Schema

Pre-Registration
Central Pathology Review Submission

Registration and Randomization
Central Review Confirmation of 1p/19q Co-deleted Status

Arm A (RT → PCV)
- **Cycle 1 only:** RT¹
- **Cycle 2 only:** 4-week rest period²
- **Cycles 3 – 8:** PCV x 6 cycles³

Arm B (RT + TMZ → TMZ)
- **Cycle 1 only:** RT⁴ + concomitant temozolomide (TMZ)⁵
- **Cycle 2 only:** 4-week rest period⁶
- **Cycles 3 – 8:** TMZ x 6 cycles⁷

Arm C (TMZ alone)
- All cycles: TMZ x 12 cycles⁸

Observation
Every 12 weeks for 1 year from completion of treatment; then every 4 months for the next 2 years; then every 6 months until PD or alternative treatment

Event Monitoring
Every 6 months until death

PD at any time
Unacceptable adverse events
Patient refusal of further observation
Alternate treatment
Intercurrent illness

Event Monitoring
Arm A
1 = Radiotherapy is performed as 33 fractions of 1.8 Gy for a total dose of 59.4 Gy. One fraction is given daily five days per week for about 6 to 7 weeks. Cycle 1 is about 6 to 7 weeks long total.
2 = Cycle 2 rest period is 4 weeks long (± 2 weeks) total.
3 = Cycles 3 to 8 are PCV chemotherapy, cycles are about 6 to 7 weeks long each.
   Day 1: CCNU 110 mg/m² orally;
   Days 8 and 29: vincristine 1.4 mg/m² 1V;
   Days 8 to 21: procarbazine 60 mg/m² orally;

Arm B
4 = Radiation therapy is performed as 33 fractions of 1.8 Gy for a total dose of 59.4 Gy. One fraction is given daily five days per week for about 6 to 7 weeks. Cycle 1 is about 6 to 7 weeks long total.
5 = Temozolomide (TMZ) is given as 75 mg/m² orally daily; Cycle 1 is about 6 to 7 weeks long total.
6 = Cycle 2 rest period is 4 weeks long (± 3 days) total.
7 = Adjuvant temozolomide (TMZ) is given as 150 or 200 mg/m² orally on days 1 to 5 only of each cycle. Cycles are about 4 weeks long each. TMZ may be extended to 12 cycles if the patient shows acceptable tolerance and no evidence of progression. Note: If patient does not complete optional cycles, they should proceed to observation phase until PD.

Arm C
8 = Temozolomide is given as 150 or 200 mg/m² orally on days 1 to 5 only of each cycle. Cycles are about 4 weeks long each:

<table>
<thead>
<tr>
<th>Generic name: procarbazine</th>
<th>Generic name: lomustine</th>
<th>Generic name: vincristine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand name: Matulane®</td>
<td>Brand name: CCNU®</td>
<td>Brand name: Oncovin®</td>
</tr>
<tr>
<td>NCCTG abbreviation: PCBZ</td>
<td>NCCTG abbreviation: CCNU</td>
<td>NCCTG abbreviation: VCR</td>
</tr>
<tr>
<td>Availability: Commercial</td>
<td>Availability: Commercial</td>
<td>Availability: Commercial</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Generic name: temozolomide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand name: Temodal®</td>
</tr>
<tr>
<td>NCCTG abbreviation: TMZ</td>
</tr>
<tr>
<td>Availability: Commercial</td>
</tr>
</tbody>
</table>
2.0 Goals

2.1 Primary Goal

To determine whether patients who receive radiotherapy with concomitant temozolomide followed by adjuvant temozolomide (RT + TMZ → TMZ) have a marginally better progression free survival (PFS) than patients who receive radiotherapy followed by PCV chemotherapy (RT → PCV).

2.2 Secondary Goals

2.21 Time to Progression
To determine whether patients who receive temozolomide (TMZ) alone have a significantly longer time to progression (neurocognitive, clinical or radiographic progression) than patients who receive radiotherapy with concomitant TMZ followed by adjuvant TMZ (RT + TMZ → TMZ) or radiotherapy followed by PCV chemotherapy (RT → PCV).

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

2.23 Descriptive Comparisons of Additional Secondary Endpoints
Perform descriptive comparisons of additional secondary outcome endpoints, including overall survival, objective tumor response, and quality of life.

2.24 Toxicity
Determine the toxicity of the treatment in each arm and perform descriptive comparisons.

2.25 Descriptive Determination of Timing of RT
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 Neurocognitive and Quality of Life Effects
Determine the neurocognitive and QOL effects in patients treated on this protocol and correlate these results with outcome endpoints.

2.27 Banking of Biospecimens
To bank blood products (i.e., plasma, DNA, and buffy coat), tumor tissue and MRI/CT images for future scientific investigations.

3.0 Patient Eligibility

3.1 Pre-Registration Inclusion Criteria

3.11 Central pathology review submission
This review is mandatory prior to registration to confirm eligibility. Patients...
must be 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

3.2.1 Age
Age ≥ 18 years of age.

3.2.2 Diagnosis
Newly diagnosed and ≤ 3 months from surgical diagnosis

3.2.3 Histological confirmation of anaplastic glioma
Histological confirmation of anaplastic glioma (oligodendroglioma, mixed, or astrocytoma [WHO grade III]), as determined by pre-registration central pathology review. 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.

3.2.4 1p/19q Co-deletion
Tumor is co-deleted for 1p and 19q.

3.2.5 Surgery
Surgery (partial or gross total resection or biopsy) must be performed ≥ 2 weeks prior to registration; patient must have recovered from the effects of surgery.

3.2.6 Laboratory Values
The following laboratory values obtained ≤ 21 days prior to registration.

- Absolute neutrophil count (ANC) ≥ 1500 /mm³
- Platelet (PLTs) count ≥ 100,000 / mm³
- Hemoglobin (Hgb) > 9.0 g/dL
- Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
- SGOT (AST) ≤ 3 x ULN
- Creatinine ≤ 1.5 x ULN

3.2.7 Pregnancy Test
Negative serum or urine pregnancy test done ≤ 7 days prior to registration, for women of childbearing potential only.

3.2.8 Neurocognitive Tests and Quality of Life (QOL) Questionnaires
Willing and able to complete neurocognitive testing without assistance and the QOL by themselves or with assistance (see Section 4.4).

3.2.9a ECOG Performance Status
ECOG performance status (PS) of 0, 1 or 2 (See Appendix I).

3.2.9b Patient Informed Consent
Provide informed written consent.

3.2.9c Return to Enrolling institution

Version Date: 4/04/14
Update #05
Willing to return to enrolling institution for follow-up during the Active Monitoring Phase (that is, the active treatment and observation portion) of the study.

3.29d Mandatory Tissue Samples for Correlative Research
Patient willing to provide tissue samples for correlative research purposes (see Sections 6.17, 17.3, and 17.52-17.53).

3.3 Registration Exclusion Criteria

3.31 Fetal / Newborn Toxicity
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 during this study and for up to 6 months following the completion of temozolomide treatments.

3.32 Prior Treatment for a CNS neoplasm
Received any prior surgery, radiation therapy or chemotherapy for any CNS neoplasm. Note: Patients who have had a prior low grade glioma with/without surgery and who now have anaplastic glioma with no prior radiation or chemotherapy are eligible for the study.

3.33 Concurrent Illness or Disease
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 Immunocompromised Status
Concomitant serious immunocompromised status (other than that related to concomitant steroids).

3.35 HIV Positive Patients Receiving Retroviral Medications
Patients known to be HIV positive and currently receiving retroviral therapy. Note: Patients known to be HIV positive, but without clinical evidence of an immunocompromised state, are eligible for the study.

3.36 Uncontrolled Intercurrent Illness
Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.37 Other Investigational Agents
Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.
3.38 Other Active Malignancies
Other active malignancy within 5 years of registration. Exceptions: Non-melanotic skin cancer or carcinoma-in-situ of the cervix. Note: If there is a history of prior malignancy, the patient must not be receiving other specific treatment (other than hormonal therapy) for their cancer.

3.39a Significant Cardiovascular History
History of myocardial infarction ≤ 6 months, or congestive heart failure requiring use of ongoing maintenance therapy for life-threatening ventricular arrhythmias.

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

3.4 Inclusion of Women and Minorities
Both men and women of all races and ethnic groups are eligible for this study.