

North Central Cancer Treatment Group

N0543: A Phase II Trial of Pharmacogenetic-Based Dosing of Irinotecan, Oxaliplatin, and Capecitabine as First-Line Therapy for Advanced Small Bowel Adenocarcinoma

Addendum 2 – February 15, 2008

Summary

- Consent form revisions due to additional reviews related to oxaliplatin investigator brochure (IB) version 8, dated May 17, 2007.
- Administrative/Editorial Changes.

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

Title page Title page has been revised to include Addendum 2 and a new NCI version date.

Protocol Resource Page

Page 2: The following personnel has been added as a contact for questions regarding protocol document, consent form, or regulatory issues:

Patricia A. Aggen
NCCTG *Research Base* Protocol Coordinator
Phone: 507/538-6232
Fax: 507/284-5280
E-mail: aggen.patricia@mayo.edu

NCCTG *Research Base* Pathology Coordinator has been revised. Helen Tollefson and Christine Maszk have been removed from the protocol and replaced as follows:

Rachael Meyers
NCCTG *Research Base* Pathology Coordinator
Phone: 507/284-5369
Fax: 507/284-9628
E-mail: meyers.rachael@mayo.edu

Section 3.0 Patient Eligibility

Page 10: Text was added to Section 3.12 for clarification as follows:
3.12 Patient willingness to provide a serum sample for analysis for celiac disease (tissue transglutaminase antibodies: **see Section 14.0**).

Section 4.0 **Test Schedule**

Page 14: Footnote 9 has had an editorial correction to one of the references located in parentheses as follows:

- 9. Blood samples for UGT1A1 genotyping and celiac disease testing are mandatory (see Sections 14.2 and 17.12). Celiac testing is a...

Section 6.0 **Registration/Randomization Procedures**

Pages 14-15: Because of a department name change, the following sections referring to Randomization Center have been changed to Registration Office as follows:

- 6.11 To pre-register a patient, call (507/284-4130) or fax (507/284-0885) a completed eligibility checklist to the **Registration Office** ~~Randomization Center~~ between 8:00 a.m. and 4:30 p.m. central...

- 6.13 Prior to accepting the pre-registration, the **Registration Office** ~~Randomization Center~~ will verify the following:

- 6.21 To register a patient, call (507/284-4130) or fax (507/284-0885) a completed eligibility checklist to the **Registration Office** ~~Randomization Center~~ between...

Section 8.0 **Dosage Modification Based on Adverse Events**

Page 23: In Section 8.1, the “At Time of Retreatment” table has been revised for clarification in the “Gastrointestinal” row as follows:

Gastrointestinal	Diarrhea		
	Grade 2		If Grade ≥2, therapy may be held for up to 2 weeks at the physician's discretion. If Grade ≥2 diarrhea after 2 weeks, discontinue therapy.
	Grade ≥3/4		If Grade ≥ 3 2 diarrhea at start of cycle, hold and check weekly then treat based on interval adverse event. If Grade ≥2 diarrhea after 2 weeks, discontinue therapy.

Section 10.0 Adverse Event (AE) Reporting and Monitoring

Page 30: In Section 10.21, under the table the second to the last bullet has been revised with a new e-mail address as follows:

For SAEs related to irinotecan, the NCCTG SAE Coordinator will forward a copy of all AdEERS reports to: Pfizer at ~~clinical~~safety MRA/SSRcasecommunications@metropolitanresearch.com (fax 1-866-997-8322).

Section 14.0 Translational/Pharmacologic Studies

Page 39: Section 14.11 has had an editorial correction as follows:

14.11 Mandatory samples for UGT1A1 and celiac testing regardless of treatment assignment include:

- Blood/Blood Products (Section 14.2 and 17.12)

Page 41: Section 14.33 has been added for clarification as follows:

14.33 When an appropriate request is submitted, the NCCTG Operations Office will forward the appropriate block/slides to Dr.Thibodeau's laboratory and the NCCTG Research Base TACMA Laboratory, Stable 13-10B, Mayo Clinic Rochester (Attn: TACMA Supervisor) for processing as outlined in Sections 14.4211 and 14.4212, respectively.

Section 15.0 Drug Information

Page 58: The following text has been added at the end of the oxaliplatin CAEPR due to review of oxaliplatin investigator brochure (IB) version 8 dated May 17, 2007:

Based on the oxaliplatin investigator brochure, dated May 17, 2007, Tumor Lysis Syndrome has been added as a potential adverse event associated with oxaliplatin.

Section 17.0 Pathology Considerations for Quality Control

Page 70: Because of a department name change, the following section referring to Randomization Center has been changed to Registration Office as follows:

17.14 Dr. Ames' laboratory UGT1A1 result will be reported in 2-3 business days from receipt of sample. Results will be faxed to the submitting institution, the NCCTG **Registration Office** ~~Randomization Center~~, and the principal investigator.

Page 72: Section 17.28 has been added for clarification as follows:

17.28 One or two slides will be identified by the reviewing pathologist for inclusion in the pathology files for this study. These slides are being stored for quality assurance purposes only and no future research will be conducted on them. All remaining diagnostic slides will be returned to the submitting institution.

Appendix I Consent Form

Page 8: Consent form risks have been revised for oxaliplatin per review of oxaliplatin investigators brochure (IB), Version 8, dated May 17, 2007 as follows:

Oxaliplatin Side Effects

Likely Common (occurring greater than 5% of the time):

- Feeling sick to your stomach (nausea)
- Throwing up
- Frequent bowel movements or loose stools (diarrhea)
- Numbness or tingling in the hands, feet, mouth and/or throat, which can be made worse with exposure to cold weather or cold drinks
- Feeling of tightness or fullness in the throat (may feel as if it is difficult to breathe or swallow)
- Fever (with or without an infection)
- Low back pain
- Hot flashes
- Lowering of the ~~number of white blood cells, red blood cells, and platelets~~ **count you have in your blood, which** ~~(may put you at risk of infection, result in increased risk of bleeding or bruising)~~ *(This risk has been separated into three separate risks – see next two risks)*
- **Lowering of the red blood cells in the blood, which may cause tiredness and shortness of breath** *(this risk separated from above risk that combined lowering of white blood cells, red blood cells, and platelets)*
- **Lowering of the white blood cell count, which may cause an increased risk of infection** *(this risk separated from above risk that combined lowering of white blood cells, red blood cells, and platelets)*
- **Abnormal liver function tests**

Less ~~common~~-likely (occurring 1% to 5% of the time):

- Soreness, redness, inflammation, or leaking of the drug into the tissue in the area where the drug is injected
- Pain and skin irritation with oxaliplatin infusion
- Loss of hair
- Redness, swelling or sores of the lips, tongue, mouth or throat.
- Redness or other rash-like skin condition
- Depression
- Anxiety
- Changes in weight
- Chills/stiffening of the muscles (rigors)
- Loss of body water (dehydration)

Page 9:

Rare, but serious (occurring less than 1% of the time):

- Nausea and vomiting associated with inactivity of the muscles in the intestines, which may require hospitalization for fluids
- Inflammation or infection of the bowel
- Confusion or other mental changes
- Feeling of imbalance (as if you might fall down)
- Rash or allergic reaction
- Change in vision (blurring)
- Hearing loss that in rare cases may be permanent
- Change in your heart beat while receiving oxaliplatin (rapid heart beat)
- ~~Abnormal~~ **Serious liver function or spleen damage is possible**
- Serious infection starting from the bowel if you have bad diarrhea and low blood counts. This may lead to death.
- Anemia and kidney damage (Hemolytic Uremic Syndrome)
- Destruction of cancer cells may damage the kidneys and change calcium levels, which may lead to the need for temporary kidney dialysis (Tumor Lysis Syndrome)
- Lung problems including cough, shortness of breath, or trouble breathing caused by scar tissue in the lungs (pulmonary fibrosis). This may be life-threatening.
- Being very tired
- Changes in blood tests measuring body salts
- Temporary decrease in vision – should be reported to your doctor
- Higher risk of blood clots
- Restlessness, muscle movements that you can't control, or extrapyramidal side effects
- **Serious infusion related allergic reaction**
- **Leukemia**

The following side effects have been reported for patients taking part in other Oxaliplatin research studies. It is not known that these side effects were related to Oxaliplatin or not:

Pages 9-10:

- Ringing in the ears
- Vertigo: fluid imbalance in the ears, causing sensation of movement even while sitting or standing still.
- Problems with infection of the eye, eye lids, or tear duct glands
- Inflammation of the nerves in the back of the eye or inflammation in the back of the eye, which could lead to problems with vision.
- Fluid in the stomach
- Constipation
- Dry mouth

- Increased passing of gas
- Bleeding from the intestine
- Ulcers
- Inflammation of the pancreas (otherwise known as pancreatitis)
- Weakness
- Flu like symptoms
- Swelling in the legs
- Infections (bacterial, fungal, viral, or other unusual infections) that could be life-threatening
- Oxaliplatin may alter accurate monitoring of warfarin
- Pain or inflammation in the joints of the back or elsewhere in the body, stomach pain, chest pain, headache
- Problems with nerve function, affecting both feeling as well as motor control (ability to move around)
- Seizures
- Problems with speech
- Bleeding into the nervous system with potential serious consequences
- Inability to fall or remain asleep
- Problems with blood in the urine
- Problems with retaining urine in the bladder
- Problems with kidney function
- Pneumonia
- Inflammation or damage to the lung, which could interfere with breathing
- Blood clots to the lung or elsewhere, which could be life-threatening
- Uncontrolled blood clotting or bleeding
- Increases/decreases in blood pressure
- Inflammation of the blood vessels

Appendix V BAP Specimen Processing Instructions

Page 1 of 1 Footnote 1 has been revised as follows for clarification:

1. Record receipt of specimens ~~in the Research Accessioning Tracking System (RATS).~~

In the second sentence of number 3, the following text was revised to reflect a name and Mayo address change:

A 3.0 mL aliquot of serum will be forwarded to Tricia **Brantner**
(8-4128)Shugart, Guggenheim **10-02 6-19** for celiac testing...