

North Central Cancer Treatment Group

N027D: A Phase I Study of CCI-779 and Temozolomide in Combination with Radiation Therapy in Glioblastoma Multiforme

Addendum 1 – March 16, 2007

Summary

- The cycles of the treatment have been clarified.
- Accrual rates have been revised based on sites involved in this study.
- The research bloods being drawn to evaluate inhibition of mTOR in PBMCs are being deleted. Further review of previous studies using this surrogate marker demonstrates that these assays are not reliable and not felt to be useful.
- The weekly chemistry during CCI-779/TMZ and RT has been deleted and will only be done during Week 4 of radiation. This was originally included in error and is excessive. The standard of care for CCI-779 would be testing every 4 to 8 weeks.
- If an institution uses IMRT, credentialing is necessary.
- Prophylactic treatment with bactrim has been added at the start of CCI-779 in order to help prevent pneumocystis carinii pneumonia (PCP).
- Clarification has been made to the protocol regarding MRI analysis.
- TMZ side effects in the consent have been updated to be consistent with the information provided in Section 15.29d.
- Administrative/Editorial Changes

A replacement protocol is provided. Please replace the current copy with the one attached. Please keep this addendum with your protocol

Title page: Now reflects Addendum 1 and revised NCI version date.

Wenting Wu, Ph.D. replaces Karla Ballman as study statistician.

Protocol Resource

Page 2: **Janis Wobschall** replaces Lori Bratvold as the NCCTG Research Base Protocol Development Coordinator

Christine Maszk is added as a second NCCTG Research Base Pathology Coordinator

“**Paraffin-embedded Tissue Pathology**” is now reflected under the “Questions” column for the NCCTG Research Base Pathology Coordinators.

Schema

Page 4:

Schema has been revised to provide clarification regarding the length of a cycle of treatment and to also include that bactrim has been added in order to help prevent PCP:

- Third box now indicates: CCI-779 + RT + TMZ* followed by **4-6 week rest period** then CCI-779 + TMZ***** (maximum 6 cycles) (**Pneumocystis carinii pneumonia [PCP] prophylaxis starts with cycle 1**)
- * Cycle 1 length = 7 weeks + ~~4-6 weeks for DLT observation (up to 13 weeks)~~
- ** Cycles 2 **length (rest period) = 4-6 weeks**
- *** Cycles **3-8 length = 4 weeks**

Section 2.0

Page 15:

Goals

Section 2.13 has been revised as follows for clarification with regard to the MRI analysis:

To evaluate for early response to therapy with an automated morphological MRI change detector and with **the** physiological MR imaging techniques ~~including of~~ diffusion-weighted imaging **and**, perfusion-weighted imaging, ~~and chemical shift imaging.~~

Section 2.21 has been deleted due to the removal of the research bloods to evaluate inhibition of mTOR in PBMCs:

~~Determine the inhibition status of mTOR signaling pathways in PBMC following weekly dosing with CCI-779 in all patients treated on trial.~~

Remaining sections have been renumbered.

Section 4.0

Pages 17-18:

Test Schedule

Section 4.0 table has the following changes:

- Column headings for Cycle 1 and Cycles 2-8 have been added to the table to identify which events are to be done under which cycle.
- The former column labeled “First week of adjuvant CCI-779/TMZ” has been deleted due to the identification of the cycles of treatment and it was redundant with the next column (Before each cycle adjuvant CCI-779/TMZ [6 cycles total]).
- To make consistent throughout the protocol, the observation column has been revised to read “Observation: q2 mo x 1 yr, q3 mo x 1 yr, the q6 mo x 3 yrs ~~then annually until 10 yrs from registration~~”
- The following row and associated footnote 11 have been deleted due to the removal of the PBMC research bloods:
~~PBMC—ALL PATIENTS
(involves multiple blood
draws—see Section 14.21)
11.—Day 1 and Day 8 of cycle 1 only (See Section 14.21).~~
- The following has been added to the row for research bloods:
PK –MAYO CLINIC ROCHESTER ONLY: FIRST 10 PATIENTS...
- MRI or CT row now indicates (see **Section 4.1**).
- A row plus footnote 12 has been added to delineate the research MRI for Mayo Rochester patients only: **MAYO CLINIC ROCHESTER ONLY: Research MRI^R (see Section 4.1)**
- Footnote #3 now indicates that the neuro exam and MMSE will be done every other cycle...(before cycles **3, 5, and 7** rather than 1, 3, and 5) due to the identification of the cycles.
- Footnote #4 now clarifies that the chemistry panel is only done during this time period: **Only during Week 4 of radiation** rather than ~~weekly during the first 2 cycles of CCI-779 then once per cycle at the treating physician’s discretion.~~
- Footnote #5 indicates the following due to the identification of the cycles of treatment: Patients will be re-imaged just prior to cycles **4, 6, and 8** (rather than 1, 2, 4, and 6) and also references “**See Section 4.1**”.

- Footnote #11 now reads: Day 1 and Day 8 of Cycle 1 ~~only~~ and **Day 1 and Day 8 Cycle 3**. See Section ~~14.21~~ **14.25 for PK timing**.
- Footnote #12 is newly added as a result of the research MRI being done on Mayo Rochester patients only:
Research MRI after the first week of CCI-779 will be performed only on patients enrolled at Mayo Clinic Rochester. MR spectroscopy will only be performed at Mayo Clinic Rochester.
- Footnote #13 is newly added describing cycle 2:
Cycle 2 = 4-6 week rest period following RT; no protocol treatment given.
- Footnote #14 is newly added to reflect that CBCs are required for cycles 3 and 4:
In addition to a CBC prior to each cycle, in Cycle 3 a CBC should be obtained weekly and on Cycle 4, a CBC should be obtained on day 21 just prior to third dose of CCI-779.
- Reference to new footnote #14 has been placed by the X in the column “Before each cycle adjuvant CCI-779/TMZ (6 cycles total)” for the “Hematology group.”

Pages 18-19: Former Section 14.6 (MRI Imaging) has been moved to Section 4.1 as follows for better placement of the information and clarification with regard to MRI analysis:

4.1 MRI imaging

- 4.11 MRI analysis: **Anatomical** MRI data sets collected will be analyzed using a computer program designed to detect subtle changes in **volume of tumor enhancement and signal abnormality** ~~signal volume~~. **Diffusion-weighted and perfusion-weighted MRI data sets will be evaluated through segmentation of areas of anatomical MRI abnormality.** These analyses will be performed in addition to human observer evaluations of response. Tumor response, as defined in section 11.0, will be defined strictly by human observers.
- 4.111 All clinical MRI data will be automatically archived on the electronic archive system. The data from this system will be retrieved using DICOM and then stored on a storage server within the Radiology Informatics Laboratory at Mayo Clinic. For each exam pair (current study, prior study), all images are spatially registered to the current study ~~FLAIR~~ **T1-weighted post-gadolinium** sequence using a **3D** normalized mutual information algorithm. A user then draws ROIs on the 2 studies in regions of normal **appearing** white matter ~~and normal gray matter~~. A brain mask is created to exclude extracranial tissues. At that point, the **automated** change detector creates feature images for normal white matter, gray matter, CSF, as well as edema, necrosis, and enhancing tumor for each study. It then applies a series of rules to create change maps between the two studies, and create colorized renditions of the changes found superimposed on the post-gadolinium images of the current exam. It also uses an additional set of rules about location and size of changes to render its verdict if there is progression, regression, or stability. ~~The purpose of this study is to evaluate the reliability of a computerized change detector program compared to human observers.~~ **Subtle changes in volume of tumor enhancement and T2 signal abnormality can be detected more accurately and objectively in this manner.**

- 4.112 For each evaluation cycle, diffusion-weighted imaging (DWI) **and**, perfusion-weighted imaging (PWI) ~~and chemical shift imaging (CSI)~~ data will be collected and analyzed, to evaluate for response of tumor to therapy. ~~Specifically, measures such as cerebral blood volume (CBV) for PWI, and major metabolic concentrations (creatine, choline, NAA) and their ratios will be compared between time points.~~ **Segmentation of images will be performed, based on areas of abnormality on anatomical images. ADC values from diffusion-weighted imaging (DWI), and rCBV from perfusion-weighted imaging (PWI) will then be compared between serial MRI scans.**
- 4.113 For patients enrolled at MCR and who are imaged 1 week after starting CCI-779, the pre- and post-treatment scans will be specifically compared to determine whether early changes in MR imaging characteristics can be identified that may predict for response to CCI-779.

Section 6.0
Pages 19-21:

Registration Procedures

Section 6.1 now includes site registration and IMRT credentialing prior to pre-registration of patients and remaining sections have been renumbered.

Old Section 6.12 is now paragraph 1 under new Section 6.11.

Section 6.12 - IMRT credentialing is required by NCI and RPC and this has been added to the protocol.

Remaining sections have been renumbered.

Section 6.33 now indicates **tissue** sample rather than ~~blood~~ due to the removal of the PBMC testing and the fact that a tissue sample for banking purposes is being requested.

Section 7.0
Page 22:

Protocol Treatment

The following text has been added to Section 7.21 due to the addition of bactrim in order to help prevent PCP:

Prophylaxis for PCP is required on this protocol. Patients who do not have known allergies to sulfa drugs should receive Bactrim DS PO, 1 tablet three times a week. If patients develop drug reaction to bactrim, have pre-existing allergy to sulfa drugs, or cannot tolerate bactrim for another reason, patients should be treated with pentamidine 300 mg by inhalation once every 4 weeks. Only patients that cannot tolerate either drug regimen will be treated on trial without PCP prophylaxis. Prophylaxis should start with the initiation of cycle 1 and continue until CCI-779 is discontinued.

Page 23: Section 7.214 has been re-written to indicate the cycles of treatment and to clarify the language in the first sentence:

Patients will be observed for DLTs during the first cycle of ~~adjuvant adverse events encountered during the first cycle of treatment.~~ **Although the dose escalations and MTD will be defined based on DLTs occurring during concomitant RT/TMZ/CCI-779 (cycle 1), if significant DLTs are encountered during the 4-6 week rest period (cycle 2) or the first cycle of adjuvant CCI-779 (cycle 3), then the dosing schedule and dose escalation schema will be re-evaluated.**

Page 24: Section 7.225 was changed to indicate that the cohort of 10 patients at the MTD will come from Mayo Clinic Rochester:

After the MTD of CCI-779 is defined, then an additional 10 patients will be enrolled to document tolerability of this regimen and to perform extensive PK analysis of CCI-779 in combination with TMZ. **These 10 patients will be enrolled at Mayo Clinic Rochester to facilitate the research MRI scans.**

Page 25: Section 7.315 has been rewritten to indicate the IMRT credentialing information: IMRT is an acceptable method for planning and treatment delivery (~~see Appendix VIII~~). **The NCI has indicated that cooperative group protocols must include certain requirements when IMRT is allowed. Appendix VIII describes these requirements. Item 13 of Appendix VIII stipulates that institutions must be credentialed to use IMRT when treating patients on cooperative group protocols. This protocol requires that institutions that plan to treat patients using IMRT be credentialed before registering patients on the trial. Please review Appendix VIII then visit the 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.**

CTVs will be defined essentially as described in Sections 7.313 and 7.314.

Section 9.0

Ancillary Treatment

Page 30: Section 9.2 has been deleted as follows due to PCP prophylaxis now being required:
~~PCP prophylaxis will be at the discretion of the treating physician.~~

Due to the deletion of Section 9.2 all remaining sections have been renumbered.

Section 12.0

Descriptive Factors

Pages 37-38: Section 12.9a has been deleted as follows as there are no fresh frozen tissue samples coming in for this study and remaining sections have been renumbered:

~~Fresh frozen tissue available: Yes vs. no.~~

Section 13.0

Page 38:

Treatment/Follow-up Decision at Evaluation of Patient

Section 13.3 now incorporates old Section 13.5 since the information was redundant:

Patients who have PROG will go to the event-monitoring phase. **Event monitoring information will be collected and entered every 3 months until 5 years from on-study.** Further treatment with chemotherapy or radiotherapy may be used at the discretion of the primary physician.

Remaining sections have been renumbered.

Section 13.5 now clarifies the cycles:

Upon completion of ~~6~~ **7** weeks of concomitant therapy of RT and CCI-779/TMZ **and a 4-6 week rest period**, treatment with adjuvant CCI-779/TMZ will continue until 6 cycles have been completed or one of the following criteria applies:

Section 14.0

Pages 39-40:

Translational/Pharmacologic Studies

Sections 14.1 and 14.2 have been replaced due to the removal of the PBMC and to clarify the instructions for the PK samples for the cohort of 10 patients from Mayo Clinic Rochester once the MTD is reached:

Page 41:

The following Note statement has been added to Section 14.3 for emphasis:

Note: Central pathology review for eligibility will still be performed at NCCTG research base; please see Section 17.0.

Section 14.31 reflects a new address:

NCCTG Operations Office
RO_FF_03_24-CC/NW Clinic 3-24
200 First Street SW
Rochester, MN 55905
ATTN: NCCTG **Research Coordinator** ~~Helen Tollefson~~
~~Phone: 507-266-0724~~

The last sentence of the first bullet in Section 14.31 has been bolded for emphasis as follows:

Do not bake or place covers slips on the slides.

The second paragraph following the bulleted items in Section 14.31 has been revised to reflect current contact information as follows:

The block/slides will be forwarded to the NCCTG Research Base **Tissue and Cell Molecular Analysis (TACMA) Biospecimen Laboratory, Guggenheim 4036 Stable 13-10B**, Mayo Clinic Rochester.

A typographical error has been corrected in the first sentence of Section 14.32 as follows:

The remaining material will be stored for future research depending on the patient consent permission (see Section 6.25) in order to be suitable for **immunohistochemistry (IHC)** and to perform DNA extraction.

Page 42: Section 14.4 information regarding PBMC analysis has been replaced with PK analysis information:

~~14.4 — PBMC analysis: Samples for PBMC analysis will be obtained at time points around the first administration of CCI-779 (see section 14.2 for details regarding schedule). The phosphorylation status of ribosomal S6 protein following *ex vivo* stimulation of isolated PBMCs with PHA and PMA will be used to assess the efficacy of mTOR inhibition.~~

14.4 Blood product analysis

Pharmacokinetic analysis: Extensive PK analysis will be performed on an expanded cohort of patients enrolled at the MCTD. Whole blood for CCI-779 and sirolimus level determination will be drawn with 1) the first administration of CCI-779, prior to the initiation of combined modality therapy (Day 1 and Day 8 Cycle 1) and 2) the first administrations of adjuvant CCI-779 given in combination with the adjuvant TMZ (Day 1 and Day 8 Cycle 3) (see Section 14.25 for details regarding schedule). CCI-779 and sirolimus levels will be determined by Taylor Technologies in collaboration with Wyeth Ayerst.

Page 42: The heading of Section 14.5 now reads:
Tissue molecular analyses

The fourth sentence of the first paragraph in Section 14.5 has been corrected as follows:

IHC staining will be performed by the **NCCTG Research Base Mayo Cancer Center Tissue and Cell Molecular Analysis (TACMA)** Shared Resource or in Dr. Sarkaria's laboratory.

Page 42: Old Section 14.6 has been moved to Section 4.1 for better placement of the information.

Section 16.0 Statistical Considerations and Methodology

Page 53: Section 16.24 has been revised based on sites involved in this study as follows:

Accrual Time and Study Duration: We anticipate an annual accrual rate of approximately ~~18~~ **26** newly diagnosed GBM **patients** per year from the participating sites (**Mayo Clinic – Rochester, Mayo Clinic – Scottsdale, Mayo Clinic – Jacksonville, and University of Alabama**) based on the experience with the Phase II component of NCCTG N0177. We assume that on average, it takes about ~~12~~ **13** weeks to enroll, treat, and evaluate 3 patients (**enroll: 6 weeks, cycle 1: 7 weeks**). Based on these assumptions, we estimate the duration of **the Phase I part of the study** this will be between ~~7~~ **9 months (9 patients)** to ~~46~~ **36 months (36 patients)**. **The expansion cohort of 10 patients will only be enrolled from Mayo Clinic – Rochester. Thus, we anticipate an annual accrual rate of approximately 20 newly diagnosed GBM patients per year from Mayo Clinic – Rochester. The duration of the expansion cohort study will be approximately 33 weeks (enroll: 26 weeks, cycle 1: 7 weeks), i.e., roughly 8 months.**

Page 54: Old Section 16.32 (PBMC analysis) has been deleted due to the removal of the PBMC samples and all remaining sections have been renumbered.

Page 55: New Section 16.32 (previously Section 16.33) has been revised as follows for clarification with regard to MRI analysis:

16.32 **MRI analysis:** Subtle changes in tumor volume as assessed ~~by~~ **through use of an automated change detector, as well as changes in parameters from diffusion-weighted and perfusion-weighted imaging**, ~~computer-generated values~~ will be evaluated for association with patient outcome. In particular, logistic regression and Cox proportional hazards models will be used to determine the association between changes in tumor volume (as assessed by a software package) and tumor response and 12-month survival (logistic regression) and progression-free and overall survival (Cox proportional hazards models). These changes will also be evaluated for correlation with other translation variables (e.g. MGMT promoter methylation status, downstream mTOR signaling status, biomarkers, gene expression profiles).

~~Chemical shift imaging (CSI): A choline to NAA ratio (Cho:NAA) and a choline to creatine (Cho:Cr) ratio will be computed for each voxel in the imaged volume. Average Cho:NAA and Cho:Cr ratios will be calculated for all voxels in the PRESS voxel. At present, the best summary statistic for describing the change in CSI between two scans of the same patient has not been identified. As a consequence, it is not known what level of change between two scans should be used to classify a patient as a responder/non-responder or progressor/non-progressor. As a result, several different summary statistics will be explored. Some examples of summary statistics that will be assessed include the difference in the mean of the ratios (across all voxels) of one scan and the mean of the ratios in the second scan and the difference in the median of the ratios of one scan and the median of the ratios of the second scan. Other possibilities include using a trimmed mean or using the maximum value rather than the mean or median. The correlation of each potential summary statistic and the outcome variables (TTP and OS) will be assessed using Cox proportional hazards models. The summary measure with the largest correlation will be selected. Thresholds for declaring a response (progression) will be determined from the selected summary statistic in a similar fashion as described for the anatomical change measure. In particular, a threshold will be selected that produces the largest difference, which is statistically significant, in the median TTP (OS) between the patients deemed responders (progressors) and those deemed non-responders (non-progressors) based on the threshold (see details above). From evaluating the number of standard deviations between the Cho:NAA ratio within an abnormal voxel and that within normal control voxels using a regression technique, the choline to NAA index (CNI) can be obtained. Twice the CNI or greater (CNI2) would be considered to be compatible with metabolically active tumor. The summary statistic for describing the change between two scans of the same patient will be the difference in the number of voxels with CNI2. The correlation of this summary statistic and the~~

~~outcome variables (TTP and OS) will be assessed using Cox proportional hazards models. Thresholds for declaring a response (progression) will be determined in a similar fashion as described for CSI and the anatomical change measure.~~

~~Diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI): From image sections encompassing the tumor and its surrounding signal abnormality, the sections being the same in number and anatomical location between all serial exams in any given patient, the mean apparent diffusion coefficient (ADC) and a measure of tumor perfusion, the full-width half maximum (FWHM) multiplied by the peak height (PH) of the perfusion curve, will be calculated. The summary statistics for describing the change between two scans of the same patient will be the difference in ADC and in FWHM x PH. The correlation of these summary statistics and the outcome variables (TTP and OS) will be assessed using Cox proportional hazards models. Thresholds for declaring a response (progression) will be determined in a similar fashion as described for CSI and the anatomical change measure. All brain voxels in these sections will be evaluated in this manner, as for CSI but with multiple image sections, therefore including the tumor as well as normal appearing brain around the visible tumor. Visual determinations of increased or decreased tumor perfusion between studies using normal appearing white matter perfusion as a reference, and increased or decreased tumor water restriction, will also be made.~~

Section 17.0

Page 57:

Pre-registration Pathology Considerations

The second sentence in Section 17.1 has been revised to include an alternative telephone number as follows:

A call needs to be made to the NCCTG pathology coordinator (507/266-0724 or **507/266-8919**) after pre-registration but prior to forwarding the following material:

Section 17.2 has the following address correction:

NCCTG Operations Office
RO_FF_03_24-CC/NW Clinic ~~NW Clinic 3-24~~
200 First Street SW
Rochester, MN 55905
ATTN: **NCCTG Research Coordinator Helen Tollefson**

The first paragraph following the address in Section 17.2 has been corrected as follows:

If materials have been previously submitted to Dr. C. Giannini and/or associates for a consult review fax a copy of this review to ~~Helen Tollefson~~ **pathology coordinator** (507/284-9628) to verify grade 4 astrocytoma.

Section 18.0**Records and Data Collection Procedures**

Page 59:

Footnote 4 now indicates **5** years of followup rather than 10 for consistency throughout the document.

Appendix 1A**Consent Form**

Page 1:

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

The second paragraph has been revised as follows due to PCP prophylaxis now being required in this study and to define the cycles:

CCI-779 is given 7 – 10 days before the start of radiation. Once radiation therapy is started, TMZ is taken by mouth every day for 6 weeks and CCI-779 is given once a week for those 6 weeks. **This is Cycle 1 (7 weeks in length).** You will then go off treatment from 4 to 6 weeks (**Cycle 2**); the length of time will be decided by your doctor. If your cancer has not gotten worse, then you will get CCI-779 and TMZ for about 6 months. During this time you will get CCI-779 once every week. You will take TMZ for the first 5 days of the first week of every cycle (**Cycles 3-8** [one cycle equals 28 days]). **The combination of TMZ and CCI-779 has been associated with a particular type of pneumonia that can be prevented with antibiotics (either bactrim or pentamidine. Your doctor will decide with you which medication you will need to take to protect you from pneumonia.**

Page 2:

First paragraph has the following deleted as it is redundant with information found under “When I am finished taking taking CCI-779 and Temozolomide”:

~~Once you complete all treatment, you will be followed with the same tests (excluding the pregnancy test) as mentioned previously; every 2 months in the first year, then every 3 months in year 2, then every 6 months for 3 years and then annually for 5 years.~~

When I am finished taking CCI-779 and Temozolomide has the following revised statement in order to make clear how often the follow-up tests and procedures will be done:

You will need these tests and procedure done ~~regularly~~ **every 2 months for 1 year then every 3 months for 1 year then every 6 months for 3 years from the time you went on study:**

Page 3:

Calendar of Events table has been rewritten and divided into separate tables per cycle.

Page 4:

How long will I be in the research study? Now indicates for consistency throughout the study that the patient will be followed for **5** years rather than 10.

Pages 5-6: The risks for TMZ have been updated as follows to be consistent with Section 15.29d of the protocol:

Likely

- Nausea, and/or vomiting
- Headache
- Constipation
- Drowsiness/Fatigue
- Decrease in blood counts that may result in infection, bleeding, or anemia
- Diarrhea
- Fever
- Arm and leg swelling
- **Dizziness**
- **Difficulty falling asleep**
- **Infection in mouth**

Less Likely

- Decreased ability to carry out daily activities
- Pneumonia
- Loss of appetite
- Weight loss and/or decrease in appetite
- Weakness
- Sores in your mouth
- Hair loss
- Numbness or tingling
- Abdominal pain/jaw pain
- Skin rash
- Weakness of hands and feet
- Liver damage
- Changes in your blood chemistries
- **Convulsions (violent spasms or jerking of the body)**
- **Weakness affecting one side of the body**
- **Increased sleepiness**
- **Poor coordination and difficulty walking**
- **Confusion**
- **Anxiety**
- **Depression**
- **Problems with memory**
- **Itchy skin**
- **Dysphagia (difficulty swallowing)**
- **Weight gain**
- **Sores in mouth, esophagus (food tube), reproductive organs, or urinary system**
- **Low red blood cells causing tiredness**
- **Abnormal secretion of body hormones or steroids**

- **Bladder incontinence (leaking from the bladder)**
- **Bladder infection**
- **Frequent urination**
- **Back pain**
- **Muscle pain**
- **Double vision**
- **Cough and infection in the lungs or throat**
- **Trouble seeing**
- **Sore throat**
- **Sinus infections**

Pages 9-10:

Biological Samples for Research

Throughout this section, reference to “~~and/or blood~~” has been deleted due to the removal of the PBMC testing.

An editorial correction has been made to this statement: This study also has laboratory tests that will be ~~performed~~ **done** to study small samples of your tissue.

The following has been deleted due to the deletion of the PBMC testing:

~~The following samples will be sent to laboratories associated with NCCTG and Wyeth Ayerst where the tests will be done:~~

- ~~• **ALL PATIENTS** Peripheral Blood Mononuclear Cells (PBMC) blood samples: These blood samples (about 5 tablespoons total) will be taken just before the first dose of CCI-779 starts, just before the end of the first dose of CCI-779, and 7 days after the first dose of CCI-779 is done.~~

~~1. I agree to provide blood sample(s) to NCCTG for research testing planned as part of this study.~~

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

Appendix 1B

Page 1:

Consent Form

The title of this study is now designated for the **MTD Cohort of Patients**

Why is this research study being done?

The following have been deleted because the highest dose of CCI-779 has been reached and the study is now at the maximum tolerated dose level:

- ~~• Find the highest safe dose of CCI-779, an investigational agent, to give with radiation and TMZ, which can safely be given without causing bad side effects.~~
- ~~• Find the highest safe dose of CCI-779 in combination with TMZ after radiation is complete, that can safely be given without causing bad side effects.~~

The following bullet has been added to address the use of the research MRI:

See if the use of a special research MRI can determine an early response to treatment

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

The second paragraph has been revised as follows due to PCP prophylaxis now being required in this study and to define the cycles:

CCI-779 is given 7 – 10 days before the start of radiation. Once radiation therapy is started TMZ is taken by mouth every day for 6 weeks and CCI-779 is given once a week for those 6 weeks. **This is Cycle 1 (7 weeks in length).** You will then go off treatment from 4 to 6 weeks (**Cycle 2**); the length of time will be decided by your doctor. If your cancer has not gotten worse, then you will get CCI-779 and TMZ for about 6 months. During this time you will get CCI-779 once every week. You will take TMZ for the first 5 days of the first week of every cycle (**Cycles 3-8** [one cycle equals 28 days]). **The combination of TMZ and CCI-779 has been associated with a particular type of pneumonia that can be prevented with antibiotics (either bactrim or pentamidine. Your doctor will decide with you which medication you will need to take to protect you from pneumonia.**

Page 2: Paragraph 1 has the following statement added due to the research MRI being done on this cohort of patients:

You will have an additional research MR scan of the head one week after starting treatment with CCI-779.

Page 2: Paragraph 3 now defines the time points that the PKs will be done:

Extra blood will be taken for research use during this study. This extra blood will be sent to an outside lab to complete the research. This is a requirement to be a part of this study. These blood samples will be taken on **Day 1 before you start treatment, at 30 minutes, and at hours 1, 2, 6, and 14 and Day 8 of Cycles 1 and 3** ~~before you start treatment, at 30 minutes, and and after your first dose of CCI-779 before radiation, and again before and after your first dose of CCI-779 after the 4-6 rest period following radiation~~ (about 2 ~~10-14~~ **tablespoons total for Day 1 and Day 8**). These blood samples would be used to find out how much CCI-779 is in your blood and what effects it has on your blood. You and/or your health plan will not have to pay the costs of these tests which are only done for research purposes.

When I am finished taking CCI-779 and Temozolomide has the following revised statement in order to make clear how often the follow-up tests and procedures will be done:

You will need these tests and procedure done **every 2 months for 1 year then every 3 months for 1 year then every 6 months for 3 years from the time you went on study:**

Page 3: Calendar of Events Table

Calendar of Events table has been rewritten and divided into separate tables per cycle.

Page 4: How long will I be in the research study? now indicates for consistency throughout the study that the patient will be followed for **5** years rather than 10.

Pages 5-6: The risks for TMZ have been updated as follows to be consistent with Section 15.29d of the protocol:

Likely

- Nausea, and/or vomiting
- Headache
- Constipation
- Drowsiness/Fatigue
- Decrease in blood counts that may result in infection, bleeding, or anemia
- Diarrhea
- Fever
- Arm and leg swelling
- **Dizziness**
- **Difficulty falling asleep**
- **Infection in mouth**

Less Likely

- Decreased ability to carry out daily activities
- Pneumonia
- Loss of appetite
- Weight loss and/or decrease in appetite
- Weakness
- Sores in your mouth
- Hair loss
- Numbness or tingling
- Abdominal pain/jaw pain
- Skin rash
- Weakness of hands and feet
- Liver damage
- Changes in your blood chemistries
- **Convulsions (violent spasms or jerking of the body)**
- **Weakness affecting one side of the body**
- **Increased sleepiness**
- **Poor coordination and difficulty walking**
- **Confusion**
- **Anxiety**
- **Depression**
- **Problems with memory**
- **Itchy skin**
- **Dysphagia (difficulty swallowing)**
- **Weight gain**
- **Sores in mouth, esophagus (food tube), reproductive organs, or urinary system**
- **Low red blood cells causing tiredness**
- **Abnormal secretion of body hormones or steroids**

- **Bladder incontinence (leaking from the bladder)**
- **Bladder infection**
- **Frequent urination**
- **Back pain**
- **Muscle pain**
- **Double vision**
- **Cough and infection in the lungs or throat**
- **Trouble seeing**
- **Sore throat**
- **Sinus infections**

Page 10: Biological Samples for Research

For consistency, the wording throughout this section has been revised as follows:
tissue and/or blood and/or tissue

The following portion of the section “Biological Samples for Research” has been rewritten due to the removal of the PBMC testing and information has been added regarding the lab tests done on the tissue along with the opt-out question

~~This study also has laboratory tests that will be performed to study small samples of your blood and/or tissue.~~

~~The following samples will be sent to laboratories associated with NCCTG and Wyeth Ayerst where the tests will be done:~~

- ~~• **ALL PATIENTS** Peripheral Blood Mononuclear Cells (PBMC) blood samples: These blood samples (about 5 tablespoons total) will be taken just before the first dose of CCI-779 starts, just before the end of the first dose of CCI-779, and 7 days after the first dose of CCI-779 is 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.~~

~~You can take part in the treatment portion of this study without taking part in these research laboratory tests.~~

Please read the following statements and mark your choice:

1. I agree to provide blood sample(s) to NCCTG for research testing planned as part of this study.

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

2. I agree to provide a tissue sample to NCCTG for research testing planned as part of this study.

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

This study also has laboratory tests that will be done to study small samples of your tissue and/or blood.

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.

You can take part in the treatment portion of this study without taking part in these research laboratory tests.

Please read the following statements and mark your choice:

I agree to provide a tissue and/or blood sample to NCCTG for research testing planned as part of this study.

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

Appendix VI MR imaging pulse-sequence parameters

This appendix has been revised as follows for clarification with regard to MRI analysis:

Series 1: Sagittal T1-**weighted**. 5 skip 1 mm. cover whole head

Series 2,3,4,6, and 7 are all acquired in the oblique axial plane (aligned with anterior commissure-posterior commissure line). Slice thickness is 4mm, with 0 gap.

Series 2: Diffusion Weighted. TR 13400, TE minimum, B-value = 1000. 128x256. 1 NEX. Freq dir = R/L. Phase Correction on.

Series 3: FLAIR. TR 11,000, TE 147, TI 2250. Freq dir = A/P, 256x192 1NEX

Series 4: T1-**weighted**. TR 400-600, TE min full, Freq dir = A/P, 256x192 1 NEX

~~Series 5: Chemical Shift Imaging - Shimming; PRESS CSI, TE 144, TR 1500, 16x16 matrix, 1 NEX~~

Series ~~6~~ **5**: Perfusion. TR 2225, TE 60, SE-EPI, 128 x 96 10 slice locations located through tumor. 5mm thick slices with 1mm gap. 20cc Gad is injected at 4cc/sec 10 seconds after scanning begins. After all contrast is injected, there is a 20cc saline 'chaser' also injected at 4cc/sec. Images are then processed to produce **relative Cerebral blood volume (rCBV), Mean Transit time (MTT), and Time to Peak (TTP) images maps.**

Series ~~7~~ **6**: T2-**weighted**. TR 4000, TE 100, 256 x 192, 0.75 NEX, Flow compensation on. BW = 15.6

Series ~~8~~ **7**: T1-**weighted**. ~~T1~~ TR 400-600, TE min full, Freq dir = A/P, 256x192 2 NEX

Series ~~9~~ **8**: Coronal T1-**weighted**. TR 400-600, TE min full, Freq dir = A/P, 256x192 2 NEX, 4mm skip 1mm

Note that the T1- and T2-weighted sequences above are acquired with fast spin echo technique. If a 3T MR scanner is available, patients will undergo the same sequences, but with except that series 8 would not be needed, and 3D anatomical imaging would be performed, with smaller partition thickness. After images are acquired, the diffusion images are post-processed to create apparent diffusion coefficient maps. The perfusion images are post-processed to produce rCBV, MTT, and TTP maps. All of these are spatially registered to the FLAIR (series 3), such that they will have the same orientation and number of slices as the T1s, T2s, and FLAIRs. They are automatically transferred to the clinical archive using DICOM storage commitment. Images are then transferred from the DICOM archive to a research server where they are anonymized and further processing done. Anatomical images can then be spatially registered to the post-gadolinium T1-weighted series (series 7), such that they will have the same orientation and number of slices.

Appendix VII Pill Diary

The appendix heading and title have been updated to reflect the correct title as follows:

Appendix VII Pill Diary

~~Patient Medication Diary~~ Pill Diary