

North Central Cancer Treatment Group

N0775: A Randomized Phase II Trial of Temozolomide (TMZ) and Avastin® or
ABI-007/Carboplatin (CBDCA) and Avastin® in Patients with Unresectable Stage IV
Malignant Melanoma

Addendum 15 – May 27, 2011

Summary

- The Research Base Protocol Specialist has been revised
- Section 15.0 and the consent form revisions due to the review of Temozolomide Investigator Brochure dated December 3, 2010

**Replacement pages are included. Please incorporate into the
protocol and keep this addendum with your protocol.**

Title Page Reflects the addition of Addendum 15 and a new NCI version date.

Protocol Resources

Page 2: **Tamra Chomjak** has replaced Sara Braun as the Research Base Protocol Specialist. The phone number and e-mail have been revised accordingly.

Section 15.0 Drug Information

Page 54: Section 15.49a has been revised due to the review of Temozolomide Investigator Brochure dated December 3, 2010. Changes are as follows:

Known potential adverse events: (Please see the temozolomide package insert for a comprehensive list of adverse events) Hematological: Thrombocytopenia, leukopenia, myelodysplastic syndrome, neutropenia, lymphopenia, anemia, aplastic anemia. Gastrointestinal: Nausea, vomiting, anorexia. Hepatic: Elevated liver enzymes (reversible) Skin: Rash (could be severe), psoriasis, **pruritus, severe skin rash (Stevens Johnson syndrome; erythema multiforme; epidermal necrolysis)**. Other: Constipation, diarrhea, stomatitis, fatigue, decreased performance status, headache, lack of interest in or ability to carry out daily activities, hemiparesis, pneumonitis, change in kidney function tests, **pyrexia, pain (including abdominal), myalgia, arthralgia, amnesia, depression, anxiety, asthenia, dizziness, tingling or burning in your arms or legs, dyspnea, cough, edema, urinary urgency, seizures, abnormal coordination, paralysis, allergic reaction (fever, chills, swelling of body, shortness of breath), later development of secondary leukemia, lymphoma, or other cancers**. Re-activation of hepatitis infection is possible.

Appendix I **Consent Form**

Pages 10/11: Based on review of Temozolomide Investigator Brochure dated December 3, 2011, the “Rare but serious risks of temozolomide have been revised, as follows:

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

- Problem with the bone marrow that causes decreased production of red cells, white cells, or platelets that can sometimes turn into blood cancer called myelodysplastic syndrome
- Convulsions
- Weakness on one side of your body (Hemiparesis)
- Abnormal coordination
- Inability to move an arm or leg (paralysis)
- **Allergic reactions, including severe skin reaction rash or skin peeling as with a severe sunburn (Stevens Johnson syndrome; erythema multiforme; epidermal necrolysis)**
- **Fever, chills, swelling of body, shortness of breath** (Allergic reaction)
- Re-activation of hepatitis infection if you have previously been diagnosed with Hepatitis (a type of infection in the liver)
- A blood disorder in which the body’s bone marrow does not make enough new blood cells (Aplastic anemia)
- Inflammation in the lungs (Pneumonitis)
- Change in kidney function tests (tests that show the kidneys are working)
- **Later development of secondary leukemia, lymphoma or other cancers**

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A Randomized Phase II Trial of Temozolomide (TMZ) and Avastin® or ABI-007/Carboplatin (CBDCA) and Avastin® in Patients with Unresectable Stage IV Malignant Melanoma

*For any communications regarding this protocol,
please call the protocol resource person on the following page*

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Drug Availability

DCTD Supplied Investigational Agents: None.

Drug Company Supplied Investigational Agents: (IND Exempt)

ABI-007 supplied by Abraxis Oncology

Avastin® supplied by Genentech

Carboplatin supplied by Abraxis Oncology

Temozolomide supplied by Schering Plough

***Investigator having NCI responsibility for this protocol**

√Study contributor(s) not responsible for patient care.

Document History	(Effective Date)	Document History	(Effective Date)
Activation	August 15, 2008	Addendum 8	March 26, 2010
Addendum 1	December 26, 2008	Addendum 9	May 21, 2010
Addendum 2	May 15, 2009	Addendum 10	July 23, 2010
Addendum 3	May 29, 2009	Addendum 11	October 15, 2010
Addendum 4	June 26, 2009	Addendum 12	November 26, 2010
Addendum 5	August 14, 2009	Addendum 13	December 10, 2010
Addendum 6	September 11, 2009	Addendum 14	February 18, 2011
Addendum 7	February 12, 2010	Addendum 15	May 27, 2011

Study Participants **Date Activated**
Entire NCCTG August 15, 2008

NCI Version Date: May 18, 2011

Add
1,2,12,15

Protocol Resources

Questions:	Contact Name:
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*No waivers of eligibility per NCI

radioactive dose is recovered over 7 days; 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is as unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolites(s) (17%). Overall clearance of temozolomide is about 5.5 L/hr/m².

- 15.46 Drug-drug interactions: In a multiple dose study, administration of temozolomide with ranitidine did not change the C_{max} or AUC values for temozolomide or MTIC. Population analysis indicates that administration of valproic acid decreases the clearance of temozolomide by about 5%. The clinical implication of this effect is not known. Population analysis failed to demonstrate any influence of co-administered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H₂-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.
- 15.47 Capsule constituents: The capsule also contains anhydrous lactose, colloidal anhydrous silica, sodium starch glycolate, tartaric acid and stearic acid. The capsule shells contain gelatin, titanium dioxide, and sodium lauryl sulphate.
- 15.48 Storage: The capsules should be stored at 25°C but temperatures between 15 and 30 degrees centigrade are permissible.
- 15.49a Known potential adverse events: (Please see the temozolomide package insert for a comprehensive list of adverse events) Hematological: Thrombocytopenia, leukopenia, myelodysplastic syndrome, neutropenia, lymphopenia, anemia, aplastic anemia. Gastrointestinal: Nausea, vomiting, anorexia. Hepatic: Elevated liver enzymes (reversible) Skin: Rash (could be severe), psoriasis, pruritus, severe skin rash (Stevens Johnson syndrome; erythema multiforme; epidermal necrolysis). Other: Constipation, diarrhea, stomatitis, fatigue, decreased performance status, headache, lack of interest in or ability to carry out daily activities, hemiparesis, pneumonitis, change in kidney function tests, pyrexia, pain (including abdominal), myalgia, arthralgia, amnesia, depression, anxiety, asthenia, dizziness, tingling or burning in your arms or legs, dyspnea, cough, edema, urinary urgency, seizures, abnormal coordination, paralysis, allergic reaction (fever, chills, swelling of body, shortness of breath), later development of secondary leukemia, lymphoma, or other cancers. Re-activation of hepatitis infection is possible.

Add 7,15

Temozolomide is potentially mutagenic and should be handled with appropriate precautions by both staff and patients. Capsules should not be opened. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes. Procedure for proper handling and disposal of anticancer drugs should be considered.

15.49b Special populations

- 15.49b1 Creatinine clearance: Population pharmacokinetic analysis indicates that creatinine clearance over the range of 36-130 mL/min/m² has no effect on the clearance of temozolomide after oral administration. The pharmacokinetics of temozolomide have not been studied in patients with severely impaired renal function (CL_{cr} < 36 mL/min/m²). Caution should be exercised when temozolomide is administered to patients with severe renal impairment. Temozolomide has not been studied in patients on dialysis.

- Hair loss or thinning

Rare but serious (events that occur less than 2-3% of the time):

- Secondary leukemia and/or myelodysplastic syndrome (damage to the bone marrow that affects normal blood cell production).

Temozolomide

Add 7 Likely risks of temozolomide (events occurring greater than 20% of the time)

- Feeling sick to your stomach (nausea)
- Throwing up (vomiting)
- Decreased appetite (Anorexia)
- Difficulty in passing stools (constipation)
- Headache
- Fatigue
- Fever (Pyrexia)

Add 7 Less likely risks of temozolomide (events occurring less than or equal to 20% of the time)

- Fall in the white blood cell counts that leads to a higher risk of infection (Neutropenia)
- Fall in the platelet count leading to a higher risk of bleeding (Thrombocytopenia)
- Fall in the red blood cell count leading to anemia (feeling tired and low energy) (Anemia)
- A low number of a particular white blood cell, which is important to the immune system (Lymphopenia)
- Sores in the mouth (Stomatitis)
- Loose stools (diarrhea)
- Pain in the abdomen or stomach
- Change in liver function tests (tests that show how the liver is working)
- Rash (Psoriasis)
- Itchiness (Pruritis)
- Lack of interest in or ability to carry out daily activities
- Weakness (Asthenia)
- Dizziness
- Anxiety
- Depression
- Memory loss (Amnesia)
- Muscle pain (Myalgia)
- Joint pain (Arthralgia)
- Tingling or burning in your arms or legs
- Shortness of breath (Dyspnea)
- Cough
- Swelling in your arms or legs (Edema)
- Increased need to pass urine

Add 7,15 Rare but serious risks of temozolomide (events occurring less than 2-3% of the time)

- Problem with the bone marrow that causes decreased production of red cells, white cells, or platelets that can sometimes turn into blood cancer called myelodysplastic syndrome
- Convulsions
- Weakness on one side of your body (Hemiparesis)
- Abnormal coordination
- Inability to move an arm or leg (paralysis)
- Allergic reactions, including severe skin rash or skin peeling as with a severe sunburn (Stevens Johnson syndrome; erythema multiforme; epidermal necrolysis)
- Fever, chills, swelling of body, shortness of breath (Allergic reaction)
- Re-activation of hepatitis infection if you have previously been diagnosed with Hepatitis (a type of infection in the liver)
- A blood disorder in which the body's bone marrow does not make enough new blood cells (Aplastic anemia)

- Inflammation in the lungs (Pneumonitis)
- Change in kidney function tests (tests that show the kidneys are working)
- Later development of secondary leukemia, lymphoma or other cancers

As with any medication, allergic reactions are a possibility.

The risks of drawing blood include pain, bruising or rarely infection at the needle site.

Add 1

Reproductive risks: You should not become pregnant or father a baby while on this study and for up to 6 months after your last dose of study drugs. The drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study and for up to 6 months after your last dose of study drugs. Check with your health care provider about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

MRI: There are now reports of really rare kidney problems. There is a very small risk that you may have kidney damage from the contrast used during the test or an allergic reaction. There are no known health risks from the magnetic field of this imaging device.

CT scan: There is a small risk that you may have an allergic reaction or kidney damage (usually temporary and mild) to the contrast used during the test. You will be exposed to radiation during these tests. The amount of radiation you would get has a low risk of harmful effects.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the research study?

Taking part in this study may or may not make your health better. While doctors hope study drugs will be more useful against melanoma compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about the study drugs as a treatment for melanoma. This information could help future melanoma patients.

What other choices do I have if I do not take part in this research study?

You do not have to be in this study to receive treatment for your cancer.

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment for the cancer, but getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.