Rationale

There is an expanding body of knowledge related to molecular events in AO, which has generated considerable excitement. Recent investigations have identified several markers of potential prognostic or predictive significance in oligodendrogliomas, including 1p/19q deletion, t(1;19)(q10;p10) translocation, PTEN mutation status; EGFR and PDGFR amplification, MGMT gene promoter methylation status, IDH-1 and IDH-2 mutations, and more global genomic and proteomic analyses.

Translational tumor tissue investigations within CODEL explore the molecular phenotype and signaling events within codeleted anaplastic and low grade gliomas, and correlations with patient outcome. In addition, the study will identify the timing and extent of deterioration in neurocognitive status (and QOL), using validated test instruments, and attempt to dissect that change which is due to tumor progression, or from adverse effects of treatment. These data will be of great importance in optimizing the design of future studies involving patients with codeleted oligodendroglial tumors.
Objective

Primary

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

Secondary

• Time to progression: To determine whether patients who receive RT + TMZ → TMZ have a significantly longer time to progression (clinical or radiographic progression) as compared with patients who receive radiotherapy followed by adjuvant PCV chemotherapy (RT → PCV).
• Neurocognitive and quality of life correlates.
• Translational correlative analyses involving exploratory molecular biomarker status (methylomic and sequencing analyses) and neuroimaging findings with outcome.
Alliance N0577 (CODEL): Phase III Intergroup Study of Radiotherapy with Concomitant and Adjuvant Temozolomide Versus Radiotherapy With Adjuvant PCV Chemotherapy in Patients with 1p/19q Co-deleted Anaplastic Glioma or Low Grade Glioma (CODEL)

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Mayo Clinic and Moffitt Cancer Center

**Treatment Schedule**

**Arm A – RT→PCV**

<table>
<thead>
<tr>
<th>Pretreatment medication</th>
<th>Prophylaxis for Pneumocystis carinii pneumonia (PCP) as warranted (see Sections 7.35 and 9.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td>Dose Level</td>
</tr>
<tr>
<td>RT</td>
<td>5940 cGy/33 fractions for anaplastic glioma or 5040 cGy/28 fractions for low grade</td>
</tr>
<tr>
<td>A 4-week rest period&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Procarbazine</td>
<td>60 mg/m&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>CCNU</td>
<td>110 mg/m&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4 mg/m&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Arm B – RT+TMZ→TMZ**

<table>
<thead>
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<tbody>
<tr>
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</tr>
<tr>
<td>TMZ</td>
<td>75 mg/m&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>A 4-week rest period&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>TMZ</td>
<td>150 or 200 mg/m&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Note:** Recent Update 10 allows proton irradiation or conventional IMRT; adds EORTC to study to increase accrual. Mandatory tumor tissue submission for DNA, RNA preparation for subsequent targeted sequencing, methylomics and whole exon sequencing; translational correlative analyses to identify new potential therapeutic targets in the 1p19q codeleted, IDH mutated cohort. MRI neuroimaging studies will be centrally submitted to IROC subsequent correlative analyses.
Registration Inclusion Criteria

- Diagnosis: Newly diagnosed and ≤ 3 months from surgery
- Histological confirmation of anaplastic glioma or low grade glioma
- Histological confirmation of anaplastic glioma (oligodendroglioma, mixed, or astrocytoma (WHO grade 2 or 3)) or low grade glioma (WHO grade 2), as determined by pre-registration central pathology review.
- Tumors have to be 1p19q codeleted and IDH mutated by any methodology and by locally-determined analysis.
- Patients with codeleted low grade gliomas must also be considered "high risk" by clinical criteria and must be either: age ≥ 40 and any surgical therapy, or age < 40 and subtotal resection or biopsy.
- Co-deletion: Tumor tissue must show co-deletion for the relevant portions of chromosomes 1p and 19.
Funding Support

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