Neuro-Oncology Program

The goals of the Neuro-oncology Committee are: 1) to improve duration and quality of life of brain tumor patients; 2) to develop interventions for disease and treatment-related effects on neurocognitive function and QOL; 3), to identify prognostic and predictive variables that correlate with outcome 4) improved and maximize the efficiency of clinical trial conduct and methodology.

Capsule Summary:

For newly diagnosed GBM, there are several protocols. The Phase I portion of N0874 (Phase I-II study of RT+TMZ + SAHA) is open and the Phase II will open to group when the MTD has been identified. The Phase I portion of N0877 (Phase I-II RT+ TMZ + Dasatanib vs placebo) is also open and the Phase II randomized component will open when the MTD is determined. RTOG R0825 (Phase III trial of RT+TMZ + bevacizumab or placebo) was also activated to Group.

For recurrent GBM, three Phase II trials are open. N0572 (sorafenib and temsirolomus) continues to accrue for patients who have failed prior bevacizumab; accrual has been reached for those with no history of prior angiogenesis inhibitors. N0872, a Phase I-II study of dasatanib + bevacizumab is open for the Phase I component and the Phase II study will open to group soon. Additional concepts are in development for recurrent GBM and AA patients.

For grade 3 glioma, there are two intergroup Phase III trials. N0577 / CODEL study (RT vs RT+TMZ vs TMZ) is for patients with anaplastic oligodendroglia/mixed glioma with 1p/19q deletions; this trial is activated and investigators are encouraged to open this trial as soon as possible. The trial for non-deleted Grade 3 gliomas, EORTC 26053 / CATNON study (RT vs. RT+TMZ → Observation or TMZ), is activated as well. 1p/19q will be performed free of charge at the time of central review. Investigators are encouraged to activate both trials since patients are likely to be eligible for one or the other trial. For N0577, there is added per capita compensation which is funded by the NCI Trial Complexity Grant, and we have obtained B1QSF supplemental funding which will provide additional site reimbursement for preparation and mailing of biopecimens When applying to CTSU for these trials, sites are reminded to send in their radiation oncology and neurocognitive testing certifications or the CTSU approval will be delayed.

For low grade glioma, NCCTG has activated the Phase III ECOG E3F05 (RT vs RT+TMZ).

For newly diagnosed brain mets, the Phase III intergroup study N0574 (SRS vs. SRS + whole brain RT) is still open. This study has a neurocognitive endpoint, and as sequential assessments are necessary to obtain this endpoint, investigators should make sure that they obtain serial neurocognitive studies beyond the baseline, and even after tumor progression if possible. The
study has been amended to provide additional patients who have met this endpoint and investigators are encouraged to help reach accrual goal. A new Phase III intergroup trial, N107C, will open soon and will compare the efficacy of post surgical stereotactic radiosurgery to whole brain radiotherapy for patients with CNS metastases.

**Detailed Report: Cancer Treatment Trials:**

**Newly Diagnosed Glioblastoma** (grade 4 astrocytoma):

**N057K**: Phase I–II evaluation of RT + TMZ followed by adjuvant TMZ + everolimus (RAD001) has reached group accrual goals.

**N0874**: Phase II RT+TMZ+SAHA is a joint effort between NCCTG and the American Brain Tumor Consortium (ABTC). The Phase I is open and accruing, and the Phase II will open when the P2D has been identified.

**N0877** is a Phase I-II randomized study of RT+TMZ+ dasatanib vs placebo. The Phase I is open and the Phase II will open when the MTD has been established

**R0825** is an RTOG Phase III intergroup study that NCCTG has endorsed, which is randomized study of RT+TMZ + avastin vs. placebo is open.

**Newly Diagnosed Anaplastic Gliomas** (grade 3)

**EORTC 26053 / CATNON** is a Phase III randomized study of RT vs. RT + TMZ followed by either observation or adjuvant TMZ for patients with anaplastic gliomas that either have no or one deletion for 1p or 19q. RTOG will lead this study in the US and NCCTG has endorsed the study. Patients are stratified by MGMT status, and the study contains neurocognitive/QOL and translational components. Overall survival is the primary endpoint. This study has been activated and sites are encouraged to open this trial

**NCCTG N0577 / CODEL** is a Phase III Intergroup study of RT vs RT/TMZ vs TMZ for anaplastic oligodendrogloma or mixed anaplastic glioma with combined deletions of 1p and 19q. RTOG, ECOG, NCIC and EORTC will participate in the trial via CTSU. The primary endpoint for the RT vs RT/TMZ component is overall survival; a neurocognitive/clinical/radiographic endpoint is being utilized to compare the TMZ vs. RT arms. Temozolomide is provided, the 1p/19q analysis is done free of charge to the patient, and there are supplemental trial complexity support or credits, cancer control credit, and supplemental funding for specimen submission. This study is open to Group

**Low Grade Glioma:**

**E3F05** is an ECOG/NCCTG Phase III study for newly diagnosed high risk low-grade
glioma patients, comparing RT vs RT+TMZ. The primary endpoint is 5 year survival. This study is activated to Group.

Recurrent Glioblastoma and Grade 3 Anaplastic Astrocytoma:

**N0572** The Phase II component of this study, testing the combination of Sorafenib and CCI-779 in recurrent GBM patients, remains open for accrual. This study has three arms, one for patients who have received prior bevacizumab, and one for those who have not, and an exploratory arm to assess target activity in tumor in patients who are undergoing surgery for clinical reasons. The arm for patients not receiving prior angiogenesis inhibitors has completed accrual, but both other arms are available for patient entry.

**N0779** is a Phase II study of the combination with sorafenib and bevacizumab for recurrent GBM, which has reached accrual and analysis is in progress.

**N0872** is a Phase I/II study of the combination of dasatanib and bevacizumab for recurrent GBM, is open for the Phase I and the Phase II will open to Group soon.

Recurrent Oligodendroglioma and Mixed Oligoastrocytoma:

**N0272** is a Phase II trial of imatinib for recurrent oligodendroglioma/mixed glioma and has nearly reached accrual goals. The group is reminded that this study contains an extra arm for patients with grade 2 or 3 oligos or mixed gliomas, who have failed multiple (i.e., > 2) regimens for recurrence, our only trial to do so.

CNS Metastases:

**N0574**: For patients with unresectable newly diagnosed brain mets, the Phase III intergroup study **N0574** (SRS vs. SRS + whole brain RT) is still open. This study has a neurocognitive endpoint, and as sequential assessments are necessary to obtain this endpoint, investigators should make sure that they obtain serial neurocognitive studies beyond the baseline, and even after tumor progression if possible. The study has been amended to provide additional patients who have met this endpoint and investigators are encouraged to help reach accrual goal.

**N107C**: For patients with at least one resectable CNS met, a new Phase III intergroup trial, N107C, will open soon and will compare the efficacy of post surgical stereotactic radiosurgery to whole brain radiotherapy for patients with CNS metastases.

Translational Studies

Translational correlative studies accompany nearly all of the recent and active treatment protocols, including **N0272, N0577, N027D, N0572, N0574, N057K, E3F05, R0525,**
Many of the new trials include tissue analyses for prognostic factors, and even assignment of protocol based on markers at baseline. Patients eligible for N0577 and EORTC 26053 will have determinations of 1p/19q status prior to study treatment. Methylguanine methyltransferase (MGMT) gene promoter hypermethylation status, and gene profiling performed at MD Anderson will be used as stratification factors for RTOG 0825.

Quality of life and neurocognitive correlative investigations accompany many of our trials, including N0272, N0776, N0779, N0872, N0874, N0877, N0572, N0577, N0574, E3F05, and R0825.

The group members are again to be congratulated on a superb job of acquiring and mailing of tissue and blood specimens obtained from patients on our trials who have provided consent for the translational tissue correlative analyses. Many of these correlative studies provide the scientific rationale for design of our clinical trials, and support the overall goals of the Neuro-oncology committee. We recognize that this component takes time from busy practices, and the NCCTG is very appreciative of your efforts.

**Database Studies.**

N047D “compared different potential outcome endpoints for determination of treatment efficacy in our clinical trials, and found that progression free survival at 6 months (PFS6) correlated reasonably with a survival endpoint (OS12), confirming its usefulness as the primary endpoint in our recurrent disease trials. A manuscript has been published. 94-72-53, "Diagnostic and Prognostic Markers in Low-Grade Gliomas" and 94-72-52, "Diagnostic and Prognostic Markers in Anaplastic Astrocytoma and Anaplastic Oligoastrocytoma" continues to mature and collect specimens, for which credit is given.

**Recently Completed Studies – Update**

RTOG 0525, the intergroup effort with NCCTG, NCIC, and EORTC reached accrual in June, 2008, and initial outcome data will be presented at the upcoming ASCO 2011 meeting.