



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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## Operations Office

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Date: December 10, 2010

To: Primary Clinical Research Associates

From: Sara M. Braun  
Research Protocol Specialist III

Re: 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

Attached are updated form(s) for this protocol. Edits are as follows:

<b>CRF Title</b>	<b>Brief Description of Edit</b>
Adverse Event Form	<ul style="list-style-type: none"><li>Added "CTCAE v3.0" to CTC Adverse Events term on all 3 pages.</li></ul>
Baseline Adverse Events Form	<ul style="list-style-type: none"><li>Added "CTCAE v3.0" to CTC Adverse Events term</li></ul>

If you have any questions, please feel free to contact me.

Thank you.

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 13 – December 10, 2010

**Summary**

- In compliance with the NCI/CTEP mandate (dated May 28, 2010), expedited adverse event reporting requirements were converted from CTCAE v3.0 to CTCAE v4.0 (affected sections 10.1 and 10.11) while routine data collection via Case Report Forms (which includes the Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form) will remain using CTCAE v3.0 (clarifications added to sections 8.1, 8.2, 8.5, 8.7, 10.22, 10.3, 10.31, and 16.3). Effective January 1, 2011, expedited reporting via AdeERS must use CTCAE v4.0 while the remainder of the data collection for legacy trials will continue to use CTCAE v3.0.
- 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 13 and a new NCI version date.

**Section 8.0** **Dosage Modification Based on Adverse Events**  
Pages 21-24: The first column headers in the Sections 8.1, 8.2, 8.5, and 8.7 tables have been revised to add CTCAE v3.0 for clarification.

**Section 10.0** **Adverse Event (AE) Reporting and Monitoring**  
Page 30: Section 10.1 and Section 10.11 have been revised as follows to update the required AE reporting from CTCAE v3.0 to CTCAE v4.0.  
10.1 ~~This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 for adverse event monitoring and reporting. The CTCAE v3.0 can be accessed from the CTEP home page <http://ctep.cancer.gov>.~~ **CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized until December 31, 2010 for AE reporting. CTCAE v4.0 will be utilized for expedited adverse event reporting only, beginning January 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE v3.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (<http://ctep.cancer.gov>).**

10.11 Adverse event monitoring and reporting is a routine part of every ...

Expedited adverse event reporting requires submission of an electronic Adverse Event Expedited Reporting System (AdEERS)...

**Effective with Addendum 13, and beginning January 1, 2011, expedited AdEERS reporting for this protocol has been updated by the NCI/CTEP to use CTCAE v4.0. Therefore;**

- 1) Events requiring expedited reporting through AdEERS must be reported through the AdEERS system in CTCAE v4.0.**
- 2) The events reported via AdEERS must ALSO be reported through routine reporting (i.e., Case Report Forms) using CTCAE v3.0.**
- 3) Routine data collection via Case Report Forms, including the "Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form", will remain using CTCAE v3.0 for this study.**

Page 31: The third bullet has been corrected in Section 10.21 as follows:  
 SECONDARY MALIGNANCIES (defined as “cancer caused by treatment for a previous malignancy,” e.g., treatment with radiation or chemotherapy) are to be reported through AdEERS using ~~“Neoplasms benign, malignant and unspecified (incl. cysts and polyps) —Other, specify”~~ **as noted in Section 10.22.**

Page 32: With the removal of the Secondary AML/MDS Report Form text has been revised in Section 10.22 for clarification as follows:

EVENT TYPE	REPORTING PROCEDURE
Secondary AML/MDS	Reporting for this event required during and after completion of study treatment via AdEERS <del>using CTCAE v3.0.</del> <b>Through December 31, 2010, continue using CTCAE v3.0:</b> Report Myelodysplasia as “Blood/Bone Marrow - Myelodysplasia” and Leukemias as “Blood/Bone Marrow - Other (Specify, __)”. <b>Beginning January 1, 2011, AdEERS will only accept CTCAE v4.0 for this study:</b> Report these events using “Neoplasms benign, malignant and unspecified (incl cysts and polyps) <del>—Other, specify”</del> <b>and including the appropriate adverse event:</b> - <b>Leukemia secondary to oncology chemotherapy OR</b> - <b>Myelodysplastic syndrome OR</b> - <b>Treatment related secondary malignancy</b>

<p>Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report</p>	<p>Complete a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form within 5 working days <b>using CTCAE v3.0</b> of the date the clinical research associate (CRA) is aware of the event(s) necessitating the form.</p> <p>If an AdEERS report has been submitted, this form does not need to be submitted.</p> <p>Submit the Non-AER form electronically via the NCCTG Remote Data Entry System within 5 working days of the date the CRA is aware of the event(s) necessitating the form.</p> <p><b>You must use CTCAE v3.0 for data submission with this form. The events reported on this form must also appear on the Case Report Forms (i.e., routine data) for this study.</b></p>
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Pages 33-34

Section 10.3 and Section 10.31 have been revised for clarification. In Section 10.3 the first column header in the chart has added (CTCAE v3.0) after the word (Category) and Section 10.31 has been revised as follows:

10.31 Submit to the NCCTG Research Base via the Adverse Event Form the following AEs **using CTCAE v3.0** experienced by a patient and not...

**Section 16.0**

**Statistical Considerations and Methods**

Page 60:

A new sentence has been added to Section 16.3 for clarification as follows:

**CTCAE v3.0 will be used to determine grading for these stopping rules.**

## 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.

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

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

NCI Version Date: November 30, 2010

## 8.0 Dosage Modifications Based on Adverse Events

Follow the modifications in this table for dose modifications. These modifications should be regarded as guidelines to produce mild-to moderate, but not debilitating side effects. If multiple toxicities are seen, administer dose based on greatest reduction required for any single toxicity observed. A total of 2 dose reductions are allowed on trial. If a patient requires a 3<sup>rd</sup> dose reduction based on adverse events, but the physician feels the patient is benefiting from treatment, the patient may remain on study at the discretion of the treating physician, otherwise the patient should be taken off study, proceed to observation and go to event monitoring per section 18.0.

**ALERT:** ADR reporting may be required for some adverse events(See Section 10.0)

### 8.1 Dose modifications for ABI-007 and carboplatin regimen based on **interval adverse events** during treatment (days 8, 15)

Use Common Terminology Criteria for Adverse Events (CTCAE) v. 3.0 unless otherwise specified.			
CTCAE v3.0 Category	Adverse Event	Agent	Dose Reduction
Blood/Bone Marrow	ANC <1000 or PLT <50,000	ABI-007	<u>Day 8</u> - Omit dose that day and retreat at same dose level on day 15 if counts have recovered. <u>Day 15</u> -Omit dose <u>that</u> day.
	PLT ≥50,000 and <75,000	ABI-007	<u>Day 8</u> -Reduce dose by one level and use reduced dose for day 15. <b>Note:</b> there is only one dose reduction per cycle. <u>Day 15</u> - reduce dose level by one dose level
Neurology	Neuropathy ≥ grade 2	ABI-007	Omit dose <u>that</u> day. If resolved to ≤grade 1 by next scheduled dose, then reduce by one dose level. If not resolved in 4 weeks, discontinue study treatment and proceed to observation and then to event monitoring.
All other non-hematologic adverse events	≥ Grade 3	ABI-007	Omit dose that day. If resolved to ≤grade 1 then resume treatment with dose reduced by one dose level. If not resolved in 4 weeks, discontinue study treatment and proceed to observation and then to event monitoring.

8.2 At time of **re-treatment with subsequent cycles** (day 1)

Add 13

Use Common Terminology Criteria for Adverse Events (CTCAE) v. 3.0 unless otherwise specified.			
CTCAE v3.0 category	Adverse Event	Agent	Dose Reduction
Blood/bone marrow	ANC < 1500 or PLT < 75,000	ABI-007 CBDCA	Hold until ANC and/or PLT above these levels. May hold treatment up to 4 weeks. Then resume treatment with dose reduced by one dose level. If not recovered in 4 weeks, discontinue study treatment and proceed to observation and then event monitoring.
AST or Alkaline Phosphatase	≥ grade 2	ABI-007	Hold until resolved to ≤grade 1 then dose reduce by one level. If not resolved in 4 weeks, discontinue study treatment and proceed to observation and then event monitoring
Neurology	Neuropathy ≥ grade 2	ABI-007 CBDCA	Hold until resolved to ≤grade 1 then resume treatment with dose reduced by one level. If not resolved in 4 weeks, discontinue study treatment and proceed to observation and then event monitoring
All other non-hematologic adverse events	≥ Grade 3	ABI-007 CBDCA	Hold until resolved to ≤grade 1 then resume treatment with dose reduced by one level. If not resolved in 4 weeks, discontinue study treatment and proceed to observation and then event monitoring.

Add 5

## 8.3 Dose reductions for ABI-007 and Carboplatin

**PRE-ADDENDUM #5 PATIENTS:** Patients enrolled PRIOR to the activation of Addendum #5 WILL BEGIN TREATMENT at dose level 0 and are allowed a maximum of 2 dose reductions (dose level -1 and dose level -2)

Dose level	Dose of ABI-007	Dose of Carboplatin
0	100 mg/m <sup>2</sup> /day	AUC 6
-1	80 mg/m <sup>2</sup> /day	AUC 5
-2	64 mg/m <sup>2</sup> /day	AUC 4

**POST-ADDENDUM #5 PATIENTS:** Patients enrolled AFTER the activation of Addendum #5 WILL BEGIN TREATMENT At dose level -1 and are allowed a maximum of 2 dose reductions (dose level -2 and dose level -3)

Dose level	Dose of ABI-007	Dose of Carboplatin
-1	80 mg/m <sup>2</sup> /day	AUC 5
-2	64 mg/m <sup>2</sup> /day	AUC 4
-3	50 mg/m <sup>2</sup> /day	AUC 3

- 8.4 If ABI-007 is temporarily held due to an adverse event (days 8 or 15), Avastin® can be continued if there are no contraindications to its administration. If ABI-007 and carboplatin are held on day one due to an adverse event, Avastin® should also be held.

- 8.5 Dose modifications for Temozolomide

Add 1,13

Use Common Terminology Criteria for Adverse Events (CTCAE) v3.0 unless otherwise specified.			
CTCAE v3.0 CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
<b><i>BASED ON INTERVAL ADVERSE EVENT</i></b>			
Blood/Bone Marrow	Hematologic: ANC <1000 or PLT <75,000	TMZ	Reduce dose by one dose level.
<b><i>AT SCHEDULED RETREATMENT</i></b>			
Blood/Bone Marrow	Hematologic: ANC <1500 or PLT <75,000	TMZ	Hold Rx until blood counts are above these levels then reduce by one dose level. If not recovered in 4 weeks, proceed to observation and then event monitoring
Other	Grade 3 or 4		Hold Rx until resolved to ≤ grade 1 then reduce by one dose level. If not resolved in 4 weeks, proceed to observation and then event monitoring.

- 8.6 Dose reductions for Temozolomide

Dose Level	Dose of temozolomide
0	200 mg/m <sup>2</sup> /day
-1	150 mg/m <sup>2</sup> /day
-2	100 mg/m <sup>2</sup> /day

If temozolomide is held on day 1, Avastin® should also be held.

## 8.7 Dose modifications for Avastin®

Add 4,13

TREATMENT MODIFICATIONS FOR AVASTIN®		
CTCAE v3.0 CATEGORY	ADVERSE EVENT	TREATMENT MODIFICATION
Allergy/immunology	Hypersensitivity reaction Grade 4	Discontinue treatment and proceed to observation and then event monitoring
Blood/bone marrow	PLT < 50,000/mm <sup>3</sup> (on day 1 of cycle)	Hold Avastin® until platelet count >75,000/mm <sup>3</sup> If not recovered in 4 weeks, proceed to observation and then event monitoring
	PLT < 50, 000/mm <sup>3</sup> (on day 15 of cycle)	Omit dose that day.
Gastrointestinal	Bowel perforation	Discontinue treatment and proceed to observation and then event monitoring
	Bowel Obstruction Grade 1	Continue patient on study for partial bowel obstruction NOT requiring medical intervention.
	Grade 2	Discontinue Avastin® for partial obstruction requiring medical intervention. Patient may restart upon complete resolution. (See Section 9.8)
	Grade 3 or 4	Discontinue Avastin® for complete obstruction. If surgery is necessary, patient will go to observation and then event monitoring. At the discretion of the treating physician, patient may restart Avastin® (off study) after full recovery from surgery (See Section 9.8)
	Fistula, GI-abdominal Any Grade	Discontinue treatment and go to observation and then event monitoring.
	Leak (including anastomotic), GI –Any grade	Discontinue treatment and got to observation and then event monitoring.
Cardiac General	Hypertension	See section 8.8 for dose modifications and management
	Other: Congestive heart failure Grade 3 Grade 4	Hold Avastin® until resolution to Grade ≤ 1 If not resolved in 4 weeks, discontinue study treatment and proceed to observation and then event monitoring  Discontinue treatment and proceed to observation and then event monitoring

## 10.0 Adverse Event (AE) Reporting and Monitoring

Add 13

- 10.1 CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized until December 31, 2010 for AE reporting. CTCAE v4.0 will be utilized for expedited adverse event reporting only, beginning January 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE v4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (<http://ctep.cancer.gov>).

- 10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE. Next, determine whether the event is expected or unexpected (refer to Section 10.12) and if the adverse event is related to the medical treatment or procedure (see Section 10.13). With this information, determine whether an adverse event should be reported as an expedited report (see Section 10.2). **Important:** All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Section 10.3 and 18.0).

Expedited adverse event reporting requires submission of an Adverse Event Expedited Reporting System (AdEERS) report(s). Other expedited reporting requirements and systems may also apply. Expedited and/or routine reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.2 and 10.3. All expedited AE reports must also be sent to the local Institutional Review Board (IRB) according to local IRB's policies and procedures.

Add 13

Effective with Addendum 13, and beginning January 1, 2011, expedited AdEERS reporting for this protocol has been updated by the NCI/CTEP to use CTCAE v4.0. Therefore;

- 1) Events requiring expedited reporting through AdEERS must be reported through the AdEERS system in CTCAE v4.0.
  - 2) The events reported via AdEERS must ALSO be reported through routine reporting (i.e., Case Report Forms) using CTCAE v3.0.
  - 3) Routine data collection via Case Report Forms, including the "Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form", will remain using CTCAE v3.0 for this study.
- 10.12 Expected vs. Unexpected
- The determination of whether an AE is expected is based on the agent-specific information provided in Section 15.0 of this protocol.
  - Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of this protocol.

### 10.13 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).  
 Probable - The adverse event *is likely related* to the agent(s).  
 Possible - The adverse event *may be related* to the agent(s).  
 Unlikely - The adverse event *is doubtfully related* to the agent(s).  
 Unrelated - The adverse event *is clearly NOT related* to the agent(s).

### 10.14 The definition of a serious adverse event (SAE) is any of the following:

- Any death that occurs while the patient is enrolled in the study including the follow-up period or within 30 days of completing the study.
- Immediately life threatening adverse event.
- Requires inpatient hospitalization.
- Prolongation of an existing hospitalization.

- Congenital anomaly/birth defect
- Medically important event\*
- Disability/incapacity (persistent or significant)

\* Medically important events that may not result in death, be life-threatening or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the experience may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

10.2 Expedited Adverse Event Reporting Requirements

10.21 Requirements for Expedited **Investigational** Reporting via AdEERS for Adverse Events That Occur Within 30 Days<sup>1</sup> of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 3		Grade 3		Grades 4 & 5
	Unexpected and Expected	Unexpected and Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unexpected and Expected
<b>Unrelated Unlikely</b>	Not Required	Not Required	Not Required <sup>2</sup>	Not Required	Not Required <sup>2</sup>	Not Required	Not Required <sup>2</sup>
<b>Possible Probable Definite</b>	Not Required	Not Required	7 Calendar Days	Not Required	7 Calendar Days	Not Required	24-Hour; 3 Calendar Days

<sup>1</sup> Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under an IND require reporting as follows:

AdEERS 24-hour notification followed by complete report within 3 calendar days for:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 4 unexpected events
- Grade 5 expected events and unexpected events

<sup>2</sup> Although expedited reporting via AdEERS is not required for hospitalizations or Grade 4 or 5 events with attribution of unlikely or unrelated, other expedited and routine reporting requirements must be adhered to. Please refer to the sections below for related instructions.

**Please see additional instructions and/or exceptions below under section entitled “Additional Instructions or Exceptions.”**

- Expedited AE reporting timelines defined:
  - “24 hours; 3 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 3 calendar days of the initial 24-hour report.
  - “7 calendar days” - A complete AdEERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.
- Any event that results in persistent or significant disability/incapacity, congenital anomaly, or birth defect must be reported via AdEERS if the event occurs following treatment with an agent under an IND.
- **SECONDARY MALIGNANCIES** (defined as “cancer caused by treatment for a previous malignancy”, e.g., treatment with radiation or chemotherapy) are to be reported through AdEERS as noted in Section 10.22. Secondary malignancies are not considered metastasis of the initial neoplasm. Secondary malignancy is unrelated to the first cancer that was treated, and may occur months or even years after initial treatment.

Note: Second Primary malignancy (malignancy **not** due to prior treatment) should not be reported through AdEERS.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all expedited reports.

**Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements**

- The NCCTG SAE Coordinator will forward a copy of all AdEERS reports to:
  - The NCCTG IND Coordinator who will notify the FDA as warranted by the event and stipulated in the U.S. Code of Federal Regulations.
  - Genentech Drug Safety Fax (650)225-4682 or (650) 225-4683
  - Abraxis BioScience, Inc., Drug Safety and Surveillance Department  
E-mail: SAE-REPORTING@abraxisbio.com
  - Abraxis Oncology, a division of AbraxisBioScience, Inc.  
E-mail: [AbraxisMedAffairs@abraxisbio.com](mailto:AbraxisMedAffairs@abraxisbio.com)
  - Schering Plough Drug Safety Surveillance (DSS) Fax: (973) 921-7422.
- In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report **MUST** be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP website and will NO LONGER be accepted.

Add 2

Add 12

Add 12,13

10.22 Other Required Expedited Reporting

EVENT TYPE	REPORTING PROCEDURE
Secondary AML/MDS	Reporting for this event required during and after completion of study treatment, via AdEERS.  Through December 31, 2010, continue using CTCAE v3.0: Report Myelodysplasia as “Blood/Bone Marrow - Myelodysplasia” and Leukemias as “Blood/Bone Marrow - Other (Specify, __)”.  Beginning January 1, 2011, AdEERS will only accept CTCAE v4.0 for this study: Report these events using “Neoplasms benign, malignant and unspecified (incl cysts and polyps)” <i>and including the appropriate adverse event:</i> - Leukemia secondary to oncology chemotherapy OR - Myelodysplastic syndrome OR - Treatment related secondary malignancy
Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report	Complete a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form within 5 working days using CTCAE v3.0 of the date the clinical research associate (CRA) is aware of the event(s) necessitating the form.  If an AdEERS report has been submitted, this form does not need to be submitted.  Submit the Non-AER form electronically via the NCCTG Remote Data Entry System within 5 working days of the date the CRA is aware of the event(s) necessitating the form.  You must use CTCAE v3.0 for data submission with this form. The events reported on this form must also appear on the Case Report Forms (i.e., routine data) for this study.

10.3 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per Common Terminology Criteria for Adverse Events (CTCAE) v3.0 grading unless otherwise stated:

Add 13

Category (CTCAE v3.0)	Adverse/Event Symptoms	Baseline	Each Evaluation
Allergy/Immunology	Allergic reaction/ hypersensitivity (including drug fever)		X
Blood/Bone Marrow	Hemoglobin	X	X
	Neutrophils/granulocytes (ANC/AGC)	X	X
	Platelets	X	X
	Leukocytes (total WBC)	X	X
Cardiac General	Hypertension	X	X
	Cardiac ischemia/infarction	X	X
Constitutional Symptoms	Fatigue (asthenia, lethargy, malaise)	X	X
	Fever (in the absence of neutropenia, where neutropenia is defined as $ANC < 1.0 \times 10^9/L$ )		X
Dermatology/Skin	Wound complication, non-infectious	X	X
Gastrointestinal	Nausea		X
	Vomiting		X
Hemorrhage/Bleeding	Hemorrhage, CNS		X
	Hemorrhage GI <ul style="list-style-type: none"> <li>• Abdomen NOS</li> </ul>		X
	Hemorrhage pulmonary/upper respiratory <ul style="list-style-type: none"> <li>• Bronchopulmonary NOS</li> </ul>		X
Infection	Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection)( $ANC < 1.0 \times 10^9/L$ , fever $\geq 38.5$ degrees C)		X
Metabolic/laboratory	Proteinuria	X	X
Neurology	Leukoencephalopathy (radiographic findings)		X
	Neuropathy: sensory	X	X
Pain	Pain <ul style="list-style-type: none"> <li>• Joint</li> <li>• Muscle</li> <li>• Pain-Abdomen NOS</li> </ul>	X	X
		X	X
		X	X
Vascular	Thrombosis/thrombus/embolism		X

Add 13

- 10.31 Submit to the NCCTG Research Base via the Adverse Event Form the following AEs using CTCAE v3.0 experienced by a patient and not specified in Section 10.3:
- 10.311 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.
- 10.312 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure
- 10.313 Grade 5 AEs (Deaths)
- 10.3131 Any death within 30 days of the patient's last study treatment or procedure.
- 10.3132 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.
- 10.32 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

## 11.0 Treatment Evaluation Using RECIST Criteria

- 11.1 Schedule of Evaluations: For the purpose of this study, tumor measurements should be reevaluated every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 8 weeks following initial documentation of objective response.
- 11.2 Definitions of Measurable and Non-Measurable Disease
- 11.21 Measurable disease is defined as at least one lesion whose longest diameter can be accurately measured as  $\geq 2.0$  cm for conventional CT and MRI, or as  $\geq 1.0$  cm for spiral CT. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However CT is preferable. 11.22 All other lesions (or site of disease), including small lesions (longest diameter  $\leq 2.0$  cm for conventional CT and MRI, or  $\leq 1.0$  for spiral CT or any lesion evaluable only by physical examination) are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.
- 11.3 Guidelines for Evaluation of Measurable Disease
- 11.31 Measurement methods: All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers. The same method of assessment and the same technique should be used

## 16.233 Immunomodulatory/angiogenesis profile of therapy.

The percent change in the number of T, B, NK and dendritic cells from pretreatment levels as well as the percent change in plasma concentrations of IL-1 $\beta$ , IL-1 $\alpha$ , IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12(p70), IL-13, IL-15, IL-17, G-CSF, GM-CSF, IFN- $\gamma$ , IP-10, MCP-1, MIP-1 $\alpha$ , MIP-1 $\beta$ , PDGF, RANTES, TNF- $\alpha$ , and VEGF will be determined. Each of these factors will be plotted against time with the points belonging to a particular individual connected. Each graph will be visually inspected for trends across time.

For each marker, the number of patients with at least a 2-fold increase/decrease in the number of cells/plasma concentration (marker specific response) after the first cycle of treatment will be determined. The marker profile of those who derived clinical benefit and those who did not will be tabled to visual compare and contrast the pattern of marker-specific response between these patient groups to find similarities and differences. For each marker, a 95% confidence interval for the difference in proportion of marker responds between those who remained PR for at least 6 months and those who did not will be constructed.

- 16.3 Monitoring: The principal investigator and the study statistician will review the study periodically (at least twice a year) to identify accrual, toxicity, and endpoint problems that might be developing. The study statistician will prepare a report containing accrual, adverse event, and efficacy data which will be submitted to the Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) on an annual basis. CTCAE v3.0 will be used to determine grading for these stopping rules.

Add 13

Enrollment will be temporarily halted to a given regimen after 5 patients have been randomized to the regimen. If 2 or more of 5 patients on a given regimen develop a grade 3 or severer non-hematologic toxicity or grade 4 or severer hematologic toxicity excluding grade 4 neutropenia and grade 4 thrombocytopenia (as these are expected toxicities that will trigger dose modification) that are considered possibly, probably, or definitely related to treatment, enrollment to the regimen will remain closed. The study team will review all adverse event data. A trial recommendation will be formulated and presented to the MCCC DSMB – the study may permanently close or may re-open to accrual after CTEP and IRB approvals of protocol/consent form modifications. If at most one patient of these 5 patients develops a grade 3 or severer non-hematologic toxicity or grade 4 or severer hematologic toxicity excluding grade 4 neutropenia and grade 4 thrombocytopenia, enrollment will be re-opened for the regimen.

Add 5

For regimen A, pre-Addendum #5 regimen B, and post-Addendum #5 regimen B: If three or more patients among the first 10 patients randomized to that regimen develops a grade 3 or severer non-hematologic toxicity or grade 4 or severer hematologic toxicity excluding grade 4 neutropenia and grade 4

## FORMS PACKET

### **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**

- Contents:
- Eligibility checklist (9/11/2009)
  - \* Forms completion instructions
  - On-study form (3/28/2008)
  - ✓ Baseline adverse events form (8/24/2010)
  - ✓ Adverse event form (8/24/2010)
  - Pretreatment RECIST measurement form (12/11/2007)
  - Active monitoring RECIST measurement form (12/5/2007)
  - Baseline blood specimen submission form (12/5/2007)
  - Active monitoring blood specimen submission form (12/5/2007)
  - Research Tissue Submission Form (11/19/2010)
  - Regimen A evaluation/treatment form (3/28/2008)
  - Regimen B evaluation/treatment form (7/20/2009)
  - End of active treatment/cancel notification form (3/2/2009)
  - Evaluation/observation form (3/28/2008)
  - Event monitoring form (1/9/2008)
  - Grade 4 or 5 non-AER reportable events/hospitalization form (2/6/2008)

✓ designates revised/new forms

\*Generic forms completion instructions are available on the NCCTG web site under “the CRA link in the Remote Registration and Data Entry section and are titled “Remote Data Entry Screen Instructions (Forms Completion).”

The specific forms instructions take precedence over the generic forms instructions, so it is very important to review them in addition to the generic forms instructions.

PLACE LABEL HERE

**NORTH CENTRAL CANCER TREATMENT GROUP**

Protocol Number: N0775

Patient ID: \_\_\_\_\_ Patient Initials: \_\_\_\_\_

L F M

Institution Number: \_\_\_\_\_

Institution: \_\_\_\_\_

**BASELINE  
ADVERSE EVENTS FORM**

**ALL ITEMS MUST BE COMPLETED**

Are data amended? (*check one*)  Yes  No  
(if data are amended, please circle in red when using paper form)

<b>Required Baseline Adverse Events from Section 10.0 of Protocol</b>		
<b>CTC Adverse Events Term (CTCAE v.3.0)</b>	<b>MedDRA Code (v.10.0)</b>	<b>CTC Adverse Event Grade</b>
Hypertension	10020772	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4
Fatigue (asthenia, lethargy, malaise)	10016256	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4
Neuropathy: sensory	10034620	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4
Pain - <i>Selects</i>		
- Joint	10023222	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4
- Muscle	10028411	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4
Hemoglobin	10019483	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4
Neutrophils/granulocytes (ANC/AGC)	10029366	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4
Platelets	10035528	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4
Leukocytes (total WBC)	10048552	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4
Proteinuria	10037020	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4
Cardiac ischemia/infarction	10028601	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4
Wound complication, non-infectious	10048031	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4

PLACE LABEL HERE

**NORTH CENTRAL CANCER TREATMENT GROUP**

Protocol Number: N0775

Patient ID: \_\_\_\_\_ Patient Initials: \_\_\_\_\_

L F M

Institution Number: \_\_\_\_\_

Institution: \_\_\_\_\_

**ADVERSE EVENT FORM**

**ALL ITEMS MUST BE COMPLETED**

Pg. 1 of 3

**Are data amended? (check one)**  Yes  No  
 (if data are amended, please circle in red when using paper form)

Current Cycle Number (adverse events associated with this cycle): \_\_\_\_\_

Evaluation Date: (mm/dd/yyyy) \_\_\_/\_\_\_/\_\_\_\_\_

CTC Adverse Event Term (CTCAE v.3.0)	MedDRA Code (v. 10.0) (must be completed)	CTC Adverse Event Grade (highest grade this cycle)  <b>INCLUDE GRADE 0's</b>	CTC AE Attribution Code (If Grade > 0)  1 = Unrelated 2 = Unlikely 3 = Possible 4 = Probable 5 = Definite	Has an adverse event expedited report been submitted?*(Enter 1 for Yes or 2 for No)
--------------------------------------	---	--	---	---

**Required Adverse Events from Section 10.0 of Protocol**

Allergic reaction/hypersensitivity (including drug fever)	10020751	0 1 2 3 4 5 (death)	1 2 3 4 5	___
Hemoglobin	10019483	0 1 2 3 4 5 (death)	1 2 3 4 5	___
Neutrophils/granulocytes (ANC/AGC)	10029366	0 1 2 3 4 5 (death)	1 2 3 4 5	___
Platelets	10035528	0 1 2 3 4 5 (death)	1 2 3 4 5	___
Leukocytes (total WBC)	10048552	0 1 2 3 4 5 (death)	1 2 3 4 5	___
Hypertension	10020772	0 1 2 3 4 5 (death)	1 2 3 4 5	___
Fatigue (asthenia, lethargy, malaise)	10016256	0 1 2 3 4	1 2 3 4 5	___
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10 <sup>9</sup> /L)	10016558	0 1 2 3 4 5 (death)	1 2 3 4 5	___
Nausea	10028813	0 1 2 3 4 5 (death)	1 2 3 4 5	___
Vomiting	10047700	0 1 2 3 4 5 (death)	1 2 3 4 5	___
Hemorrhage, CNS	10022763	0 1 2 3 4 5 (death)	1 2 3 4 5	___
<b>Hemorrhage GI - Select</b>				
- Abdomen NOS	10055291	0 1 2 3 4 5 (death)	1 2 3 4 5	___

\* See Section 10.0 of the protocol.

PLACE LABEL HERE

**NORTH CENTRAL CANCER TREATMENT GROUP**

Protocol Number: N0775

Patient ID: \_\_\_\_\_ Patient Initials: \_\_\_\_\_

L F M

Institution Number: \_\_\_\_\_

Institution: \_\_\_\_\_

**ADVERSE EVENT FORM**

**ALL ITEMS MUST BE COMPLETED**

Pg. 2 of 3

Are data amended? (*check one*)  Yes  No  
 (if data are amended, please circle in red when using paper form)

Current Cycle Number (*adverse events associated with this cycle*): \_\_\_\_\_

CTC Adverse Event Term (CTCAE v.3.0)	MedDRA Code (v. 10.0) (must be completed)	CTC Adverse Event Grade (highest grade this cycle)  <b>INCLUDE GRADE 0's</b>	CTC AE Attribution Code (If Grade > 0)  1 = Unrelated 2 = Unlikely 3 = Possible 4 = Probable 5 = Definite	Has an adverse event expedited report been submitted?*( Enter 1 for Yes or 2 for No)
---	---	---	--	---

**Required Adverse Events from Section 10.0 of Protocol**

*Hemorrhage pulmonary/upper respiratory - Select*

- Bronchopulmonary NOS	10065746	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 (death)	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	___
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10 <sup>9</sup> /L, fever ≥ 38.5° C)	10016288	<input type="checkbox"/> 0 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 (death)	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	___
Proteinuria	10037020	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 (death)	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	___
Leukoencephalopathy (radiographic findings)	10024382	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	___
Neuropathy: sensory	10034620	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 (death)	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	___

*Pain - Selects*

- Joint	10023222	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	___
- Muscle	10028411	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	___
Thrombosis/thrombus/embolism	10043607	<input type="checkbox"/> 0 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 (death)	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	___
Cardiac ischemia/infarction	10028601	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 (death)	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	___
Wound complication, non-infectious	10048031	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 (death)	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	___

\* See Section 10.0 of the protocol.

PLACE LABEL HERE

**NORTH CENTRAL CANCER TREATMENT GROUP**

Protocol Number: N0775

Patient ID: \_\_\_\_\_ Patient Initials: \_\_\_\_\_

L F M

Institution Number: \_\_\_\_\_

Institution: \_\_\_\_\_

**ADVERSE EVENT FORM**

**ALL ITEMS MUST BE COMPLETED**

Pg. 3 of 3

Are data amended? (check one)  Yes  No  
(if data are amended, please circle in red when using paper form)

Current Cycle Number (adverse events associated with this cycle): \_\_\_\_\_

Were (other) adverse events assessed during this report period?

1  Yes, and reportable adverse events occurred

3  Yes, but no reportable adverse events occurred (Stop here)

2  No (Stop here)



**Adverse Events\*\* beyond those required in Section 10.0 of the protocol. Record grade 2 with attribution of possible, probable or definite and all grade 3, 4 and 5 regardless of attribution.**

Other CTC Adverse Event Terms not listed (CTCAE v.3.0)	MedDRA Code (v. 10.0) (must be completed)	CTC Adverse Event Grade (highest grade this cycle)	CTC AE Attribution Code (If Grade > 0) 1 = Unrelated 2 = Unlikely 3 = Possible 4 = Probable 5 = Definite	Has an adverse event expedited report been submitted?*(Enter 1 for Yes or 2 for No)
	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 (death)	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	—
	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 (death)	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	—
	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 (death)	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	—
	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 (death)	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	—
	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 (death)	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	—
	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 (death)	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	—
	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 (death)	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	—
	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 (death)	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	—
	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 (death)	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	—
	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 (death)	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	—
	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 (death)	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	—

\* See Section 10.0 of the protocol.

\*\* Both hematologic and nonhematologic Adverse Events must be graded on this form as applicable.