade of oligodendroglial tumors. J Neuropathol Exp Neurol. 2001 Aug;60(8):808-16.

Duffy, D.E. and T.J. Santner, Confidence intervals for a binomial parameter based on multistage tests. Biometrics, 1987. 43: p. 81-93.

Felsberg J, Erkwoh A, Sabel MC, Kirsch L, Fimmers R, Blaschke B, Schlegel U,Schramm J, Wiestler OD, Reifenberger G: Oligodendroglial tumors: refinement of candidate regions on chromosome arm 1p and correlation of 1p/19q status with survival.Brain Pathol. 2004 Apr;14(2):121-30.

Fleming, T.R., One-sample multiple testing procedure for phase II clinical trials. Biometrics, 1982. 38(1): p. 143-51.

Fortin D, Macdonald DR, Stitt L, Cairncross JG.: PCV for oligodendroglial tumors: in search of prognostic factors for response and survival. Can J Neurol Sci. 2001 Aug;28(3):215-23.

Gonzalez-Gomez P, Bello MJ, Arjona D, Lomas J, Alonso ME, De Camp JM, Vaquero J, Isla A, Gutierrez M, Rey JA: Promotor hypermehtylation of muyltiple genes in astrocytic gliomas. Int J Oncol 2003 22:601-8.

Hegi ME, Diserens A-C, Hamou M-F, Gorlia T, Weller M, Kros JM, Hainfeller J, Bogdahn U, Cairncross G, Stupp R. Temozolomide targets only glioblastoma with a silenced MGMT-gene. Results of a translational companion study to EORTC 26981/NCIC CE.3 of Radiotherapy ± TMZ. Eur.J.Can.Supplements 2004 2(8),13..

Ino Y, Betensky RA, Zlatescu MC, Sasaki H, Macdonald DR, Stemmer-Rachamimov AO, Ramsay DA, Cairncross JG, Louis DN. Molecular subtypes of anaplastic oligodendroglioma: implications for patient management at diagnosis. Clin Cancer Res. 2001 Apr;7(4):839-45

Jaeckle KA, Hess KR, Yung WK, Greenberg H, Fine H, Schiff D, Pollack IF, Kuhn J, Fink K, Mehta M, Cloughesy T, Nicholas MK, Chang S, Prados M; North American Brain Tumor Consortium. Phase II evaluation of temozolomide and 13-cis-retinoic acid for the treatment of recurrent and progressive malignant glioma: a North American Brain Tumor Consortium study. J Clin Oncol. 2003 Jun 15;21(12):2305-11.

Jaeckle KA, Eyre HJ, Townsend JJ, Schulman S, Knudson HM, Belanich M, Yarosh DB, Bearman SI, Giroux DJ, Schold SC: Correlation of tumor O6 methylguanine-DNA methyltransferase levels with survival of malignant astrocytoma patients treated with bis-chloroethylnitrosourea: A Southwest Oncology Group Study. J Clin Oncol 1998 16: 3310-3315.

Jenkins RB, Blair H, Flynn H, Passe S, Law M, Ballman KV, Gianninn C, Buckner JC: A t(1;19)(q10;p10) mediates the combined deletions of 1p and 19q in human oligodendrogliomas. Proc Am Assoc Canc Res 2006; (Abstr 5545).

Jenkins, Robert B. M.D.; Ballman, Karla V. Ph.D.; Giannini, Caterina M.D.; Arusell, Robert M. M.D.; Blair, H E; Flynn, H; Passe, Sandra; Brown, Paul D. M.D.; Shaw, Edward G. M.D.; Buckner, Jan C M.D., NCCTG 94-72-53: Diagnostic and prognostic significance of a t(1:19)(q10:p10) patients (pts) with low-grade oligodendroglioma and astrocytoma, Proc Am Soc Clin Oncol 24:18S , 59S, 2006.

Jeremic B, Milicic B, Grujicic D, Samardzic M, Antunovic V, Dagovic A, Aleksandrovic: Combined treatment modality for anaplastic oligodendroglioma and oligoastrocytoma: a 10-year update of a phase II study. J Int J Radiat Oncol Biol Phys. 2004 Jun 1;59(2):509-14.

Jeremic B, Shibamoto Y, Gruijicic D, Milicic B, Stojanovic M, Nikolic N, Dagovic A, Aleksandrovic J. Combined treatment modality for anaplastic oligodendroglioma: a phase II study. J Neurooncol. 1999 Jun;43(2):179-85.

Johnson MD, Vnencak-Jones CL, Toms SA, Moots PM, Weil R Allelic losses in oligodendroglial and oligodendroglioma-like neoplasms:analysis using microsatellite repeats and polymerase chain reaction. Arch Pathol Lab Med. 2003 Dec;127(12):1573-9.

Kamiryo T, Tada K, Shiraishi S, Shinojima N, Kochi M, Ushio Y: Correlation between promoter hypermethylation of the O-6 methylguanine-deoxyribonucleic acid methyltransferase gene and prognosis in patients with high-grade astrocytic tumors treated with surgery, radiotherapy, and 1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2-chloroethyl)-3 nitrosoruea-based chemotherapy. Neurosurgery 2004 54:349-57.

Kamiya M, Nakazato Y: The expression of cell cycle regulatory proteins in oligodendroglial tumors. Clin Neuropathol. 2002 Mar-Apr;21(2):52-65.

Lebrun C, Fontaine D, Ramaioli A, Vandenbos F, Chanalet S, Lonjon M, Michiels JF, Bourg V, Paquis P, Chatel M, Frenay M: Long-term outcome of oligodendrogliomas. Nice Brain Tumor Study Group. Neurology. 2004 May 25;62(10):1783-7.

Lee JJ, Feng L. Randomized phase II designs in cancer clinical trials: current status and future directions. J Clin Oncol. 2005 Jul 1;23(19):4450-7.

Levin VA, Yung WK, Bruner J, Kyritsis A, Leeds N, Gleason MJ, Hess KR, Meyers CA, Ictech SA, Chang E, Maor MH: Phase II study of accelerated fractionation radiation therapy with Carboplatin followed by PCV chemotherapy for the treatment of anaplastic gliomas. Int J Radiat Oncol Biol Phys. 2002 May 1;53(1):58-66.

Martin JB, Taphoorn, Stupp R, Coens C, Osoba D, Kortmann R, van den Bent MJ, Mason W, Mirimanoff RO, Baumert BG, Eisenhauer E, et al. The Lancet Oncology, Volume 6, Issue 12, December 2005, 937-944.

Meyers CA, Brown :D. Role and relevance of neurocognitive assessment in clinical trials of patients with CNS tumors. J Clin Oncol 24:1305-9, 2006.

Miettinen HE, Paunu N, Rantala I, Kalimo H, Paljarvi L, Helin H, Haapasalo H.Cell cycle regulators (p21, p53, pRb) in oligodendrocytic tumors: a study by novel tumor microarray technique. J Neuro-oncol. 2001 Oct; 55(1):29-37.

Molleman M, Wolter M, Felsberg J, Collins VP, Reifenberger G: Frequent promoter hypermethylation and low expression of the MGMT gene in oligodendroglial tumors. Int J Cancer (2005) 20: 379-85.

Nayak A, Ralte AM, Sharma MC, Singh VP, Mahapatra AK, Mehta VS, Sarkar C. p53 protein alterations in adult astrocytic tumors and oligodendrogliomas. Neurol India. 2004 Jun;52(2):228-32.

Paleologos NA, Macdonald DR, Vick NA, Cairncross JG. Neoadjuvant procarbazine, CCNU, and vincristine for anaplastic and aggressive oligodendroglioma. Neurology. 1999 Sep 22;53(5):1141-3.

Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trials. Biometrics 31 (1): 103-115, 1975 Mar.

Puduvalli VK, Hashmi M, McAllister LD, Levin VA, Hess KR, Prados M, Jaeckle KA, Yung WK, Buys SS, Bruner JM, Townsend JJ, Davis R, Sawaya R, Kyritsis AP. Anaplastic oligodendrogliomas: prognostic factors for tumor recurrence and survival. Oncology. 2003 65(3):259-66.

O'Brien PC, Fleming TR: A multiple testing procedure for clinical trials. Biometrics 197935:549-556..

Paz M, Yaya-Tur R, Rojas-Marcos I, Reynes G, Pollan M, Aguirre-Crus L, Garcia-Lopez J Piquer J, Safont MJ, Balana C, Sanchez-Cespedes M, Garcia-Villanueva M, Arribas L, Esteller M: CpG island hypermethylation of the DNA repair enzyme methyltransferase predicts response to temozolomide in primary gliomas. Clin Canc Res (2004) 10:4933-4938

Rubinstein LV, Korn EL, Freidlin B, Hunsberger S, Ivy SP, Smith MA. Design issues of randomized phase II trials and a proposal for phase II screening trials. J Clin Oncol. 2005 Oct 1;23(28):7199-206.

Sasaki H, Zlatescu MC, Betensky RA, Ino Y, Cairncross JG, Louis DN: PTEN is a target of chromosome 10q loss in anaplastic oligodendrogliomas and PTEN alterations are associated with poor prognosis. Am J Pathol. 2001 Jul;159(1):359-67.

Simon, R., Optimal two-stage designs for phase II clinical trials. Control Clin Trials, 1989. 10(1): p. 1-10.

Taphoorn MJ, Klein M: Cognitive deficits in adult patients with brain tumours. Lancet Neurology 2004 3:159-68.

Taylor, B. V., J. C. Buckner, et al: Effects of radiation and chemotherapy on cognitive function in patients with high-grade glioma. J Clin Oncol 1998 16: 2195-201.

Smith JS, Perry A, Borell TJ, Lee HK, O'Fallon J, Hosek SM, Kimmel D, Yates A, Burger PC, Scheithauer BW, Jenkins RB. Alterations of chromosome arms 1p and 19q as predictors of survival in oligodendrogliomas, astrocytomas, and mixed oligoastrocytomas. J Clin Oncol. 2000 Feb;18(3):636-45.

Smith JS, Wang XY, Qian J, Hosek SM, Scheithauer BW, Jenkins RB, James CD: Amplification of the platelet-derived growth factor receptor-A (PDGFRA) gene occurs in oligodendrogliomas with grade IV anaplastic features J Neuropathol Exp Neurol. 2000 Jun;59(6):495-503.

Soffietti R. Chemotherapy of anaplastic oligodendroglial tumours. Expert Opin Pharmacother. 2004 Feb;5(2):295-306.

Sposto R, Stram DO. A strategic view of randomized trial design in low-incidence paediatric cancer. Stat Med. 1999 May 30;18(10):1183-97.

Spreen O, Strauss E: A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary (ed 2nd). New York, Oxford University Press, 1998.

Streffer J, Schabet M, Bamberg M, Grote EH, Meyermann R, Voigt K, Dichgans J, Weller M. A role for preirradiation PCV chemotherapy for oligodendroglial brain tumors. J Neurol. 2000 Apr;247(4):297-302.

Stupp R, Mason WP, Van Den Bent J, Weller M, Fisher B, Taphoorn M, Brandes AA, Cairncross G, Lacombe D, Mirimanoff RO: Concomitant and adjuvant temozolomide (TMA) and radiotherapy (RT) for newly diagnosed glioblastoma multiforme (GBM). Conclusive results of a randomized phase III trial by the EORTC brain and RT groups and NCIC Clinical Trials Group. Proc Am Soc Clin Oncol 2004 23: 1 (Abstr 2).

Thiessen B, Maguire JA, McNeil K, Huntsman D, Martin MA, Horsman D: Loss of heterozygosity for loci on chromosome arms 1p and 10q in oligodendroglial tumors: relationship to outcome and chemosensitivity. J Neurooncol. 2003 Sep;64(3):271-8.

van den Bent MJ, Chinot O, Boogerd W, Bravo Marques J, Taphoorn MJ, Kros JM, van der Rijt CC, Vecht CJ, De Beule N, Baron B. Second-line chemotherapy with temozolomide in recurrent oligodendroglioma after PCV (procarbazine, lomustine and vincristine) chemotherapy: EORTC Brain Tumor Group phase II study 26972. Ann Oncol. 2003 Apr;14(4):599-602.

van den Bent MJ, Keime-Guibert F, Brandes AA, Taphoorn MJ, Kros JM, Eskens FA, Carpentier AF. Temozolomide chemotherapy in recurrent oligodendroglioma. Neurology. 2001 Jul 24; 57(2):340-2.

van den Bent MJ, Taphoorn MJ, Brandes AA, Menten J, Stupp R, Frenay M, Chinot O, Kros JM, van der Rijt CC, Vecht ChJ, Allgeier A, Gorlia T; European Organization for Research and Treatment of Cancer Brain Tumor Group. Phase II study of first-line chemotherapy with temozolomide in recurrent oligodendroglial tumors: the European Organization for Research and Treatment of Cancer Brain Tumor Group Study 26971. J Clin Oncol. 2003 Jul 1;21(13):2525-8.

van den Bent MJ, Dellatre JY, Brandes AA et al: First analysis of EORTC trial 26951, a randomized phase III study of adjuvant PCV chemotherapy in patients with highly anaplastic oligodendroglioma. Proc Am Soc Clin Oncol 2005 23:16S Part I, 1502 (Abstr)

van den Bent MJ, Carpentier AF, Alba AA et al: Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organization for Research and Treatment of Cancer Phase III trial. J Clin Oncol 24:2715-2722, 2006

Vogelbaum MA, Berkey B, Peereboom D et al: RTOG 0131: Phase II trial of pre-irradiaton and concurrent temozolomide in patient siwht newly diagnosed anaplastic oligodendrogliomas and mixed anaplastic oligodendrogliomas. J Clin Oncol (2005) 23:119s (Abstr 1520)

Watanabe T, Nakamura M, Yonekawa Y, Kleihues P, Ohgaki H. Promoter hypermethylation and homozygous deletion of the p14ARF and p16INK4a genes in oligodendrogliomas. Acta Neuropathol (Berl). 2001 Mar;101(3):185-9.

Watanabe T, Yokoo H, Yokoo M, Yonekawa Y, Kleihues P, Ohgaki H. Concurrent inactivation of RB1 and TP53 pathways in anaplastic oligodendrogliomas. J Neuropathol Exp Neurol. 2001 Dec;60(12):1181-9.

Wechsler D: Manual for the Wechsler Adult Intelligence Scale (ed 3rd). San Antonio, TX, The Psychological Corporation, 1997.

Weitzner MA, Meyers CA, Gelke CK, et al: The Functional Assessment of Cancer Therapy (FACT) scale. Development of a brain subscale and revalidation of the general version (FACT-G) in patients with primary brain tumors. Cancer 75:1151-61, 1995.

NCI Informed Consent Template for Cancer Treatment Trials
(English Language)

***NOTES FOR LOCAL INVESTIGATORS: [NOTE: Retain this section and asterisk item below for NCCTG model consents]**

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer…What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at *https://cissecure.nci.nih.gov/ncipubs/* or call 1-800-4-CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

**These notes for {authors and} investigators are instructional and should not be included in the informed consent form given to the prospective research participant.*

N0577, Phase III Intergroup Study of Radiotherapy versus Temozolomide alone versus Radiotherapy with Concomitant and Adjuvant Temozolomide for Patients with 1p/19q Codeleted Anaplastic Glioma

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

Add 1

Why is this research study being done?

The research in this study is investigational. This study is being carried out under the sponsorship of the North Central Treatment Group (NCCTG).

Add 1

This research study is being done in people like you who have a certain type of brain tumor, called "anaplastic glioma." In addition, some of your tumor cells must also be missing parts of chromosomes 1 and 19. These chromosomes are missing parts only in the tumor cells, and are not typically missing in your normal body cells. This type of anaplastic glioma has a more favorable outcome than other types of anaplastic glioma. Standard therapy at this point in time is surgery followed by radiation therapy.

Add 1

The two main reasons this research study is being done are to see if:

- people have longer survival if they get treatment with the combination of both radiation therapy temozolomide chemotherapy as compared to people who receive treatment with radiation therapy alone.
- people treated with temozolomide therapy alone (no radiation therapy) have a better or worse quality of life and mental function than those patients who are treated with either the combination of radiation therapy and temozolomide or radiation therapy alone. Survival will also be monitored in the people getting temozolomide alone.

There are three possible treatments that you might get while on this study. You will be "randomized" into one of the study groups (radiation therapy alone [Arm A], radiation therapy alone with temozolomide given during and after radiation therapy [Arm B], and temozolomide alone [Arm C]). Randomization means that you are put into a group by chance (as in a roll of the dice). A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. If you are put on this study during the first portion of the trial, you will have a one in three chance of getting any one of these three treatments. Late in the trial, only the first two treatments will be included in the study.

Add 1

If you are put on this study in the later portions of the trial, you will have a 50/50 chance of getting either radiation therapy alone or radiation therapy along with temozolomide given during and after the radiation therapy.

How many people will take part in the research study?

About 488 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical history
- Complete physical exam
- Neurological history and exam
- Routine blood tests (including pregnancy tests, if necessary)
- Scans of the head with contrast (for tumor measurement)

A portion of your tumor tissue taken at the time of your surgery will be sent to laboratories associated with the North Central Cancer Treatment Group (NCCTG) to be tested for deletion (absence) of portions of chromosome 1p and 19q. You would not be eligible for this particular trial if the portions of both of these chromosomes are not missing.

During the study

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.

- Medical history
- Complete physical exam
- Neurological history and exam
- Routine blood tests
- Scans of the head with contrast (for tumor measurement)

If you are in group 1 (Arm A), you will get radiation therapy Monday through Friday for about 6-7 weeks.

If you are in group 2 (Arm B), you will get radiation therapy Monday through Friday as well as daily (7 days a week) temozolomide by mouth for about 6-7 weeks. You will then have a 4-week treatment break. You will then get temozolomide alone week 1 (days 1 through 5) every 28 days for up to one year.

If you are in group 3 (Arm C), you will get temozolomide week 1 (days 1 through 5) every 28 days for up to one year.

The chart below shows what will happen to you. The left-hand column shows the day in the cycle and the right-hand column tells you what to do on that day.

Group 1 (Arm A) - Cycle 1 (no future cycles)

	Day	What you do
	Within 21 days of starting the study	• Medical history • Complete physical exam • Neurological history and exam • Routine blood tests (including pregnancy tests, if necessary and additional blood [about 3 tablespoons] for research purposes if agreed to) • Scans of the head with contrast (for tumor measurement) • Complete patient questionnaires • Brief memory and thinking tests
	Monday through Friday for up to 7 weeks	• Radiation therapy
	Every other week until radiation therapy is completed	• Get routine blood tests (can be done weekly if study doctor feels it is needed).
	4-6 weeks after radiation therapy is completed	• Medical history • Complete physical exam • Neurological physical exam • Routine blood tests • Scans of the head with contrast (for tumor measurement) • Complete patient questionnaires • Brief memory and thinking tests
Add 1	Observation following radiation therapy will be every 8 weeks for 18 months from start of treatment and then every 12 weeks unless your disease gets worse	• Medical history • Complete physical exam • Neurological physical exam • Scans of the head with contrast (for tumor measurement) • Routine blood tests if your study doctor thinks they are needed
Add 1	About every 6 months during the time of observation unless your disease gets worse and at the time your disease gets worse	• Complete patient questionnaires • Brief memory and thinking tests

Group 2 (Arm B) - Cycle 1

Day	What you do
Within 21 days of starting the study	• Medical history • Complete physical exam • Neurological history and exam • Routine blood tests (including pregnancy tests, if necessary and additional blood [about 3 tablespoons] for research purposes if agreed to) • Scans of the head with contrast (for tumor measurement) • Complete patient questionnaires • Brief memory and thinking tests
During radiation therapy	• Begin radiation therapy on a weekly basis, Monday through Friday, for up to 7 weeks • Begin temozolomide by mouth and continue taking on a daily basis (7 days a week) for up to 7 weeks. Take in the morning with a full glass of water (1 cup) on an empty stomach or one to two hours after food. Because temozolomide can sometimes cause an upset stomach, your study doctors will give you an anti-nausea pill to take before you take your temozolomide. A diary that keeps track of when you take your temozolomide will need to be filled out every day as you take a capsule. Give to the doctor when you see him/her the next time. Temozolomide treatment has been associated with an increased risk of infection, and these types of infections can be prevented with antibiotics (either Bactrim or pentamidine or dapsone). Your doctor will decide with you which medication you will need to take to protect you from these infections.
Every other week until radiation therapy is completed	• Get routine blood tests (can be done weekly if study doctor feels it is needed).
4 week rest period	• Nothing will need to be done during this time period.

Group 2 (Arm B) - All future cycles

Day	What you do
Before re-starting treatment	• Medical history • Complete physical exam • Neurological history and exam • Routine blood tests • Scans of the head with contrast (for tumor measurement)

Day	What you do
Days 1 through 5 every 28 days for 6 cycles (cycle = 28 days)*	• Temozolomide by mouth. Take in the morning with a full glass of water (1 cup) on an empty stomach or one to two hours after food. Because temozolomide can sometimes cause an upset stomach, your study doctors will give you an anti-nausea pill to take before you take your temozolomide. A diary that keeps track of when you take your temozolomide will need to be filled out every day as you take a capsule. Give to the doctor when you see him/her the next time. Temozolomide treatment has been associated with an increased risk of infection, and these types of infections can be prevented with antibiotics (either Bactrim or pentamidine or dapsone). Your doctor will decide with you which medication you will need to take to protect you from these infections.
At 10 weeks	• Scans of the head with contrast (for tumor measurement) • Complete patient questionnaires • Brief memory and thinking tests
Every other cycle	• Scans of the head with contrast (for tumor measurement)
Every cycle	• Medical history • Complete physician exam • Neurological history and exam • Routine blood tests
When all temozolomide treatment has ended, the items listed will be done every 8 weeks until you are 18 months from start of treatment and then they will be done every 12 weeks unless your disease gets worse	• Medical history • Complete physical exam • Neurological history and exam • Routine blood tests if your study doctor thinks they are needed • Scans of the head with contrast (for tumor measurement)
About every 6 months following the 10-week time point noted above unless your disease gets worse	• Complete patient questionnaires • Brief memory and thinking tests

*Your study doctor might have you keep taking temozolomide for 12 cycles, depending on how well you are doing.

Group 3 (Arm C) - Cycles 1 -12

Day	What you do
Within 21 days of starting the study	• Medical history • Complete physical exam • Neurological history and exam • Routine blood tests (including pregnancy tests, if necessary and additional blood [about 3 tablespoons] for research purposes if agreed to) • Scans of the head with contrast (for tumor measurement) • Complete patient questionnaires
Days 1 through 5 every 28 days for 12 cycles (cycle = 28 days)	• Temozolomide by mouth. Take in the morning with a full glass of water (1 cup) on an empty stomach or one to two hours after food. Because temozolomide can sometimes cause an upset stomach, your study doctors will give you an anti-nausea pill to take before you take your temozolomide. A diary that keeps track of when you take your temozolomide will need to be filled out every day as you take a capsule. If you should make a mistake on the diary, draw through the mistake with one line and then sign off with your initials by the correction. Give to the doctor when you see him/her the next time. Temozolomide treatment has been associated with an increased risk of infection, and these types of infections can be prevented with antibiotics (either Bactrim or pentamidine or dapsone). Your doctor will decide with you which medication you will need to take to protect you from these infections.
Every cycle	• Medical history • Complete physical exam • Neurological history and exam • Routine blood tests
Every other cycle	• Scans of the head with contrast (for tumor measurement)
Cycle 3	• Complete patient questionnaires • Brief memory and thinking tests
When all treatment has ended, the items listed will be done every 8 weeks until you are 18 months from start of treatment and then they will be done every 12 weeks unless your disease gets worse Add 1	• Medical history • Complete physical exam • Neurological history and exam • Routine blood tests (including pregnancy tests, if necessary and additional blood for research purposes if agreed to) • Scans of the head with contrast (for tumor measurement)
About every 6 months following Cycle 3 time point noted above unless your disease gets worse Add 1	• Complete patient questionnaires • Brief memory and thinking tests

This study also has laboratory tests that will be done to study small samples of tissue. No additional biopsies will be done to get this tissue.

The tissue will be sent to laboratories associated with NCCTG, where the tests will be done. These tests will be done in order to understand how your cancer responds to treatment. It is hoped that this will help investigators better understand your type of cancer. The results of these tests will not be sent to you or your study doctor and will not be used in planning your care. These tests are for research purposes only and you will not have to pay for them.

Neurocognitive/Quality of Life Study

We want to know your view of how your life has been affected by cancer and its treatment. This "neurocognitive/quality of life function" study looks at how you are feeling physically and emotionally during your cancer treatment. It also looks at how you are able to carry out your day-to-day activities. You will be asked to participate by having your symptoms, quality of life, and neurocognitive function evaluated.

This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer.

You will be asked to complete a brief cognitive evaluation (paper and pencil tasks administered by an examiner) and 1 questionnaire booklet. It takes about 20 minutes to complete the cognitive evaluation and 15 minutes to complete the questionnaire booklet.

If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

How long will I be in the research study?

You will be in the treatment part of the study for up to 1 to 1½ years, depending on which treatment group you are randomized to. After you are done with your treatment, the study doctor will ask you to visit the office for follow-up exams unless your disease gets worse. We would also like to keep track of your medical condition. Keeping in touch with you and checking on your condition every year helps us look at the long-term effects of the study.

Can I stop being in the research study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the research study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop treatment. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the temozolomide include:

Likely *(events occurring greater than 20% of the time)*

- Nausea (feeling sick to your stomach)
- Vomiting (throwing up)
- Decreased appetite
- Constipation
- Headache
- Fatigue
- Fever
- Hair loss

Less Likely *(events occurring less than or equal to 20% of the time)*

- Fall in the white blood cell counts that leads to a higher risk of infection
- Low number of a particular white blood cell, which is important to the immune system (lymphopenia)

Add 1

- Fall in the platelet count leading to a higher risk of bleeding
- Fall in the red blood cell count leading to anemia (feeling tired and low energy).
- Sores in the mouth
- Diarrhea
- Pain in the abdomen
- Change in liver function tests (tests that show how the liver is working)
- Rash
- Itchiness
- Lack of interest in or ability to carry out daily activities
- Weakness
- Dizziness
- Confusion
- Blurred vision
- Anxiety
- Depression
- Memory loss
- Muscle or joint pain
- Tingling or burning in your arms or legs
- Shortness of breath
- Cough
- Swelling in your arms or legs
- Increased need to pass urine

Rare but serious *(events occurring less than 2-3% of the time)*

- Myelodysplastic syndrome (problem with the bone marrow that causes decreased production of red cells, while cells, or platelets that can sometimes turn into blood cancer)
- Convulsions
- Weakness on one side of your body
- Abnormal coordination
- Paralysis
- Severe skin reaction (rash/flaking or shedding of outer layer of skin)
- Allergic reaction that can include chest pain and tightness, difficulty breathing, feeling hot, flushed and anxious, swelling around the eyes, dizziness, feeling sick to the stomach, a fall in blood pressure, back pain, and numbness and tingling

- Re-activation of hepatitis infection (if you have previously been diagnosed with Hepatitis – a type of infection in the liver)

Add 1
- A blood disorder in which the body's bone marrow does not make enough new blood cells (aplastic anemia)

Add 1
- Inflammation of the lungs (pneumonitis)
- Change in kidney function tests (tests that show the kidneys are working)

Add 1

Risks and side effects related to the radiation therapy include:

Likely (*events occurring greater than 20% of the time)*
- Short-term reddening and drying of the skin, fatigue, and hair loss within treated area

Less Likely *(events occurring less than or equal to 20% of the time)*
- Nausea (feeling sick to your stomach)
- Vomiting (throwing up)
- Headache

Rare but serious
- Seizures
- Coma
- Lower white blood cell and platelet counts raising the risk of infection and bleeding
- Radiation therapy at these dose levels also may cause damage to normal brain, but this is rare
- Specific effects depend upon the location of the area(s) of damage but may be a decrease in judgment, memory, emotions, vision, hearing, sensation, or ability to control movement.

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breast feed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your health care provider about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the research study?

Taking part in this study may or may not make your health better. We do know that the information from this study will help doctors learn if there is any advantage to give temozolomide with the radiation therapy as compared to just giving the radiation therapy alone. For patients treated on Arm C (temozolomide alone), it is possible (although unproven) that there might be benefit from the delay in getting radiation therapy-induced side effects. This information could help future brain tumor patients.

What other choices do I have if I do not take part in this research study?

You do not have to be in this study to receive treatment for your cancer.

Your other choices may include:
- Getting treatment or care for your cancer without being in a study

Add 1
- Getting radiation and temozolomide off study
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- NCCTG
- EORTC (European Organisation for Research and Treatment of Cancer)
- The Cancer Trials Support Unit (CTSU), a service sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials
- Schering-Plough, manufacturer of temozolomide
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this research study?

You and/or your health plan/ insurance company will need to pay for all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The study agent, temozolomide, will be provided free of charge while you are taking part in this study.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . *You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.*
Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this research study?

It is important that you tell your study doctor, _____ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this research study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the research study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number]*.

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). *[*Only applies to institutions using the CIRB.]*

About Using Biological Samples for Research

Additional blood (about 3 tablespoons) will be taken at the time of your routine blood tests. This additional blood will be stored for future research purposes only. The research that may be done with your blood is not designed specifically to help you. It might help people who have cancer and other diseases in the future. Reports about research done with your blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

You can take part in the treatment portion of this study without taking part in this request for additional blood.

Please read the following statements and mark your choice:

I agree that additional blood can be taken at the time of routine blood tests for use in future research.

☐ Yes ☐ No Please initial here: _____ Date: _____

Add 1 We would also like to keep some of the tissue that is left over for future research. If you agree, this left over tissue will be kept and may be used in research to learn more about cancer and other diseases.

Add 1 The research that may be done with your left over tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Add 1 Reports about research done with your left over tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

Add 1 The choice to let us keep the left over tissue and blood sample for future research is up to you. No matter what you decide to do, it will not affect your care.

Add 1 If you decide now that your left over tissue and blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your left over tissue and/or blood. Then any left over tissue or blood that remains will no longer be used for research.

In the future, people who do research may need to know more about your health. While NCCTG may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Add 1 Sometimes left over tissue and blood is used for genetic research (about diseases that are passed on in families). Even if your left over tissue and/or blood sample is used for this kind of research, the results will not be put in your health records.

Add 1 Your left over tissue and blood will be used only for research and will not be sold. The research done with your left over tissue and blood may help to develop new products in the future.

Benefits

The benefits of research using left over tissue and blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number.

No matter what you decide to do, it will not affect your care.

Add 1 1. My left over tissue sample(s) may be kept for use in research to learn about, prevent, or treat cancer.

☐ Yes ☐ No Please initial here: _____ Date: _____

2. My blood sample may be kept for use in research to learn about, prevent, or treat cancer.

☐ Yes ☐ No Please initial here: _____ Date: _____

Add 1 3. My left over tissue sample(s) may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

☐ Yes ☐ No Please initial here: _____ Date: _____

4. My blood sample may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

☐ Yes ☐ No Please initial here: _____ Date: _____

Add 1 5. My tissue sample(s) may be kept for use in future genetic research.

☐ Yes ☐ No Please initial here: _____ Date: _____

Add 1 6. My blood sample may be kept for use in future genetic research.

☐ Yes ☐ No Please initial here: _____ Date: _____

If you want your sample(s) destroyed at any time, write to the Secretary of the _____ Institutional Review Board _____.
NCCTG has the right to end storage of the sample(s) without telling you.

Outside researchers may one day ask for a part of your sample(s) for studies now or future studies.

How do outside researchers get the sample?

Researchers from universities, hospitals, and other health organizations do research using blood and tissue. They may call NCCTG and ask for samples for their studies. NCCTG looks at the way that these studies will be done, and decides if any of the samples can be used. NCCTG sends the samples and some information about you to the researcher. NCCTG will not send your name, address, phone number, social security number, or any other identifying information to the researcher. If you allow your sample(s) to be given to outside researchers, it will be given to them with a code number. If researchers outside NCCTG use the sample(s) for future research, they will decide if you will be contacted and, if so, they would have to contact the researchers at NCCTG. Then NCCTG will contact the clinic where you registered for this study, who will contact you.

Please read the following statements and mark your choice:

Add 1 1. I permit NCCTG to give my left over tissue sample(s) to outside researchers:

☐ Yes ☐ No Please initial here:_____ Date:_____

2. I permit NCCTG to give my blood sample to outside researcher

☐ Yes ☐ No Please initial here:_____ Date:_____

3. I permit NCCTG to contact me in the future to take part in more research

☐ Yes ☐ No Please initial here:_____ Date:_____

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Printed Participant Name: _____

Participant Signature: _____

Date: _____

Printed name of person obtaining informed consent:

_____

Signature of person obtaining informed consent:

_____

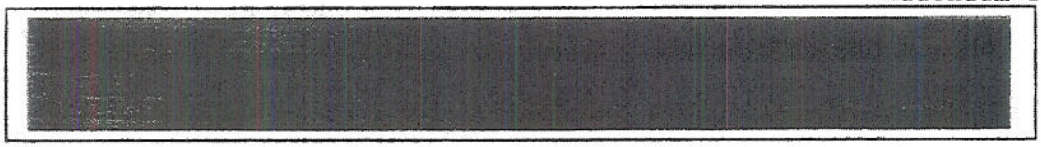
Date _____

Local IRB changes to this document are allowed. Sections "What are the risks of the research study" or "What other choices do I have if I don't take part in this research study?" should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the North Central Cancer Treatment Group Operations Office for approval before a patient may be registered to this study.

Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.

Appendix II
Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.



ATC Guidelines for the Use of IMRT (including Intra-Thoracic Treatments)
July 19, 2006

Preamble:

The Advanced Technology Consortium (ATC) has helped to develop general guidelines (*Int. J. Radiat. Oncol. Biol. Phys. 59 (2004):1257-1262*) for protocols that incorporate Intensity Modulated Radiation Therapy (IMRT) as an option. These were communicated to all clinical trial groups by the National Cancer Institute (NCI) and clearly stated that respiratory motion could cause far more problems for IMRT than for traditional treatments. The delivery of IMRT is dynamic as is the effect of breathing motion, therefore the interplay between the two can result in non-reproducible dose distributions due to the variability in how subfields are added. In addition, other patient motions may have significant effects on the summation of subfields whose intensities are based upon a static image. Thus, extra care is required in the acquisition of the CT datasets used in the planning process in order to avoid motion artifacts while still being representative of the average location of the anatomical structures. Those guidelines also explained why accounting for heterogeneities was most important for IMRT since heterogeneities could affect some subfields more than others and result in localized dose distribution differences that could be clinically significant.

The enclosed, updated version of the guidelines explicitly includes IMRT in anatomical regions where target motion can have a significant effect, such as intra-thoracic treatments. While these guidelines are intended to serve only as minimal standards for NCI-supported clinical trials, they do mandate that any protocol that requires or allows IMRT must include the following requirements in either the initial protocol or as an amendment if IMRT is to be subsequently allowed.

Protocol Requirements for IMRT (including intra-thoracic lesions):

1. The protocol must explicitly address the localization and immobilization of both the patient and the tumor. There are several commercially available systems that can help achieve immobilization. The study chair and designated QA Center shall assess the adequacy of those systems for each individual protocol. For IMRT delivery, the residual motion after compensation techniques are applied should be explicitly specified in the protocol. The current literature indicates that with present-day techniques 5 mm of residual target motion is the smallest reasonable limit for intra-thoracic anatomical structures.

2. The protocol must require that a 3-D treatment planning volumetric imaging study be used to define the target volumes and organs at risk (OAR). The imaging studies need to provide an assessment of the target volume with the patient in the treatment position, and provisions must be made to acquire images that represent the target volume without motion artifact. Some of the techniques that can be used for these purposes are: spirometry, abdominal compression, 4D CT, and inspiration and expiration scans on a fast CT scanner capable of imaging the entire planning volume in one scan sequence for each breathing phase. The steps taken to suppress/manage motion and achieve appropriate simulation should be documented and submitted for review to the appropriate QA Center.

3. Protocols must employ the nomenclature defined in the NCI IMRT Working Group Report (*Int. J. Radiat. Oncol. Biol. Phys. 51:880-914, 2001*) and the International Commission on Radiation Units and Measurements (ICRU) Reports 50 and 62 for specifying: 1) the volumes of known tumor, i.e., the gross tumor volume (GTV), 2) the volumes of suspected microscopic spread, i.e., the clinical target volume (CTV) and 3) the marginal volumes necessary to account for setup variations and organ and patient motion, i.e., the planning target volume (PTV). An internal margin (IM) should be used to compensate for variation in position, size, and shape, of the CTV during treatment. Thus the PTV for a mobile target represents a volume that encompasses the CTV, a set-up margin (SM) that specifically accounts for spatial

uncertainties in patient positioning and treatment delivery, as well as an IM for the residual internal organ motion.[i]

4. The protocol should describe the rationale for the choice of margins (IM and SM) to be used for expanding CTV to PTV.

5. The protocol must require that the effects of tissue heterogeneities be included in the dose calculations for plan evaluation, dose prescription and MU calculations.

6. The adequacy and accuracy of the dose algorithms for heterogeneity-corrected dose distributions should be demonstrated by each participating institution to the designated QA Center. The algorithm must meet the criteria of acceptability established by the QA Center.

7. The protocol must provide a clear description of the prescription dose as well as dose heterogeneity permitted in the PTV, recognizing that dose heterogeneity will generally be greater with IMRT. The protocol must also specify the volume to be covered by the prescription dose (for example, the 60 Gy isodose must cover 95% of the PTV). If 3D conformal and IMRT treatments are both allowed in a particular protocol, the dose heterogeneity requirements for IMRT and non-IMRT patients should be comparable.

8. The protocol must clearly specify the organs at risk (OARs) and/or the planning organ-at-risk volumes (PRVs) and include guidelines for contouring each OAR/PRV. Dose constraints for each OAR/PRV must also be specified.

9. The GTV, CTV, PTV, OAR, PRV, and unspecified tissue (see 12. below) must be delineated on each slice of the 3-D volumetric imaging study in which that structure exists.

10. The protocol must specify the procedures that should be in place for documenting correct, reproducible positioning of patient and target. On-board imaging to ensure reproducible positioning is acceptable. Spatially registered volumetric imaging based on kV/MV CT is also acceptable. As a minimum, however, the equivalent of orthogonal (AP and lateral) digitally reconstructed radiographs (DRRs) and corresponding orthogonal weekly portal images (film or electronic) are required.

11. Copies of all images used to define the target and anatomical structures, as well as the RT data (e.g. RT-structures, - dose and -plan) should be submitted electronically to the designated QA center for review. As a minimum, hardcopies or screen captures of the computed dose distribution (in the coronal, axial, and sagittal planes that pass through the center of each PTV) must be submitted. Isodose lines superimposed upon representative slices of the 3-D volumetric imaging study must be clear and comprehensive. Acceptable values for hot spots and cold spots must be specified by the protocol, and images showing the locations and magnitudes of the hot and cold spots must be submitted. DVHs in absolute dose for the GTV, CTV, PTV, and all PRVs and OARs specified in the protocol must be submitted for QA.

12. A DVH in absolute dose must be submitted for a category of tissue called "unspecified tissue" that is defined as tissue contained within the skin, but which is not included within any other structure. This will help ensure that the IMRT plan does not result in unintentionally high doses in normal tissues that were not selected for DVH analysis.

13. The treatment machine monitor units (MUs) generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Patient specific quality assurance measurements can suffice when the plan's delivered fluence or dose distributions are validated quantitatively. The protocol should specify criteria for acceptance of these measurements.

14. Finally, before participating in a cooperative group protocol involving IMRT, an institution must be appropriately credentialed by the QA Center designated in the protocol.

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[i] *(ICRU Report 62 refines this definition of planning target volume by introducing the concept of an Internal Margin (IM) to take into account variations in size, shape, and position of the CTV in reference to the patient's coordinate system using anatomical reference points, and the concept of a Set-up Margin (SM) to take into account all uncertainties in patient beam positioning in reference to the treatment machine coordinate*

system. Report 62 defines the volume formed by the CTV and the IM as the Internal Target Volume (ITV). The ITV represents the movements of the CTV referenced to the patient coordinate system and is specified in relation to internal and external reference points, which preferably should be rigidly related to each other through bony structures. The ITV concept is likely to be used mostly by researchers studying internal organ motion. Note however, that the introduction of the ITV concept does not change the global concept and definition of the PTV as a means of accounting for geometric uncertainty. In most cases, the practicing physician can skip having to explicitly define the ITV. However, how the IM and SM should be combined is not at all clear. Simple linear addition of the two margins will generally lead to an excessively large PTV that would exceed patient tolerance and not reflect the actual clinical consequences. Thus, the risk of missing part of the CTV must be balanced against the risk of complications due to making the PTV too large. ICRU states that a quadratic approach similar to that recommended by the Bureau International des Poids et Mesures can be used).

ICRU Report 62 introduced the concept of the planning organ-at-risk volume (PRV), in which a margin is added around the organ at risk (OAR) to account for that organ's geometric uncertainties. The PRV margin around the critical structure that must be spared is analogous to the PTV margin around the CTV. The use of PRV concept is particularly important for those cases involving IMRT because of the increased sensitivity of this type of treatment to geometric uncertainties. The PTV and the PRV may overlap, and often do so, in which case a compromise must be found when weighing the importance of each in the planning process.

Radiation Therapy Quality Control Guidelines

1. For all patients, as outlined in Section 7.0, two PTV prescriptions, PTV1 and PTV boost will be used and the prescription isodose must cover >95% of the PTV volume; therefore, the total dose in the PTV boost volume will be 5940 cGy. The minimum acceptable dose within PTV1 will be 4536 cGy (90% of 5040 cGy) for **3D** *or* 4900 cGy (90% of 5445 cGy) if **IMRT** utilized, and in the PTV boost volume, it will be 5346 cGy (90% of 5940 cGy). If the minimum dose falls below these parameters, an unacceptable deviation will be assigned. The maximum dose for the PTV boost should not exceed 6534 cGy. If the maximum doses exceed these parameters, an unacceptable deviation will be assigned.

2. Up to 5 days of treatment interruption are permitted for any reason. Interruptions of 6 to 7 treatment days will be considered an acceptable protocol violation. For interruptions of 8 days or greater, an unacceptable deviation will be assigned.

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|

Your birthdate (Day, Month, Year): |_|_|_|_|_|_|

Today's date (Day, Month, Year): 31 |_|_|_|_|_|_|

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - BN20

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
31.	Did you feel uncertain about the future?	1	2	3	4
32.	Did you feel you had setbacks in your condition?	1	2	3	4
33.	Were you concerned about disruption of family life?	1	2	3	4
34.	Did you have headaches?	1	2	3	4
35.	Did your outlook on the future worsen?	1	2	3	4
36.	Did you have double vision?	1	2	3	4
37.	Was your vision blurred?	1	2	3	4
38.	Did you have difficulty reading because of your vision?	1	2	3	4
39.	Did you have seizures?	1	2	3	4
40.	Did you have weakness on one side of your body?	1	2	3	4
41.	Did you have trouble finding the right words to express yourself?	1	2	3	4
42.	Did you have difficulty speaking?	1	2	3	4
43.	Did you have trouble communicating your thoughts?	1	2	3	4
44.	Did you feel drowsy during the daytime?	1	2	3	4
45.	Did you have trouble with your coordination?	1	2	3	4
46.	Did hair loss bother you?	1	2	3	4
47.	Did itching of your skin bother you?	1	2	3	4
48.	Did you have weakness of both legs?	1	2	3	4
49.	Did you feel unsteady on your feet?	1	2	3	4
50.	Did you have trouble controlling your bladder?	1	2	3	4

APPENDIX VII

CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

REGISTRATION/RANDOMIZATION

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. All forms and documents associated with this study can be downloaded from the N0577 Web page on the CTSU registered member Web site (http://members.ctsu.org) unless otherwise indicated below. Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, neurocognitive and IMRT (if applicable) certifications have been received by the CTSU Central Regulatory Office (CCRO) (NCCTG will forward these documents for the institutions to the CCRO - see Sections 4.4113 and 6.0) and all pertinent forms and documents are approved and on file with the CTSU.

Requirements for N0577 site registration:

- CTSU IRB Certification
- IRB/Regulatory Approval Transmittal Sheet
- Neurocognitive Certification and Central Scoring:
  Examiners require pre-certification by Dr. Jane Cerhan, Mayo Clinic Rochester, in order to participate in this protocol. Certification procedures and notification of certification are outlined in Section 4.4. A video of test administration and data collection methods will be provided on CD and/or as a link under the Site Registration documents section of the N0577 page of the CTSU Member Web site. The examiner's test booklet can be ordered by completing the Test Administrator's Packet Order Form found in the Forms Packet.

Add 1

- Quality of Life (QOL):
  - Order an adequate supply of Patient Questionnaire Booklets by completing the NCCTG Booklet Order Form located on the N0577 documents page under "site registration documents" and fax it to the NCCTG.
- Radiation Therapy:
  - Per NCI policy, all institutions that participate on protocols with a radiation therapy component must participate in the Radiological Physics Center (RPC) monitoring program. For institutions enrolling through the CTSU, a Radiation Facilities Inventory Form must be on file with CTSU. If this form has been previously submitted to CTSU, it does not need to be resubmitted unless updates have occurred at the RT facility.
  - IMRT: Centers treating with IMRT must meet the certification requirements outlined in Sections 6.0 and 7.1.

- Optional blood banking (Section 14.0): Kits are required and should be ordered prior to patient entry. Allow at least two weeks to receive kits.
- Study Agent Shipment Form (One-Time Submission) **MUST** be emailed to Clinicaltrials@biologics.com (see the form in the Forms Packet and Section 15.14 for complete instructions) prior to registration of the first patient to allow enough time (7-10 days) for Biologics, Inc. to process the form for drug shipment. Biologics, Inc. will confirm receipt of the SASF by email to the site.

Pre-study requirements for patient pre-registration on N0577

- Patient must meet all pre-registration inclusion criteria and no exclusion criteria should apply.
- Patient has signed and dated all applicable consents.

CTSU Procedures for Patient Pre-Registration (Step 1)

Contact the CTSU Patient Registration Office by calling 1-888-462-3009 and leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, i.e. within one hour, call the registrar cell phone at 1-301-704-2376. Complete the following forms:

- CTSU Patient Enrollment Transmittal Form
- N0577 Pre-registration Eligibility Checklist
- Patient must sign a consent form

Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays); however, please be aware that registrations received after 5:00 p.m. will be processed the next day. The CTSU registrar will check the investigator and site information provided to ensure that all regulatory and special credentialing requirements have been met. The registrar will also check the forms for completeness and will follow-up with the site to resolve any discrepancies. Once investigator eligibility is confirmed and enrollment documents deemed complete, the CTSU registrar will access the NCCTG remote registration system and pre-register the patient. At this time, a NCCTG data center patient identification (ID) number is assigned that will be used for tracking this patient and tissue contact information will be entered into the NCCTG remote registration system by CTSU. This patient ID number is to be used on all future forms and correspondence. The CTSU registrar will relay the patient ID number to the enrolling site and follow up with a pre-registration confirmation via e-mail or fax.

CTSU Procedures for Patient Registration (Step 2)

Upon receipt of the faxed eligibility status from the NCCTG pathology coordinator, call the CTSU Patient Registrar at 1-888-462-3009 and leave a voicemail to alert CTSU Patient Registrar that an enrollment is forthcoming. Be prepared to give your contact information and the patient's identification number assigned at pre-registration.

Complete the following forms:

- CTSU Patient Enrollment Transmittal Form (include patient identification number assigned at pre-registration)
- N0577 Registration Eligibility Checklist

Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays); however, please be aware that registrations received after 5:00 p.m. will be processed the next day. The CTSU registrar will check these forms for completeness and follow-up with the site to resolve any discrepancies. Once registration forms are deemed complete, the CTSU registrar will access the NCCTG remote randomization system to obtain a randomization assignment. The CTSU registrar will then relay the treatment assignment to the registering site and follow up with a randomization confirmation via e-mail or fax.

Treatment must begin within ≤ 14 days of patient randomization.

Add 1 A mandatory translational component is part of this study, the patient will be automatically registered onto this component (Sections 3.29b, 17.3 and 17.52-53).

DATA SUBMISSION

All case report forms (CRFs) and other documents associated with this study must be downloaded from the N0577 Web page located on the CTSU registered member Web site (http://members.ctsu.org). CTSU investigators must use the current version of the protocol-specific N0577 forms and adhere to the N0577 schedule for data submission per protocol Section 18.0. CRFs and associated reports must be submitted in the following manner:

- Patient pre-registration and registration forms should be faxed to the CTSU according to the instructions outlined above.

Add 1
- Original and amended CRFs and responses to query and delinquency letters must be mailed directly to the NCCTG Operations Office, RO FF 03 24-CC/NW Clinic, 200 First Street SW, Rochester, MN 55905, ATTN: QAS for N0577, Fax (507) 266-7240.

- **Copies of clinical reports submitted to the NCCTG Operations Office must include the Patient ID and protocol number on all pages of the report. The patient's name must be redacted.**

SPECIAL MATERIALS OR SUBSTUDIES

- Tissue submission for pathology review is mandatory and must be submitted after pre-registration but before patient enrollment, see protocol Section 17.0 for details.

- Body fluid biospecimens for banking purposes. Patient participation is optional. Complete the MML Fax Supply Order Form to request kits for collection of specimens-please note that it may take up to **two weeks for kit delivery** so ordering prior to patient entry is essential. See protocol section 14.0 for further details.

Add 1
- Neurocognitive/QOL studies are mandatory.

ADVERSE EVENT (AE) REPORTING

Assessing and submitting expedited reports

This study will utilize the CTCAE version 3.0 for toxicity and Adverse Event (AE) reporting. A link to the CTCAE guidelines is available on the CTSU registered member Web site. CTSU investigators should assess adverse events according to the instructions and tables in Section 10.0 of the protocol. All reporting should be conducted within the time frames specified in Section 10.0 of the protocol.

Events must be reported electronically using the CTEP AdEERS application. A link to the AdEERS application can be found on both the CTSU member homepage and the N0577 Web page on the CTSU member site.

Please do not copy the CTSU on expedited serious adverse event reports.

CTSU institutions must comply with the expectations of their local Institutional Review Board (IRB) regarding submission of documentation of adverse events. Local IRBs must be informed of all reportable serious adverse events.

Secondary AML/MDS/ALL reporting

All CTSU investigators are required to report secondary malignancies occurring on or following treatment on NCI-sponsored protocols. Events should be reported according to the NCCTG guidelines and conducted within the time frames specified in the protocol. Do not submit these forms to the CTSU.

Pregnancy reporting

If a female patient becomes pregnant during the study, the site should complete the Pregnancy Monitoring Form found in the Forms Packet and **fax within 24 hours to** Novartis: (973) 921-7425. Do not submit this form to the CTSU.

DRUG PROCUREMENT - EXCEPT NCIC CTG INSTITUTIONS

Commercial agents: Temozolomide

Temozolomide, will be provided free of charge by Schering-Plough and distributed by Biologics, Inc.

Information on drug formulation, procurement, storage and accountability, administration, and potential toxicities are outlined in Section 15.0 of the protocol.

Study Agent Shipment Form (One-Time Submission) **MUST** be emailed to Clinicaltrials@biologics.com (see the form in the Forms Packet and Section 15.14 for complete instructions) prior to registration of the first patient to allow enough time (7-10 days) for Biologics, Inc. to process the form for drug shipment. Biologics, Inc. will confirm receipt of the SASF by email to the site.

REGULATORY AND MONITORING

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned institutions, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTMB Monitoring Guidelines and are available for download from the CTEP web page http://ctep.cancer.gov/monitoring/guidelines.html.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the informed consent section of this protocol document; however, authorization for the release of Protected Health Information is considered separate and distinct from the Informed Consent process for participation in this clinical trial.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US institutions.

Clinical Data Update System (CDUS) Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.

PATIENT MEDICATION DIARY

Today's date _____
Patient Name_____ Patient Study ID _____
(*initials acceptable)*

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month.
2. Capsules should be taken in the morning with up to 1 cup of water on an empty stomach one hour before or one to two hours after food.
3. Record the date, the number of capsules you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. If you should make a mistake on the diary, draw through the mistake with one line and then sign off with your initials by the correction.
6. Please bring your tablet bottle and this form to your physician when you go for your next appointment.

Day	***Date***	***Dose and when taken***	***Comments***
1			
2			
3			
4			
5			

Physician's Office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study _____
3. Patient's planned daily dose_____

Physician/Nurse/Data Manager's Signature_____

ORAL desensitization to Trimethoprim-Sulfamethoxazole (TMS)

DILUTE 2.5 ml of pediatric suspension of TMS in 7.5 ml distilled water = **10mg/ml** - **BOTTLE #1**

MAKE 6: 10-fold serial dilutions of bottle #1

BOTTLE #7 = 0.00001 mg/ml

BOTTLE #6 = 0.0001 mg/ml

BOTTLE #5 = 0.001 mg/ml

BOTTLE #4 = 0.01 mg/ml

BOTTLE #3 = 0.1 mg/ml

BOTTLE #2 = 1.0 mg/ml

BOTTLE #1 = 10 mg/ml

GIVE 0.5 ml of #7 P.O. OBSERVE patient 15 minutes. If no untoward reactions occur then give 4.0 ml.

REPEAT this procedure with each of the bottles #6 --- #1.

AFTER completing schedule for bottle #1 go to full strength oral suspension in this manner: 0.5 ml, 1.0 ml, and then 2.0 ml.

If no untoward reactions occur begin to increase the dose every 30 minutes: 3.0 ml, 5.0 ml, 8.0 ml, 10.0 ml, 15.0 ml and 20.0 ml.

At this point can start Bactrim DS one tablet BID.

NOTE: 20 ml full strength oral suspension equals one Bactrim DS tablet.

Appropriate emergency drugs and equipment should be on hand including epinephrine, albuterol, hydrocortisone, etc

Appendix XI

PATIENT INFORMATION SHEET
Patient Completed Quality of Life Booklet

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. Directions on how to complete each set of questions are written on the top of each set.

2. Please complete the booklet during your scheduled clinical visit and return it to your nurse or your physician.

Thank you for taking the time to help us.

Appendix XII

NCCTG Research Base Instructions for Biospecimen Processing in BAP Shared Resource

Study Number: N0577

Summary Table of Research Blood/Blood Products Being Received in BAP for This Protocol

Collection tube description and/or additive (color of tube top)	Volume to be collected per tube (number of tubes to be collected)	Blood product to be processed in BAP	After registration but before any treatment	Further processing required by BAP?	Shipping conditions
EDTA (purple)	~2 mL (3)	Plasma	X	No	Frozen
EDTA (purple)	10 mL (1)	DNA, buffy coat	X	Yes	Cold pack
Na heparin (green)	10 mL (2)	PBMCs*	X	Yes	Cold pack

* PBMCs, peripheral blood mononuclear cells

1. Record receipt of specimens.
2. Plasma aliquots will be banked and stored in a -80ºC freezer until the end of the study or upon request.
3. Extract DNA and process buffy coat from **one** EDTA whole blood tube using the protocols entitled "Extracting Samples on the AutoGen" and "Buffy Coat Preparation from Whole Blood." DNA and buffy coat will be banked and stored in a -80ºC freezer until the end of the study or upon request.
4. Process PBMCs from two Na heparin whole blood tubes using the protocol entitled "Cryopreservation (Slow Freezing) of Lymphocytes Prior to Epstein-Barr Virus (EBV) Transformation." PBMCs will be banked and stored in liquid nitrogen until the end of the study or upon request.