

North Central Cancer Treatment Group

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

Addendum 3 – March 28, 2008

Summary

- A total of 13 patients have been accrued to this trial as of 12/1/2007, and three patients died of infections. Given this high rate of infectious deaths, the study was temporarily closed and therapy with temsirolimus was discontinued until these adverse events could be thoroughly evaluated.

In summary, therapy on dose level 0 was well tolerated with the exception of 1 case of *Pneumocystis carinii* pneumonia (PCP) that would have been preventable with PCP prophylaxis. Once PCP prophylaxis was initiated, there were no infectious complications or other dose-limiting toxicities (DLTs) at dose level 1. At dose level 2, there have been 2 DLTs of 6 patients enrolled. In addition, there have been 2 infectious deaths, both with gram-negative organisms that may have been preventable with Bactrim prophylaxis. On the basis of these cumulative data, we believe that the major toxicity from the combination of mTOR inhibition with radiation, temozolomide, and dexamethasone is an increased risk of infections. Previous studies with temsirolimus alone (250 mg/week) in recurrent glioblastoma multiforme (GBM), where most patients are on significant doses of dexamethasone, were not associated with a significant increased rate of infection. Therefore, we believe that the rates of infection seen on this protocol are related primarily to the combined immunosuppressive effects of temsirolimus combined with immune suppression associated with temozolomide. As described above, all infections would have been preventable with combined coverage for both PCP and gram-negative organisms. In general, the risk of infections increases with length of severe immunosuppression. Finally, the extent of immunosuppression with mTOR inhibitors is related to dose intensity. Therefore, we believe that the risks of infection can be reduced to an acceptable level on this protocol through 3 measures:

- 1) Limiting the duration of temsirolimus therapy to 7 weeks, just during the radiation therapy. Our previous animal studies have demonstrated significant synergy with the combination of radiation and mTOR inhibitors, and it is likely that the maximal benefit from the combination will be obtained with this combination, as opposed to extending the combination during adjuvant temozolomide.
 - 2) Maintaining antibiotic prophylaxis for both PCP and gram-negative organisms. In consultation with Dr. Andrew Badley from Mayo Clinic Infectious Diseases and Transplant Medicine, optimal antibiotic prophylaxis can be achieved with oral Bactrim. Alternatively, a combination of intravenous pentamidine and oral levofloxacin will provide similar coverage.
 - 3) Reducing the dose of temsirolimus from level 2 (75 mg/week) down to dose level 1 (50 mg) in accord with the planned dose escalation schema outlined in Section 7.2.
- Immune monitoring will be done in order to understand the effects on immune cell function and number of combining Temsirolimus with radiation and temozolomide in comparison to effects in immune cell function with radiation and temozolomide alone.
 - A CCI-779 Safety Attachment associated with Investigator Brochure, Version 11, dated February 2007 has been received. The risk section of the consent forms has been updated accordingly.
 - Administrative/Editorial Changes

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

Randomization Center is now referred to as “Registration Office” throughout the document (Schema Arm A and Arm B, Sections 3.0, 6.12, 6.21, 6.22, 6.32, 6.35, 7.15 table)

Title page: Now reflects Addendum 3 and revised NCI version date.

Allan Dietz, Ph.D. has been added as a Study Co-Chair.

Protocol Resources

Page 2: The NCCTG *Research Base* Pathology Coordinator order has been revised. Christine Maszk is now listed as the first contact and Helen Tollefson is the second contact.

Index

Page 3: Due to changes to reduce the risk of infection, the following changes have been made:
Appendix IA now indicates that it is for Arm A
Appendix IB now indicates that it is for Arm A – MTD cohort
Appendix IC is newly added for Arm B patients
Appendix IX is newly added.

Schemas

Page 4: Due to the changes to reduce the risk of infection, the following changes have been made:

Arm A has been added to the schema title.

In the treatment box, CCI-779 has been deleted from the treatment following the 4-6 week rest period.

The brand name for Temsirolimus has been added “**Torisel.**”

Page 5: Due to the changes to reduce the risk of infection, the following changes have been made:

SCHEMA – Arm B is newly added.

Due to the inclusion of the Arm B schema, repagination has occurred to the end of the document.

Section 1.0 **Background**

Pages 15-19: Section 1.9 is newly added due to the changes to reduce the risk of infection.

Section 2.0 **Goals**

Page 19: Due to the changes to reduce the risk of infection, the following sections have been revised as follows:

Section 2.11 - To determine the MTD of weekly IV CCI-779 combined with daily oral TMZ and 3D-conformal RT or IMRT ~~followed by weekly IV CCI-779 combined with adjuvant oral TMZ.~~

Section 2.12 - To assess and describe the adverse events of the combination of CCI-779/TMZ and radiation followed by ~~the combination of adjuvant CCI-779/TMZ.~~

Section 2.21 - ~~Identify potential pharmacokinetic interactions between TMZ and intravenous CCI-779~~ **Understand the effects on immune cell function and number of combining Temozolomide with radiation and temozolomide in comparison to effects on immune cell function with radiation and temozolomide alone.**

Section 3.0

Patient Eligibility

Page 19:

The opening statement in Section 3.0 has been revised as follows due to the changes to reduce the risk of infection:

Prior to checking eligibility and pre-registering a patient, contact the ~~Randomization Center~~ **Registration Office** (507/284-4130) for study status and dose level **on Arm A or to ensure a place on the protocol for patients on Arm B.**

Page 20:

Sections 3.29a and 3.29b are newly added as follows due to the changes to reduce the risk of infection:

3.29a Willingness and ability to comply with antibiotic prophylaxis with either trimethoprim/sulfamethoxazole (daily or 3x per week) or monthly IV pentamidine combined with daily levofloxacin.

3.29b Mayo Clinic Rochester (MCR) Patients ONLY: Willingness to undergo mandatory blood tests for immune monitoring (Sections 6.34, 14.1, and 14.2).

Page 21:

Section 3.39c is newly added due to changes to reduce the risk of infection.

Section 4.0

Test Schedule

Page 22:

The 4.1 heading is newly added due to the addition of Arm B.

Due to the changes to reduce the risk of infection, the following changes have been made:

Section 4.1: Column 7 has CCI-779 deleted from the heading.

Section 4.1: Footnote 2 now reads: Done last week of RT. ~~or within 10 days after RT completion.~~

Section 4.1: Research bloods are now for MCR PATIENTS ONLY and the reference to PKs has been removed. Associated footnote 11 has been changed to reference the new time points for the research blood draws.

Section 4.1: The row labeled "MCR PATIENTS ONLY" now references Section 4.3.

Section 4.1: Footnote 3 now reads: These tests are only done every other cycle of ~~CCI-779/TMZ~~ (before cycles 3, 5, and 7).

Section 4.1 table and footnotes: Footnote 14 has been removed that referenced "In addition to a CBC..."

Page 24: Section 4.2 is newly added for Arm B and all remaining sections have been renumbered.

Page 25: Section 4.3 now reflects that it is for Arm A only.

Section 6.0 **Registration Procedures**

Page 26: The opening statement in Section 6.0 has been revised as follows due to changes to reduce the risk of infection:

Prior to checking eligibility and pre-registering a patient, contact the ~~Randomization Center~~ **Registration Office** (507/284-4130) for study status and dose level **for Arm A or to ensure a place on the protocol for patients on Arm B.**

Page 27: Section 6.34 has been newly added to indicate a **mandatory** translational research due to change to reduce the risk of infection. All remaining sections have been renumbered.

Page 28: Section 6.39e has been deleted since kits will no longer be used. Section 6.39f has been renumbered to Section 6.39e.

Section 7.0 **Protocol Treatment**

Page 29: Section 7.0 has been reformatted due to changes to reduce the risk of infection. All sections have been renumbered.

Section 7.1 has been revised as follows due to changes to reduce the risk of infection:
Treatment Schedule: **Arm A** - Treatment will be administered on an outpatient basis. Patients will be treated with IV CCI-779 combined with daily TMZ and RT followed by adjuvant ~~CCI-779 and~~ TMZ. Patients should be pretreated with Benadryl 25-50 mg IV approximately 30 minutes before starting the CCI-779 infusion.

Section 7.21, old second paragraph, has been deleted due to changes to reduce the risk of infection:

~~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.~~

Section 7.11 has been revised as follows due to changes to reduce the risk of infection:
The MTD for ~~adjuvant~~ IV CCI-779 combined with ~~TMZ following~~ concomitant ~~CCI-779/TMZ/RT~~ will be identified.

Section 7.14, second paragraph, has been revised as follows due to changes to reduce the risk of infection:

Inability to deliver CCI-779 combined with TMZ/RT ~~or adjuvant CCI-779 combined with TMZ~~ owing to any of the following (all by CTCAE criteria):

Page 29: Section 7.15 has been deleted due to changes to reduce the risk of infection and all remaining sections have been renumbered:

~~Patients will be specifically observed for toxicities during the first cycle of adjuvant CCI-779, and if undue toxicities are observed (as defined above in Section 7.14) during this cycle, then the dose escalation plan will be re-evaluated.~~

Page 30: Section 7.15 Treatment Table has been revised as follows due to changes to reduce the risk of infection:

4-6 week rest period then			
Adjuvant treatment with CCI-779 and TMZ for 6 cycles (28 days = 1 cycle)			
CCI-779	Same as above	IV	Days 1, 8, 15 and 22
TMZ	200 mg/m ² /d	Oral	Days 1-5

Pages 30-31: Sections 7.161-7.1624 are newly added due to changes to reduce the risk of infection.

Page 31: Section 7.17 has been revised as follows due to changes to reduce the risk of infection:
oral TMZ (**200 mg/m²**, days 1-5) and weekly IV CCI-779 (days 1, 8, 15, and 22). A cycle will be 28 days. ~~For a given patient, if a dose reduction of CCI-779 was required during chemoradiotherapy, this lower dose of CCI-779 also will be used for adjuvant treatment.~~ As in Section **7.161** ~~7.222~~....

Section 7.18 has been revised as follows due to changes to reduce the risk of infection:
 ...rest period (cycle 2) or ~~the first cycle of adjuvant CCI-779 (cycle 3),~~ **subsequent cycles**, then the dosing schedule and dose escalation schema will be re-evaluated.

Page 32: Old Section 7.195 has been deleted due to changes to reduce the risk of infection and remaining section has been renumbered:
~~Toxicities occurring during adjuvant CCI-779 and TMZ will be monitored and if DLTs are observed in 2 or more patients on any given dose level, then the dose-escalation will be halted until the tolerability of adjuvant therapy at that dose level can be evaluated as described in sections 7.333 and 7.334.~~

New Section 7.185 has been revised as follows due to changes to reduce the risk of infection:

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~~ **evaluate the effects of the regimen on immune cell function**. These 10 patients will be enrolled at Mayo Clinic Rochester to facilitate the research MRI scans.

Page 33: Sections 7.2-7.232 are newly added for Arm B treatment due to changes to reduce the risk of infection.

Page 34: Cerebral irradiation: Section 7.31 has the following added due to changes to reduce the risk of infection: **The RT on Arms A and B will be identical. For patients on Arm A, RT may begin...**

Section 8.0 Dosage Modification Based on Adverse Event(s)

Page 37: Section 8.4 heading has been revised to outline which dose mods to follow for Arm A and Arm B due to changes to reduce the risk of infection.

Page 38: Section 8.5 has been modified due to changes to reduce the risk of infection:

Dose modifications based on interim toxicity during adjuvant ~~CCI-779~~/TMZ chemotherapy.

→ → Use Common Terminology Criteria for Adverse Events (CTCAE) v3.0 unless otherwise specified ← ←

<i>CTCAE CATEGORY</i>	<i>ADVERSE EVENT</i>	<i>AGENT</i>	<i>DOSAGE CHANGE</i>
AT THE TIME OF RETREATMENT			
Blood/bone marrow	ANC <1500 or PLTS <100,000	CCI-779 /TMZ	Hold Rx until ANC ≥1500 and PLTS ≥100,000, then modify TMZ and CCI-779 dose based on nadirs (see Section 8.6).
Metabolic/Laboratory	Hyperlipidemia ² , hypercholesterolemia, hyperkalemia, hyperglycemia Grade 3-4	CCI-779	Hold CCI-779 until grade 2 (or within 1 grade of baseline) then ↓ CCI-779 dose by 1 dose level (see Section 7.22). TMZ will continue without interruption.
Non-hematologic	Grade 3-4 ¹	TMZ/ CCI-779	Hold CCI-779 and TMZ until ≤grade 1 then modify TMZ and CCI-779 dose based on interim toxicity (see Section 8.6).
Pulmonary/upper respiratory ¹	Cough/dyspnea ≥Grade 2	CCI-779	Dose interruption. Patients should be evaluated for interstitial pneumonitis. CCI-779 should be permanently discontinued if diagnosis of pneumonitis is confirmed and considered related to CCI-779 . If not pneumonitis or CCI-779 is unrelated to breathing difficulties, hold until ≤grade 1.

1. ~~Possibly, probably or definitely related to treatment.~~

2. ~~Treatment of grade 2-4 hyperlipidemia with lipid lowering agents is allowed. Follow table guidelines for dose reduction and resumption of treatment if controlled with medical measures.~~

1. If the attribution of the toxicity can be clearly linked to only one of the 2 drugs, dose modifications for that drug only should be followed.

Section 8.6 has been modified due to changes to reduce the risk of infection:

Page 38: Dose modifications based on toxicity at the time of retreatment with adjuvant ~~CCI-779~~/TMZ chemotherapy (i.e., on day 1 of each adjuvant treatment cycle) **for Arms A and B**

→ → Use Common Terminology Criteria for Adverse Events (CTCAE) v3.0 unless otherwise specified ← ←

CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
BASED ON INTERIM TOXICITY			
Blood/bone marrow	ANC <1000 - 500 or PLTS <50,000 – 25,000		↓ TMZ dose by 25% and CCI-779 by 1 dose level (see Section 7.22).
	ANC < 500 or PLT <25,000		↓ TMZ dose by 50% and CCI-779 by 2 dose levels (see Section 7.22).
Gastrointestinal Nausea/vomiting on optimal antiemetic management	Grade 3 ³	TMZ/ CCI-779	↓ TMZ dose by 25% and CCI-779 by 1 dose level (see Section 7.22).
	Grade 4 ³		↓ TMZ dose by 50% and CCI-779 by 2 dose levels (see Section 7.22).
Metabolic/Laboratory	Hyperlipidemia, hypercholesterolemia, hyperkalemia, hyperglycemia Grade 3-4	CCI-779	↓ CCI-779 dose by 1 dose level (see Section 7.22). TMZ will continue without interruption
Pulmonary/upper respiratory ¹	Cough/dyspnea ≥Grade 2		If not pneumonitis or CCI-779 is unrelated to breathing difficulties, hold until ≤ grade 1 and re-start CCI-779 at 1 lower dose level (see Section 7.22) TMZ should Continue without interruption.
Non-hematologic	Grade 3 ³	CCI-779/ TMZ	↓ TMZ dose by 25% and CCI-779 by 1 dose level (see Section 7.22).
	Grade 4 ³		↓ TMZ dose by 50% or CCI-779 by 2 dose levels (see Section 7.22).

1. Possibly, probably, or definitely related to treatment.
2. Treatment of grade 2-4 hyperlipidemia with lipid lowering agents is allowed. Follow table guidelines for dose reduction and resumption of treatment if controlled with medical measures.

3. ~~If the attribution of the toxicity can be clearly linked to only one of the 2 drugs, dose modifications for that drug only should be followed.~~

Section 13.0

Treatment/Follow-up Decision at Evaluation of Patient

Page 47:

Section 13.0 has been reformatted due to changes to reduce risk of infection.

Section 13.15 has been revised as follows due to changes to reduce risk of infection:
 "...treatment with adjuvant ~~CCI-779~~/TMZ will continue..."

Section 13.17 has been revised as follows due to changes to reduce risk of infection:
 evaluation period (end of **Cycle 1** ~~4st adjuvant TMZ/CCI-779~~), they will be replaced.....

Page 48:

Section 13.2 is newly added due to changes to reduce risk of infection.

Section 14.0

Translational/Pharmacologic Studies

Pages 48-50:

Sections 14.1 and 14.2 have been rewritten due to the changes to reduce risk of infection.

Page 51:

The first sentence of Section 14.32 has been corrected as follows:
 The remaining material will be stored for future research depending on the patient consent permission (see Section 6.~~2536~~)...

Page 51:

Section 14.4 has been rewritten due to the changes to reduce risk of infection.

Page 53:

Section 14.6 is newly added to clarify that DNA and/or RNA specimens are only banked and no specific genetic testing is being performed in this study.

Section 15.0

Drug Information

Page 53:

The brand name for Temezirolimus has been added to "Other Names" in Section 15.1
 "**Torisel.**"

Section 16.0

Statistical Considerations and Methodology

Page 63:

The following sections have been revised due to the changes to reduce risk of infection:

Section 16.1 now reads: This Phase I clinical trial will enroll patients with GBM who are not receiving EIA. This phase I study is designed to determine the maximally tolerated dose (MTD) of CCI-779 when combined with TMZ and RT followed by ~~adjuvant CCI-779 combined with~~ adjuvant TMZ. Only the dose level of CCI-779 will be escalated (doses of TMZ and RT remain fixed) ~~and the same dose level of CCI-779 will be used for adjuvant phase that was used concomitantly with RT and TMZ.~~

Page 64:

Section 16.21 now reads: **Study design:** This is a Phase I protocol that will evaluate weekly IV CCI-779 combined with daily oral TMZ and RT followed by ~~weekly IV CCI-779 combined with~~ adjuvant TMZ for newly diagnosed GBM patients. The trial will use a standard cohort-of-3 Phase I design. The aim is to determine the MTD of CCI-779 combined with therapeutic doses of TMZ and RT followed by ~~CCI-779 combined with~~ a therapeutic dose of TMZ as adjuvant therapy following RT. CCI-779

will not be escalated above its single-agent established MTD **and only CCI-779 will be escalated and the same dose of CCI-779 will be used in the adjuvant phase as is used for concomitant therapy with TMZ and RT.**

Section 16.23 now reads: **Sample Size: For Arm A**, a minimum of 19 and a maximum of 46 patients will enter this study unless undue toxicity or other factors affect patient accrual. The minimum and maximum numbers include the 10 additional patients that will be accrued at the MTD. **For Arm B, a maximum of 10 patients will be accrued.**

Page 64:

Section 16.24 now reads: **Accrual Time and Study Duration: For Arm A**, we anticipate an annual accrual rate of approximately 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 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 will be between 9 months (9 patients) to 36 months (36 patients). The expansion cohort of 10 patients will only be enrolled from Mayo Clinic – Rochester. ~~Thus, we~~ 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.

For Arm B, the accrual of 10 patients will be open to all participating sites. Assuming 26 newly diagnosed GBM patients per year, it will take roughly 5 months to enroll 10 patients for this aim.

Pages 65-66:

Section 16.31 now reads: ~~Pharmacokinetic studies~~ **Immune monitoring studies:** Descriptive statistics (e.g., mean, median, standard deviation, inter-quartile range, range), scatterplots, and dotplots will form the basis of evaluation and presentation of this data. ~~Pharmacokinetic parameter~~ Values obtained at baseline (prior to administration of drug), **and at 3 additional time points 0.5, 1, 2, 24, and 168 hours will include absolute and relative levels of immune cells.** ~~AUC, half-life, clearance, and bioavailability.~~ These will be summarized descriptively across patients as well as across time points. In particular, values will be plotted for each patient across time. In addition, dotplots will be made of values for patients at each time point. A comparison will be made between **parameters determined in Arms A and B.** ~~the pharmacokinetic parameters obtained with CCI-779 treatment alone versus CCI-779 combined with adjuvant TMZ to determine whether TMZ affects CCI-779 pharmacokinetics.~~ Correlations between these ~~pharmacokinetic~~ **immune monitoring** values and other outcome measures such as toxicity and response will be carried out in an exploratory manner. **The trough level of CCI-779/sirolimus will be correlated with the extent of immune suppression in patients on Arm A.**

Page 67: Section 16.63 now reads: Approximately 40% of the patients enrolled in previous NCCTG high-grade glioma trials were women, and about 7% were classified as ethnic/racial minorities. If the maximum accrual for the study is achieved (i.e., ~~56~~ 46 patients), then about ~~22~~ 18 women and approximately ~~4~~ 3 members of minorities will participate in this study. The following table shows the distribution by minority and gender classification:

The table has been updated with the appropriate numbers.

Section 17.0 **Pre-registration Pathology Considerations**

Page 69: The last paragraph in Section 17.2 has been updated to reflect the **Registration Office** rather than the ~~Randomization Center~~.

Section 20.0 **References**

Page 74: Reference 42 is newly added.

Appendix IA **Consent Forms**

Page 1: The title now reflects that this consent is for **Arm A**.

Why is this research study being done?

The following reason has been newly added as it was previously inadvertently omitted:

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

The following reason has been newly added due to the changes to reduce risk of infection:

- **See what effects this therapy (good and bad) has on our immune system.**

How many people will take part in the research study? now reflects **56** subjects will be enrolled rather than 46 due to the changes to reduce risk of infection.

Page 2: **What will happen if I take part in this research study?** This section has been modified due to the changes to reduce risk of infection

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 alone** for about 6 months. During this time you ~~get CCI-779 once every week. You will~~ 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 **an increased risk of infection, and these types of infections** ~~particular type of pneumonia that~~ can be prevented with antibiotics (either ~~B~~**Bactrim** or pentamidine/**levofloxacin**). Your doctor will decide with you which medication(s) you will need to take to protect you from ~~pneumonia~~ **these infections**.

You will have these tests and exams prior to starting treatment: general physical exam, neurologic exam, routine blood tests, pregnancy test (if applicable) and MRI or CT of the head. **You will have an additional research MRI scan of the head one week after starting treatment with CCI-779.** Once treatment has started, you will have weekly general physical exams and blood tests during the course of your radiation treatments. You will also have blood tests and see your doctor before each cycle (every 28 days) of TMZ. **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.**

Mayo Clinic Rochester Patients ONLY:

This study also has mandatory laboratory tests that will be done to study small samples of blood. A blood sample will be done by drawing some blood from a vein. The blood will be taken just before treatment starts, at the end of radiation (Cycle 1), and just before Cycle 3 and Cycle 5. With the exception of the first blood draw, these research bloods can be obtained in the same blood draw as blood tests that are required for your regular care.

The blood will be sent to laboratories associated with NCCTG and Wyeth-Ayerst, where the tests will be 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.

Page 3:

Calendar of Events – Cycle 1

Week 1	<ul style="list-style-type: none"> • Coagulation blood test if you are on coumadin • Mayo Clinic Rochester Patients ONLY - Research blood draw before starting therapy • MRI or CT of the brain • Mayo Clinic Rochester Patients ONLY – research MRI
Week 2 through 7	<ul style="list-style-type: none"> • Routine blood tests • Physical exams • Week 7 – Mayo Clinic Rochester Patients ONLY – Research blood draw

Calendar of Events – Cycles 3-8

Before re-starting treatment	<ul style="list-style-type: none"> • MRI or CT of the brain • Routine blood tests • Neurological and physical exams • Mayo Clinic Rochester Patients ONLY – Research blood draw prior to Cycles 3 and 5
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Appendix IB**Consent Forms**

Page 1:

The title now reflects that this consent is for **Arm A** MTD cohort of patients.

Why is this research study being done?

The following reason has been newly added due to the changes to reduce risk of infection

- **See what effects this therapy (good and bad) has on our immune system.**

How many people will take part in the research study? now reflects **56** subjects will be enrolled rather than 46 due to the changes to reduce risk of infection.

Page 2:

What will happen if I take part in this research study? This section has been modified due to the changes to reduce risk of infection

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 alone** for about 6 months. During this time you ~~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 **an increased risk of infection, and these types of infections** ~~particular type of pneumonia that~~ can be prevented with antibiotics (either ~~B~~**Bactrim** or pentamidine/**levofloxacin**). Your doctor will decide with you which medication(s) you will need to take to protect you from ~~pneumonia-these~~ **infections**.

You will have these tests and exams prior to starting treatment: general physical exam, neurologic exam, routine blood tests, pregnancy test (if applicable), and MRI or CT of the head. **You will have an additional research MRI scan of the head one week after starting treatment with CCI-779.** Once treatment has started, you will have weekly general physical exams and blood tests during the course of your radiation treatments. You will also have blood tests and see your doctor before each cycle (every 28 days) of TMZ. **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.**

~~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 (about 2 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.~~

Mayo Clinic Rochester Patients ONLY:

This study also has mandatory laboratory tests that will be done to study small samples of blood. A blood sample will be done by drawing some blood from a vein. The blood will be taken just before treatment starts, at the end of radiation (Cycle 1), and just before Cycle 3 and Cycle 5. With the exception of the first blood draw, these research bloods can be obtained in the same blood draw as blood tests that are required for your regular care.

The blood will be sent to laboratories associated with NCCTG and Wyeth-Ayerst, where the tests will be 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.

Page 3:

Calendar of Events – Cycle 1

Week 1	<ul style="list-style-type: none"> • Coagulation blood test if you are on coumadin • Mayo Clinic Rochester Patients ONLY – Research blood draw before starting therapy • MRI or CT of the brain • Mayo Clinic Rochester Patients ONLY – research MRI
Day 1 of Week 1	<ul style="list-style-type: none"> • Research blood draw before treatment, at 30 minutes, and at hours 1, 2, 6, and 24
Day 8 of Week 1	<ul style="list-style-type: none"> • Research blood draw (one time)
Week 2	<ul style="list-style-type: none"> • Research MRI of the brain
Week 2 through 7	<ul style="list-style-type: none"> • Routine blood tests • Neurological and physical exams • Week 7 – Mayo Clinic Rochester Patients ONLY – Research blood draw

Calendar of Events – Cycles 3-8

Before re-starting treatment	<ul style="list-style-type: none"> • MRI or CT of the brain • Routine blood tests • Neurological and physical exams • Mayo Clinic Rochester Patients ONLY – Research blood draw prior to Cycles 3 and 5
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Appendices IA, IB

Pages 4-6:

Consent form

The risks for CCI-779 have been updated as follows due to the receipt of a Safety Attachment associated with Investigator Brochure, Version 11, dated February 2007.

**Risks and side effects related to the CCI-779 include those which are:
Likely (events occurring greater than 20% of the time)**

- Diarrhea
- Mouth sores
- Nausea and vomiting
- Constipation (infrequent, or difficulty in passing, stools)
- Skin rash, which may be severe
- Fingernail/toenail changes
- Acne
- Pain: Head/Headache
- Fatigue
- Weakness, loss of strength and energy
- Loss of appetite
- Weight loss
- Decreased red blood cell supply (anemia), which can cause fatigue, shortness of breath, and a possible need for red blood cell transfusions
- Decreased white blood cell supply (leucopenia), which can put you at risk for infection
- Decreased number of platelets in the blood, resulting in the potential for increased bleeding and decreased ability for clotting
- Nose bleeds
- Altered taste
- Fever and/or chills/shaking
- Mouth dryness
- Skin dryness and itchiness
- Fluid buildup in arms or legs
- High blood sugar, signs of which include great thirst, a dry mouth, and a need to urinate often
- Higher cholesterol and triglyceride levels in your blood (if severe, this can lead to blood vessel blockage, heart disease and other heart problems, or inflammation of the pancreas)
- Pain, including back pain, joint pain, muscle pain, chest pain, or abdominal pain
- Shortness of breath
- ~~Depression~~ (moved to *Less Likely* due to IB review)
- Flu-like syndrome
- Infection
- Stuffy nose
- Dry cough
- Sweating
- ~~High or low blood pressure~~ (moved to *Less Likely* due to IB review)
- ~~Dehydration~~ (moved to *Less Likely* due to IB review)
- Inflammation and sores in the GI tract
- Hair loss (moved from *Rare but serious* due to IB review)

Less Likely (events occurring less than or equal to 20% of the time)

- Increased levels of liver enzymes, which may put you at risk for liver damage
- Decreased testosterone in men with decrease in sex-drive
- Allergic reactions and hypersensitivity
- Increased blood clotting
- Abnormal amount of protein in the blood that is needed for blood clotting
- Low potassium level
- Higher acid levels in the blood
- Increased sleepiness
- Recurrence of herpes simplex infection, which may cause sores in the mouth or on the lips, inflammation of the gums and throat, and recurrence of genital herpes
- Herpes zoster, sometimes known as shingles, and results in a painful blistering red rash that is confined to one side of the body
- Reactions at the site where CCI-779 is injected, which may include tenderness, warmth, redness along the vein or at the site of the injection, itching, pain at the site of the injection, blistering, or severe skin damage
- Pale or reddened irregular, elevated patches of skin and severe itching, hives
- Wide-spreading inflammation and/or rash that goes deep into the skin
- Collection of fluid or blood in the lungs
- Inflammation of the lungs
- Catheter infection
- Infection in the bloodstream
- Fungal yeast infection
- Urinary tract infection
- Conjunctivitis (infection around the eye, also called pink eye)
- Inflammation of the tongue
- Mouth pain
- Abnormally low calcium in the blood stream, that can result in muscle cramps, abdominal cramps, spasms
- Altered levels of blood salts (phosphates)
- Increase in an enzyme that helps produce energy. An increased level may be a sign of cell damage
- Lack or loss of memory, inability to remember past experiences
- Confusion
- Dizziness
- Difficulty sleeping
- Impotence (inability to have sex)
- Changes in kidney function/kidney failure
- Collection of fluid in the body overall and/or facial area
- Difficulty swallowing
- Decreased or delayed wound healing
- Depression (*moved from Likely due to IB review*)
- High or low blood pressure (*moved from Likely due to IB review*)
- Dehydration (*moved from Likely due to IB review*)

Rare but serious (events occurring less than 2-3% of the time)

- A serious, often life-threatening allergic reaction that is characterized by low blood pressure, shock (poor tissue perfusion) and difficulty breathing
- Lung damage or fluid accumulation around the lungs
- Developing a hole in the bowel leading to life-threatening infections in the abdomen. Patients on high doses of steroids may be at increased risk for this complication
- ~~Hair loss~~ (moved to Likely due to IB review)

Appendices IA, IB

The risks and side effects for Bactrim and Pentamidine have been newly added due to the changes to reduce risk of infection:

Risks and side effects related to Bactrim include:**Likely**

- Nausea
- Vomiting
- Loose stools
- Rash
- Itching
- Sensitivity to the sun
- Allergic reactions (redness, itching, fluid retention, fever, chills)

Rare

- Severe skin reactions
- Elevation in liver function tests
- Muscle aches/pains
- Changes in white blood cell, red blood cell, platelet counts
- Changes in body salts (high potassium, low sodium, low blood sugars)
- Increase in kidney function tests

Risks and side effects related to IV Pentamidine/levofloxacin include:**Likely (events occurring greater than 10% of the time)**

- Low blood pressure
- Rash
- High or low blood sugar
- Nausea
- Vomiting
- Loose stools
- Changes in white blood cell or platelet counts
- Increase in liver function tests
- Increase in kidney tests

Less likely (events occurring 1-10% of the time)

- Bad or metallic taste in the mouth
- Low red blood cell counts
- Reaction at the injection site

Rare (events occurring less than 1% of the time)

- Irregular heart beats
- Confusion
- Dizziness
- Feeling faint
- Feeling tired

Risks and side effects related to inhaled Pentamidine/levofloxacin include:**Likely (events occurring greater than 10% of the time)**

- Shortness of breath
- Bronchospasm
- Sinus inflammation
- Headache

Appendix IC **Consent Form** – newly added for Arm B patients

Appendix IX

The sentence “At this point can start Bactrim DS one tablet BID” has been revised for clarification as follows:

At this point can start Bactrim DS one tablet ~~BID~~ **daily per prophylaxis in this protocol.**