

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 14 – February 18, 2011

Summary

- Correction and clarification to Section 7.26 regarding CBDCA calculation
- Section 15.0 and the consent form revisions due to the review of ABI-007 (Abraxane) Investigator Brochure dated August 5, 2010
- Administrative changes.

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

Title Page Reflects the addition of Addendum 14 and a new NCI version date.

Section 7.0 **Protocol Treatment**
Page 20: The third paragraph in Section 7.26 has been corrected and expanded for clarification, as follows:

For the purposes of this protocol, the GFR... The creatinine clearance is calculated by the method of Cockcroft and Gault ($\text{CrCl [mL/min]} = (140 - \text{age}) \times \text{actual body weight [Kg]} / \text{[plasma Cr [mg/dL]} \times 72]$ x [0.85 if female]). **You can also access the carboplatin dosing (Cockcroft and Gault) calculator via the NCCTG web site at <https://ncctg.mayo.edu/ncctg/group/cra/worksheet.html#CDC>.**

Section 15.0 **Drug Information**
Page 44: Section 15.126 has been updated based on review of ABI-007 Investigator Brochure Version 13 dated August 5, 2010. The following revisions have occurred:

15.126 Other: alopecia, fatigue, dyspnea, ~~fever~~, hypotension, cardiac arrhythmia, skin changes at injection site, death, pyrexia, infection, ~~hypo~~**hyper**phosphatemia, hypoalbuminemia, hypocalcemia, hyperglycemia, hypoglycemia, hyponatremia, hyperkalemia, hypermagnesemia, ~~arrhythmia~~, heart attack, epistaxis, xerosis, rash, paronychia, mood changes, eye problems (blurred vision, watery eyes or dry eyes), liver failure, kidney damage due to imbalance of salts or chemicals in the blood, abnormal liver function tests, **allergic reaction (can include breathing difficulties, flushing, low blood pressure, rash, and itching), pulmonary edema, cough. Also, rare reports of congestive heart failure and left ventricular dysfunction have been observed among individuals receiving Abraxane. Most of the individuals were previously exposed to cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history.**

Appendix I

Pages 6/7:

Consent Form

Based on review of ABI-007 Investigator Brochure Version 13 dated August 5, 2010, the following revisions have occurred:

Likely risks of ABI-007 (events occurring greater than 20% of the time)

- Fall in the number of white blood cells leading to a greater chance of infection (Leukopenia)
- Fall in the number of red blood cells leading to anemia (feeling tired and run down) (Anemia)
- Nausea (feeling sick to your stomach)
- Vomiting (throwing up)
- Diarrhea (loose stools)
- Constipation or difficult bowel movements
- Loss of appetite (Anorexia)
- Feeling of tiredness (Fatigue)
- Hair loss (Alopecia)
- Muscle pain (Myalgia)
- Joint pain (Arthralgia)
- Nerve damage with numbness and tingling, usually in the hands and feet (Peripheral neuropathy). This effect may go away when the drug is stopped but it may not go away for some patients.
- Changes in taste sensation (Dysgeusia)

Less likely risks of ABI-007 (events occurring less than or equal to 20% of the time)

- Fever (which may indicate an infection) (Pyrexia)
- Fall in the number of platelets in your blood leading to a greater chance of bleeding (Thrombocytopenia)
- Sores in the mouth and/or throat leading to painful swallowing (**Mucositis**) (*clarified*)
- Difficult or painful breathing caused by narrowing of the airways (Dyspnea)
- Abnormal liver function tests which may be a sign that your liver is not working properly
- Abnormalities in heart rhythm (abnormal electrocardiogram) (Arrhythmia)
- Infection
- ~~Decreased~~ **Increased** level of phosphorus in the blood (~~Hypophosphatemia~~ **Hyperphosphatemia**) (*revised*)
- Decreased Albumin in the blood (Hypoalbuminemia)
- Abnormally low calcium in the blood stream, that can result in muscle cramps, abdominal cramps, spasms (Hypocalcemia)
- High blood sugar (Hyperglycemia)
- Low blood sugar (Hypoglycemia)
- Decreased sodium levels in the blood (Hyponatremia)
- Elevated levels of potassium in the blood (Hyperkalemia)
- Increased magnesium in the blood (Hypermagnesemia)
- Nose bleed (Epistaxis)
- Dry skin (Xerosis)
- Rash
- An infection where the nail and skin meet at the side or the base of a finger or toenail, which can be painful (Paronychia)
- Mood changes
- Eye problems, blurred vision, watery eyes, dry eyes

Rare but serious risks of ABI-007 (events occurring less than 2-3% of the time)

- Lack of oxygen to the heart muscle which can cause damage to the heart (Heart attack)
- Liver failure
- Imbalance of salts or chemicals in the blood leading to kidney damage
- Rare reports of congestive heart failure and left ventricular dysfunction may have been observed among patients receiving Abraxane. Most of the patients were previously exposed to cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history.
- **Skin changes at the site of injection** (*new*)
- **Slowing of the heart rate (Pulse)** (*new*)
- **Allergic reaction (symptoms can include difficulty breathing, flushing, low blood pressure, rash and itching)** (*new*)
- **Pulmonary edema** (*new*)
- **Cough** (*new*)

Page 14:

The tissue sample signature line has been revised as follows for correction:

I agree to provide a tissue sample(s) to: _____ ~~laboratories~~ **the laboratory of Dr. Daniel Knauer at Abraxis Health** associated with NCCTG, for research testing planned as part of this study.

North Central Cancer Treatment Group

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		

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

NCI Version Date: February 3, 2011

should be to dose level -2 and the second dose reduction should be to dose level -3 (see section 8.3). A maximum of 2 dose reductions are allowed.

Order of Administration	Drug	Dose (per day)	Schedule	Route	Retreatment
1 st	Avastin®	10mg/kg	Days 1 and 15	IV over 90 minutes ¹	Every 28 days
2 nd	ABI-007	80mg/m ²	Days 1, 8, 15	IV over 30 minutes	Every 28 days
3 rd	CBDCA	AUC 5	Day 1	IV over 30 minutes following ABI-007	Every 28 days

1) See section 7.23 below.

- 7.21 Agent administration should occur in the order by which the agents are listed in the table.
- 7.22 Calculate dose using actual weight or estimated dry weight if fluid retention.
- 7.23 The initial Avastin® dose should be administered over a minimum of 90 minutes. If no adverse events occur, the second dose can be administered over a minimum of 60 minutes. Again, if no adverse events occur, the third and subsequent doses should be administered over a minimum of 30 minutes. If infusion-related adverse events occur, subsequent infusions should be administered over the shortest period that is well tolerated. See section 15.33 for more instructions on infusion rates.
- 7.24 To ensure complete delivery of Avastin®, the IV infusion line must be flushed with 0.9% sodium chloride.
- 7.25 Epinephrine should be immediately available during the infusion of paclitaxel and Avastin®.
- 7.26 The dose of CBDCA will be calculated by the formula of Calvert, et al.
 CBDCA dose (mg) = target AUC x (GFR + 25).

Add 12,14

Note: The glomerular filtration rate (GFR) used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min. **As of October 1, 2010, the maximum carboplatin dose for patients is 750 mg.**

For the purposes of this protocol, the GFR is considered to be equivalent to the creatinine clearance (CrCl) and can be measured or calculated (Note: When concerned about patient safety in a given patient, measure GFR). The creatinine clearance is calculated by the method of Cockcroft and Gault (CrCl [mL/min] = (140 - age) x actual body weight [Kg]/ [plasma Cr [mg/dL] x 72] x [0.85 if female]). You can also access the carboplatin dosing (Cockcroft and Gault) calculator via the NCCTG web site at <https://ncctg.mayo.edu/ncctg/group/cra/worksheet.html#CDC>.

Note: A correction factor is NOT to be used to calculate carboplatin doses based on the IDMS serum creatinine.

15.12 Known potential toxicities:

Add 7

15.121 Hematologic: Myelosuppression (neutropenia, anemia, thrombocytopenia, leukopenia)

15.122 Arthralgia, myalgia

15.123 Peripheral neuropathy

Add 7

15.124 Gastrointestinal: nausea, vomiting, diarrhea, stomatitis/pharyngitis, constipation, anorexia, mucositis, dysgeusia

15.125 Increased ALT, AST, bilirubin, alkaline phosphatase

Add 7, 14

15.126 Other: alopecia, fatigue, dyspnea, hypotension, cardiac arrhythmia, skin changes at injection site, death, pyrexia, infection, hyperphosphatemia, hypoalbuminemia, hypocalcemia, hyperglycemia, hypoglycemia, hyponatremia, hyperkalemia, hypermagnesemia, heart attack, epistaxis, xerosis, rash, paronychia, mood changes, eye problems (blurred vision, watery eyes or dry eyes), liver failure, kidney damage due to imbalance of salts or chemicals in the blood, abnormal liver function tests, allergic reaction (can include breathing difficulties, flushing, low blood pressure, rash and itching), pulmonary edema, cough. Also, rare reports of congestive heart failure and left ventricular dysfunction have been observed among individuals receiving Abraxane. Most of the individuals were previously exposed to cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history.

15.13 Drug procurement: The NCCTG research base pharmacist will obtain the drug from Abraxis Oncology. Each institution will order the drug from the NCCTG research base pharmacist. Submit the NCCTG Clinical Drug Order/Return Form request to:

Medical Oncology Pharmacist
 Mayo Clinic
 Gonda 10-178
 Rochester, MN 55905
 FAX (507) 284-3464

Add 2

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.14 Nursing guidelines:

15.141 ABI-007 is not known to cause the hypersensitivity reactions that Taxol does, secondary to the fact that ABI-007 is mixed in saline, therefore premedication is not necessary. However the patient should still be monitored closely and the infusion stopped if acute reactions occur (chest pain, back pain, flushing, diaphoresis, dyspnea, pruritus, hypotension, hypertension, bronchospasm, and/or urticaria).

15.142 Approximately 0-40% of patients may experience some degree of peripheral sensory neuropathy (numbness, tingling, burning pain, fine motor skills impairment, paresthesias, distal sensory loss) depending on the dose and schedule used. Patients receiving higher doses at shorter infusion times are at greater risk. Most cases have been reported at doses >170 mg/m²/day and with cumulative doses over multiple courses of therapy. The nerve damage may take days to months to resolve. Non-steroidal anti-inflammatory medications and opiates have not been tested with ABI-007-induced peripheral neuropathy. Consult a physician for appropriate treatment of neuropathy.

Add 11

When I am finished taking the study drugs...

Approximately 1 month after you have finished taking the study drug the following tests and exams will be done:

- History and physical exam
- Blood pressure
- Review of any side effects

Add 11

How long will I be in the research study?

You will be asked to take the study drugs until you or your doctor decide you should not continue with the study or your cancer becomes worse. After you are finished taking the study drugs, the study doctor will ask you to visit the office for follow-up exams once every 3 months for the first 2 years and then every 6 months for up to 5 years from the time you went on the study.

Can I stop being in the research study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study drugs can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what followup care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the research study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the study drugs. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the study drugs used in this study include the following:

ABI-007 (Abraxane™)

Add 7,9

Likely risks of ABI-007 (events occurring greater than 20% of the time)

- Fall in the number of white blood cells leading to a greater chance of infection (Leukopenia)
- Fall in the number of red blood cells leading to anemia (feeling tired and run down) (Anemia)
- Nausea (feeling sick to your stomach)
- Vomiting (throwing up)
- Diarrhea (loose stools)
- Constipation or difficult bowel movements
- Loss of appetite (Anorexia)
- Feeling of tiredness (Fatigue)
- Hair loss (Alopecia)
- Muscle pain (Myalgia)
- Joint pain (Arthralgia)
- Nerve damage with numbness and tingling, usually in the hands and feet (Peripheral neuropathy). This effect may go away when the drug is stopped but it may not go away for some patients.

- Changes in taste sensation (Dysgeusia)

Less likely risks of ABI-007 (events occurring less than or equal to 20% of the time)

Add
7,9,14

- Fever (which may indicate an infection) (Pyrexia)
- Fall in the number of platelets in your blood leading to a greater chance of bleeding (Thrombocytopenia)
- Sores in the mouth and/or throat leading to painful swallowing (Mucositis)
- Difficult or painful breathing caused by narrowing of the airways (Dyspnea)
- Abnormal liver function tests which may be a sign that your liver is not working properly
- Abnormalities in heart rhythm (abnormal electrocardiogram) (Arrhythmia)
- Infection
- Increased level of phosphorus in the blood (Hyperphosphatemia)
- Decreased Albumin in the blood (Hypoalbuminemia)
- Abnormally low calcium in the blood stream, that can result in muscle cramps, abdominal cramps, spasms (Hypocalcemia)
- High blood sugar (Hyperglycemia)
- Low blood sugar (Hypoglycemia)
- Decreased sodium levels in the blood (Hyponatremia)
- Elevated levels of potassium in the blood (Hyperkalemia)
- Increased magnesium in the blood (Hypermagnesemia)
- Nose bleed (Epistaxis)
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- An infection where the nail and skin meet at the side or the base of a finger or toenail, which can be painful (Paronychia)
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Rare but serious risks of ABI-007 (events occurring less than 2-3% of the time)

Add
7,9,14

- Lack of oxygen to the heart muscle which can cause damage to the heart (Heart attack)
- Liver failure
- Imbalance of salts or chemicals in the blood leading to kidney damage
- Rare reports of congestive heart failure and left ventricular dysfunction may have been observed among patients receiving Abraxane. Most of the patients were previously exposed to cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history.
- Skin changes at the site of injection
- Slowing of the heart rate (Pulse)
- Allergic reaction (symptoms can include difficulty breathing, flushing, low blood pressure, rash and itching)
- Pulmonary edema
- Cough

Avastin® (bevacizumab)

Likely risks of Avastin®

Add
2,10

- Diarrhea
- Nausea or the urge to vomit
- Vomiting
- Fatigue or tiredness
- Headache or head pain
- High blood pressure

Less likely risks of Avastin®

Add 2,10

- Lack of enough red blood cells (anemia)
- Fast heartbeat usually originating in an area located above the ventricles
- Feeling of spinning or whirling
- Belly pain
- Inflammation (swelling and redness) of the large bowel (colon)

Please read the following statements and mark your choice:

Add 14

I agree to provide a tissue sample(s) to: the laboratory of Dr. Daniel Knauer at Abraxis Health associated with NCCTG, for research testing planned as part of this study.

Yes No Please initial here: _____ Date: _____

Your research blood and tissue will be sent to laboratories associated with NCCTG, 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.

If there is left over blood and/or tissue, we would like to keep those samples for future research. If you agree, the samples will be kept and may be used in research to learn more about cancer and other diseases. Your samples may be helpful for research testing. The research that may be done with your samples may not help you but might help other people who have cancer and other diseases in the future.

Reports about research done with your samples will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Add 12

Things to Think About

The choice to let us keep the left over blood or tissue samples for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your samples can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your blood or tissue. Then any samples that remain will no longer be used for research.

In the future, people who do research may need to know more about your health. While NCCTG may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes samples are used for genetic research (about diseases that are passed on in families). Even if your samples are used for this kind of research, the results will not be put in your health records.

Your samples will be used only for research and will not be sold. The research done with your samples may help to develop new products in the future.

Benefits

The benefits of research using blood or tissue samples include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Add 12