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)

Kurt A. Jaeckle and Michael Vogelbaum

Mayo Clinic and Moffitt Cancer Center

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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 import in optimizing the design of future studies involving patients with codeleted oligodendroglial tumors.

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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.

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Treatment Schedule

Arm A –RT→PCV

Pretreatment medication Prophylaxis for Pneumocystis carinii pneumonia (PCP) as warranted (see Sections 7.35 and 9.5)				
Agent	Dose Level	Route	Day	Retreatment[1]
RT	5940 cGy/ 33 fractions for anaplastic glioma or 5040 cGy/28 fractions for low grade		1 through 5	Weekly x 6[2]
A 4-week rest period[3]				
Procarbazine	60 mg/m^2	Oral	8 through 21	6 cycles[4]
CCNU	110 mg/m^2	Oral	Day 1 only	6 cycles[4]
Vincristine	1.4 mg/m^2 [5]	IV	Day 8 and Day 29	6 cycles[4]

Arm B –RT+TMZ→TMZ

Pretreatment medication Prophylaxis for Pneumocystis carinii pneumonia (PCP) as warranted (see Sections 7.35 and 9.5)				
Agent	Dose Level[1]	Route	Day	Retreatment[2]
RT	5940 cGy/ 33 fractions for anaplastic glioma or 5040 cGy/28 fractions for low grade		1 through 5	Weekly x 6[3]
TMZ	75 mg /m^2	Oral	Daily	Weekly x 6[3]
A 4-week rest period[4]				
TMZ	150 or 200 mg/m^2	Oral	Days 1 to 5 only	6 cycles[5,6]

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 I 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.

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Eligibility Criteria

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.

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