

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 3 – April 4, 2008

**Summary**

- Comprehensive Adverse Events and Potential Risks List (CAEPR) for Oxaliplatin has been removed and replaced with the standard template. CTEP/NCI does not hold the IND so the CAEPR is unnecessary.
- Administrative/Editorial Changes.

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

**Title page**

The following Study Co-Chair has been removed from the title page:  
Thorvador Halfdanarson, M.D. (Research Base, Oncology) ✓

Drug availability information has been added to the title page for consistency with the current template as follows:

**Drug Availability**

- **Pfizer: Irinotecan (IND exempt)**
- **Sanofi-Aventis: Oxaliplatin (IND exempt)**
- **Commercially available: Capecitabine**
- **NCI/DCTD Supplied Investigational Agent(s): None.**

Title page has been revised to include Addendum 3 and a new NCI version date.

**Protocol Resource Page**

Page 2: Contact information have been revised for Rachael Meyers as follows:

Rachael Meyers  
NCCTG *Research Base* Pathology Coordinator  
Phone: (507)/~~284-5369~~ **538-1760**  
Fax: (507)/~~284-9628~~ **1902**  
E-mail: [meyers.rachael@mayo.edu](mailto:meyers.rachael@mayo.edu)

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

Page 23: In Section 8.1, the “At Time of Retreatment” table in the “Gastrointestinal” row for grade 2 diarrhea had an administrative error. The second sentence in the far right column now has the number 2 added, 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 $\geq 2$ diarrhea after 2 weeks, discontinue therapy.
	Grade $\geq 3/4$		If Grade $\geq 3$ -diarrhea at start of cycle, hold and check weekly then treat based on interval adverse event. If Grade $\geq 2$ diarrhea after 2 weeks, discontinue therapy.

**Section 14.0 Translational/Pharmacologic Studies**

Page 39: Text has been added for clarification to the first paragraph, as follows:  
 The collection of blood/blood products is mandatory for the UGT1A1 and celiac testing as part of the main study. No **additional** translational...

Page 40: In Section 14.251, the following revision has occurred for consistency with the rest of the protocol:  
 14.251 Verify ALL sections of the ~~NCCTG~~ Blood Specimen Submission Form, MCLCT Requisition Form...

Page 41: In Section 14.31, the following revisions have occurred to the bulleted section for consistency and clarification (NOTE: underlined text is bolded in protocol):

- NCCTG-Tissue Specimen Submission Form
- Surgical Pathology Report
- One formalin fixed paraffin-embedded (FFPE) tumor tissue block with representative tumor. (The FFPE tumor tissue block is necessary for MSI determination.) **A corresponding H&E slide for each submitted block must be provided to permit quality assessment (QA) of each tissue. Once the QA is completed, all slides will be returned, unless specified otherwise in Section 17.28.**
- The FFPE tissue block is preferred; however, if an institution is unable to provide a tissue block, submit the following unstained slides: ~~42 slides with~~ Twelve 5-um thick sections **mounted on charged glass slides** and ~~5 slides with~~ five 10-um thick sections **mounted on uncharged glass slides**. **Label the slides with NCCTG patient ID number, accession number, and order of sections (i.e. 1-12 for the 5-um sections and 13-17 for the 10-um sections). H&E stain every 10<sup>th</sup> slide that is cut, starting with the first cut slide (i.e. slides labeled 1 and 11).** ~~The first and last 5 um slides will be used for H&E~~

~~which will be done centrally. The slide~~ **These Slides** will be reviewed under the research base's quality assessment protocol...

Page 43: The following text revisions have occurred in Section 14.421, for consistency:  
14.421 Approximately 20% of small bowel adenocarcinomas are Microsatellite Instability (MSI) positive in longitudinal studies.<sup>19</sup> We will study tumor samples for MSI and explore whether MSI status predicts response and/or outcome. Therefore, tumor tissue (from primary tumor or biopsies) will be analyzed for microsatellite instability and immunohistochemistry for hMLH1, hMSH2, ~~and~~ hMSH6 **or PMS2**. Tumor blocks will be requested...

### **Section 15.0 Drug Information**

Page 45: The following drug information for Irinotecan was removed from Section 15.1 (first 2 bullets). The first bullet was placed on the title page for consistency with the current protocol template and the second bullet was removed from the protocol, as this agent is not supplied by NCI.

- IND exempt
- ~~NSC #616348~~

Page 48: The following drug information for Oxaliplatin was removed from Section 15.2 (first 2 bullets). The first bullet was placed on the title page for consistency with the current protocol template and the second bullet was removed from the protocol, as this agent is not supplied by NCI.

- IND exempt
- ~~NSC # 266046~~

Pages 51-53: In Section 15.27, the Comprehensive Adverse Events and Potential Risks List (CAEPR) for Oxaliplatin has been removed, including the paragraph at end of CAEPR (pages 51-58) and replaced with the standard Section 15.0 template. CTEP/NCI does not hold the IND, so this CAEPR was initially placed in the protocol in error. The following text replaces the CAEPR:

**Neurotoxicity: The most commonly observed oxaliplatin toxicity is acute and cumulative neurotoxicity, observed in patients treated at doses above 100 mg/m<sup>2</sup>/cycle. This neurotoxicity has included paresthesias and dysesthesias of the hands, feet, and perioral region as well as unusual pharyngo-laryngodysesthesias characterized by a loss of sensation of breathing without any objective evidence of respiratory distress (hypoxia, laryngospasm, or bronchospasm). Oxaliplatin neurotoxicity appears to be exacerbated by exposure to cold. Patients on this study will be counseled to avoid cold drinks and exposure to cold water or air. Should a patient develop pharyngo-laryngodysesthesia, their oxygen saturation should be evaluated via a**

pulse oximeter; if normal, an anxiolytic agent should be given and the patient observed in the clinic until the episode has resolved. Because this syndrome may be associated with the rapidity of oxaliplatin infusion, subsequent doses of oxaliplatin should be administered as a 6-hour infusion (instead of the normal 2-hour infusion). Acute and cumulative neurotoxicities are dose-limiting for oxaliplatin. The acute neurotoxicity is characterized by paresthesias and dysesthesias that may be triggered or exacerbated by exposure to cold. These symptoms occur within hours of exposure and are usually reversible over the following hours or days. Cumulative doses of oxaliplatin above  $680 \text{ mg/m}^2$  may produce functional impairment characterized by difficulty performing activities requiring fine sensory-motor coordination; impairment is caused by sensory rather than motor changes.

The likelihood of experiencing neurotoxicity is directly related to the total cumulative dose of oxaliplatin administered. The relative risk of developing neurotoxicity was 10%, 50%, and 75% in patients who received total cumulative oxaliplatin doses of  $780 \text{ mg/m}^2$ ,  $1,170 \text{ mg/m}^2$ , and  $1,560 \text{ mg/m}^2$ , respectively. Both acute and cumulative neurotoxicities due to oxaliplatin have lessened in 82% of patients within 4 to 6 months, and have completely disappeared by 6 to 8 months in 41% of patients. In addition, the likelihood that neurologic symptoms will regress has been shown to correlate inversely with cumulative dose.

Clinical ototoxicity occurs in less than 1% of patients following oxaliplatin administration, and severe ototoxicity has not been reported. Other side effects reported: speech impairments, anxiety, depression, confusion, imbalance, seizures.

**Respiratory:** Among over 50,000 patients that have been treated with oxaliplatin, there have been 11 patients that have developed respiratory problems. Four deaths occurred in these 11 patients, 2 of which were due to pulmonary fibrosis. As the relationship of such toxicity to oxaliplatin cannot be confirmed, you must closely monitor patients for unexplained respiratory problems (i.e., pulmonary fibrosis, cough, dyspnea, rales, pulmonary infiltrates, hypoxia, and tachypnea) and hold oxaliplatin until interstitial lung disease is ruled out for cases of Grade  $\geq 3$ . Other side effects reported: pneumonia, inflammation or damage to lung.

**Hematologic:** Single-agent oxaliplatin generally produces only mild hematologic toxicity; no Grade 4 anemia has been reported, and less

than 1% of patients have Grade 4 neutropenia or thrombocytopenia. When oxaliplatin is combined with 5-FU/LV schedules for which myelosuppression is dose-limiting, the resulting toxicity is greater than that observed with the 5-FU/LV regimen alone. The bolus infusion of oxaliplatin/5-fluorouracil/leucovorin may increase the risk of developing life-threatening enteric sepsis secondary to neutropenia and diarrhea. Patients with grade 4 ANC and grade 3 diarrhea should be monitored closely and hospitalization considered for appropriate hydration; treatment with antibiotics, appropriate for gram negative or anaerobic sepsis, should be instituted for fever or clinical deterioration. Patients should be monitored closely and provided with aggressive supportive care until neutropenia and diarrhea resolve. Other side effects reported: intestinal bleeding, blood clotting or bleeding problems, proteinuria.

**Gastrointestinal:** Nausea and vomiting are common side effects of oxaliplatin treatment and require premedication with antiemetic medications (anti-5HT<sub>3</sub> medications are effective). Diarrhea is also common, and occurs in 44% of patients treated with single-agent oxaliplatin and 68% of those treated with oxaliplatin plus 5-FU/LV. The addition of oxaliplatin to the regimen produces a significant increase in both the frequency and severity of diarrhea and mucositis usually expected in patients receiving 5-FU/LV on an infusion schedule. Grade 1-2 elevation of liver enzymes is common during oxaliplatin therapy. Elevation of liver enzymes is often associated with hepatic metastases. Other side effects reported: ascites, dry mouth, constipation, flatulence, inflammation or infection of the bowel, Hemolytic Uremic Syndrome, pancreatitis, ulcers.

**Cutaneous:** Erythema or skin eruptions are uncommon with single agent oxaliplatin, and the incidence of alopecia is <2%. The incidence of cutaneous toxicity is much higher in combination with 5-FU (overall - 22%; Grade 3 & 4 - 2%). When oxaliplatin in combination with 5-FU is administered by infusion, the incidence of alopecia is higher (6% overall; Grade 3 & 4 - 2%).

**Allergic Reactions:** Other platinum compounds are associated with allergic reactions, but such reactions have been uncommon with oxaliplatin and have varied from rashes to anaphylaxis. Severe allergic reactions were reported in 0.5% of patients during clinical development. One patient has died of an anaphylactic-like reaction. In all other known cases, the reaction resolved with symptomatic treatment.

**Other:** Other toxicities associated with oxaliplatin have been mild. They include fever (with or without infection) in 15% of patients receiving monotherapy and 5% of those receiving oxaliplatin in combination therapy. Transient decreased vision has been reported in <0.1% of patients. No significant cardiac toxicity has been observed in patients treated with oxaliplatin. Three patients experienced reversible supraventricular arrhythmias during oxaliplatin administration; one of these patients tolerated additional cycles of oxaliplatin with a recurrence of the arrhythmia. Few cases of phlebitis or extravasation have been observed. Tumor Lysis Syndrome has been reported in a few patients treated with oxaliplatin. This complication may lead to the need for kidney dialysis, usually on a temporary basis. Fatigue and hyponatremia have also been reported. Other side effects reported: pain or inflammation in back, joints, chest, or stomach; headache; insomnia; weight changes; rigors/chills; spleen damage; leukemia; eye infections or infections (bacterial, fungal, viral); edema; sleep difficulties; changes in blood pressure; kidney function difficulties; urinary retention.

Page 57: The following drug information for Capecitabine was removed from Section 15.3 (first 2 bullets). The first bullet was placed on the title page for consistency with the current protocol template and the second bullet was removed from the protocol, as this agent is not supplied by NCI.

- IND Exempt
- ~~NSC # 712807~~

**Section 17.0 Pathology Considerations for Quality Control**

Page 66: In Section 17.12, the following revisions have occurred in the second paragraph for clarification (NOTE: “Pharmacogenetic Sample Form” was inadvertently left in the protocol):

With every sample, **in addition to the MCLCT Requisition Form and Blood Specimen Submission Form**, ~~the Pharmacogenetic Sample Form~~, the first section of the UGT1A1 Submission/Results Form should...

Page 67: In Section 17.2 the first paragraph has been modified for clarification as follows (NOTE underlined is bolded in protocol):

Review **to confirm diagnosis** is being performed by an external...