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swog.org

Distribution Date: April 1, 2015
E-mailed Date:: March 16, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1201,** "A Randomized Phase II Pilot Study Prospectively Evaluating Treatment for Patients Based on ERCC1 (Excision Repair Cross-Complementing 1) for Advanced/Metastatic Esophageal, Gastric or Gastroesophageal Junction (GEJ) Cancer." Study Chairs: Drs. S Iqbal and H-J Lenz.

STATUS NOTICE

Study Chair: Syma Iqbal, M.D.
Phone: 323/865-3907
E-mail: iqbal@usc.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

PERMANENT CLOSURE

The above-referenced study has met its accrual goal and will permanently close to accrual **effective April 1, 2015 at 11:59 p.m. Pacific**.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Katherine A. Guthrie, Ph.D.
Shannon McDonough, M.S.
Cathryn Rankin, M.S.
Stephanie Edwards
Christine McLeod
Brian Zeller
Miriana Moran Ph.D. – Response Genetics Inc.

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Distribution Date: May 15, 2014
CTEP Submission Date: April 28, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1201,** "A Randomized Phase II Pilot Study Prospectively Evaluating Treatment for Patients Based on ERCC1 (Excision Repair Cross-Complementing 1) for Advanced/Metastatic Esophageal, Gastric or Gastroesophageal Junction (GEJ) Cancer." Study Chairs: Drs. S Iqbal and H-J Lenz.

REVISION #5

Study Chair: Syma Iqbal, M.D.
Phone: 323/865-3907
E-mail: iqbal@usc.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #5

The above referenced protocol has been revised as follows:

1. The version date has been updated in the protocol and consent form.

2. Title Page, Pages 1-3: The NCT number has been added below the title. "IND-Exempt Agents:" has been added below the "Agents" heading. "STUDY COORDINATORS" has been changed to "STUDY CHAIRS". Under Biostatisticians, Jacqueline Benedetti's name and e-mail have been replaced with Katherine A. Guthrie (kguthrie@fhcrc.org). The participants list has been removed and the new NCI approved participant table has been added to the bottom of Page 1. The Table of Contents has been updated and moved to Pages 2-3, subsequent pages have been renumbered accordingly.

3. CTSU information, Page 4: The CTSU address and contact information table has been updated with the new standard table.

4. Section 1.0, Page 6: Section headings have been added. Subsequent sections have been renumbered accordingly.

5. Section 3.0, Page 11: Information regarding Investigator Brochures for commercial drugs in this protocol has been added.

6. Section 3.5, Pages 21-27: Information regarding the CAEPR and SPEER has been removed. Sites should reference the package insert or manufacturer website for the most complete and up to date information. The version date has been removed from the top of the table and the "SPEER" column has been removed from the table. In the first footnote below the table, information about updates being distributed to all Principal Investigators has been removed as CTEP is no longer updating this information.

7. Section 5.0, Pages 30-32: Section headings have been added and subsequent sections have been renumbered accordingly.

8. Section 5.3e, Page 31: This section was added to require prestudy history and physical within 28 days prior to registration.

9. Section 5.4, Page 32: "Or their legally authorized representative" has been added after "patients".

10. Section 6.0, Page 33: Sections 6.1 and 6.2 have been renumbered to Sections 6.0a and 6.0b, respectively.

11. Sections 7.3-8.4f, Pages 33-40: Due to formatting changes, Section 7.3 and subsequent sections have been redistributed across Pages 34-40.

12. Sections 7.5-7.6, Page 35: Section headings have been added.

13. Section 8.1, Page 35: Section heading "NCI Common Terminology Criteria for Adverse Events" has been added.

14. Sections 8.5-8.7, Pages 42-43: Section headings have been added.

15. Section 8.7, Page 43: The reference to Study Coordinator has been changed to Study Chair and the reference to AdEERS has been changed to CTEP-AERS.

16. Section 9.1, Pages 44-45: The "~" was added to the calendar under prestudy history and physical exam and to the footnote section requiring the prestudy history and physical be obtained within 28 days prior to registration.

17. Section 9.2, Pages 46-47: The "~" was added to the calendar under prestudy history and physical exam and to the footnote section requiring the prestudy history and physical be obtained within 28 days prior to registration.

18. Sections 11.1-11.5, Pages 52-54: Section headings have been added. Previous Sections 11.2 and 11.3 have been combined, 11.4 and 11.5 have been combined, and 11.6-11.8 have been combined. Subsequent subsections have been renumbered accordingly.

19. Sections 13.1-13.3, Pages 54-55: Section headings have been added.

20. Section 13.4, Page 56: Information regarding the affirmation of eligibility has been added to the first sentence of the first bullet.

21. Section 13.6, Page 57: Section heading has been added.

22. Sections 14.1-14.2, Page 57: Section headings have been added.

23. Section 14.2, Page 57: SWOG standard information regarding the Master Forms has replaced outdated information.

24. Section 14.3c, Page 58: The Page number for the CTSU Participation Table has been updated from Page 2 to Page 4.

25. Sections 15.1-15.2, Pages 59 and 62: Section headings have been added. In Section 15.1a, the reference to Section 5.4 has changed to Section 5.2a.

26. Section 16.0, Page 63: The SWOG standard confidentiality information has been added below the "Monitoring" paragraph.

27. Section 16.1a, Page 63: The reference to "Appendix #" has been corrected to "Appendix 18.1".

28. Section 16.1b, Page 63: References to AdEERS have been updated to CTEP-AERS. The link for the NCI's guidelines has been updated. In the second paragraph, the sentence regarding paper AdEERS forms has been removed.

29. Section 16.1e, Page 64: The reference to AdEERS has been updated to CTEP-AERS. Due to formatting changes, this section has been displaced from Page 63 to 64.

30. Table 16.1, Page 64: References to AdEERS have been updated to CTEP-AERS throughout the table and footnotes.

31. Section 16.1f, Pages 64-65: This section has been added to include information regarding reporting pregnancy, fetal death, and death neonatal. Subsequent pages have been renumbered accordingly.

32. Section 18.0, Pages 68, 69 and 71-73: The Master Forms Set has been removed from the protocol and is now available on the **S1201** abstract page on the SWOG website (www.swog.org). Appendix 19.0 has been moved to 18.0; subsequent sections have been renumbered accordingly.

Institutions **should** update their local consent forms to include the changes to the Model Consent Form. SWOG considers that the Model Consent Form changes **do not** represent an alteration in risk/benefit ratio. Therefore, local accrual does **not** need to be suspended pending implementation of these changes. Patients need not be informed of the following changes unless required by the local IRB.

33. Model Consent Form, Page 3: Section references in the note to sites have been updated.

34. Model Consent Form, Page 14: Under "What are the costs…" in the fourth paragraph, the link for information about clinical trials and insurance coverage has been updated.

35. Model Consent Form, Page 18: “(or legally authorized representative)” was added below the Participant signature line.

Replacements are included for those pages listed above. Attach this memorandum to your copy of the protocol, insert the replacement pages, and forward to your Institutional Review Board (IRB) for review.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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January 1, 2013

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TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL INVESTIGATORS AND CLINICAL RESEARCH ASSOCIATES

FROM: SWOG Operations Office

RE: Eligibility Affirmation

MEMORANDUM

By signing the FDA 1572, every SWOG investigator has agreed to conduct studies in compliance with the protocol, and to personally conduct or supervise the investigation. A critical step in this process is verification of patient eligibility.

Effective January 1st, 2013, every registering investigator or another SWOG investigator designate is required to sign a statement on the Registration Worksheet that the eligibility criteria have been confirmed. This worksheet will not be submitted to Data Operations Office but must be maintained at the local institution for review during audits.

As part of this transition, forms and the forms list (Section 18.2) are being removed from active studies and will be posted separately on the individual protocol abstract page for each study. Subsequent pages have been renumbered accordingly. No other form, protocol, or consent form changes have been made as part of the transition.

If you have any questions, please contact the SWOG Operations Office at 210/614-8808.

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swog.org

Distribution Date: August 1, 2012
CTEP Submission Date: July 27, 2012

TO: ALL SWOG GROUP MEMBER, CCOP, AND AFFILIATE MEDICAL ONCOLOGISTS; CTSU

FROM: Kimberly F. Kaberle, Protocol Coordinator

RE: **S1201,** "A Randomized Phase II Pilot Study Prospectively Evaluating Treatment for Patients Based on ERCC1 (Excision Repair Cross-Complementing 1) for Advanced/Metastatic Esophageal, Gastric or Gastroesophageal Junction (GEJ) Cancer." Study Coordinators: Drs. S Iqbal and H-J Lenz.

REVISION #4

Study Coordinator: Syma Iqbal, M.D.
Phone: 323/865-3907
E-mail: iqbal@usc.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #4

The above referenced protocol has been revised as follows:

1. Title page: The version date has been updated.

2. Section 5.3, Page 28: This section has been revised to clarify that an additional tissue submission is required if HER-2 expression has not been tested prior to registration. In the first and second sentences, "patient consent" has been changed to "registration".

3. Section 5.4, Page 28: "This tumor specimen will also be used to assess HER-2 (if not already performed)" has been removed as an additional specimen is required for HER-2 expression testing.

4. Section 15.1, Page 53: The section title has been updated to include HER-2.

5. Section 15.1a.1a, Page 53: "Uncharged" has been changed to "charged".

6. Section 15.1a.1c, Page 53: This section has been added to include tissue sections for HER-2 testing if patient has not already had HER-2 testing done prior to registration.

Replacements are included for those pages listed above. Attach this memorandum to your copy of the protocol, insert the replacement pages, and forward to your Institutional Review Board (IRB) for review.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Jacqueline K. Benedetti, Ph.D.
Shannon McDonough, M.S.
Cathryn Rankin, M.S.
Stephanie Edwards
Christine McLeod
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Distribution Date: June 15, 2012
CTEP Submission Date: May 29, 2012

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swog.org

TO: ALL SWOG GROUP MEMBER, CCOP, AND AFFILIATE MEDICAL ONCOLOGISTS; CTSU

FROM: Kimberly F. Kaberle, Protocol Coordinator

RE: **S1201,** "A Randomized Phase II Pilot Study Prospectively Evaluating Treatment for Patients Based on ERCC1 (Excision Repair Cross-Complementing 1) for Advanced/Metastatic Esophageal, Gastric or Gastroesophageal Junction (GEJ) Cancer." Study Coordinators: Drs. S Iqbal and H-J Lenz.

REVISION #3

Study Coordinator: Syma Iqbal, M.D.
Phone: 323/865-3907
E-mail: iqbal@usc.edu

IRB Review Requirements

( ) Full board review required. Reason:
( ) Initial activation (should your institution choose to participate)
( ) Increased risk to patient
( ) Complete study redesign
( ) Addition of tissue banking requirements
( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #3

The above referenced protocol has been revised as follows:

1. Title page: The version date has been updated.

2. Section 5.1, Page 28: "or have brain metastases" has been added to the last sentence to exclude patients with brain metastases.

3. Section 15.1d.1g, Page 54: The Response Genetics, Inc. contact has been updated from Yolanda Echeverria to Nathalie Kertesz.

4. Section 15.1d.2, Page 54: The contact name has been removed and the e-mail address has been updated to S1201@responsegenetics.com.

Replacements are included for those pages listed above. Attach this memorandum to your copy of the protocol, insert the replacement pages, and forward to your Institutional Review Board (IRB) for review.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Jacqueline K. Benedetti, Ph.D.
Shannon McDonough, M.S.
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Distribution Date: May 1, 2012
CTEP Submission Date: April 26, 2012

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swog.org

TO: ALL SWOG GROUP MEMBER, CCOP, AND AFFILIATE MEDICAL ONCOLOGISTS; CTSU

FROM: Kimberly F. Kaberle, Protocol Coordinator

RE: **S1201,** "A Randomized Phase II Pilot Study Prospectively Evaluating Treatment for Patients Based on ERCC1 (Excision Repair Cross-Complementing 1) for Advanced/Metastatic Esophageal, Gastric or Gastroesophageal Junction (GEJ) Cancer." Study Coordinators: Drs. S Iqbal and H-J Lenz.

REVISION #2

Study Coordinator: Syma Iqbal, M.D.
Phone: 323/865-3907
E-mail: iqbal@usc.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #2

The above referenced protocol has been revised as follows:

1. Title page: The version date has been updated. Under "Statisticians", Bryan Goldman has been removed and replaced with Shannon McDonough, M.S. (smcdonou@fhcrc.org).

2. CTSU Information, Page 2: Under "For patient eligibility questions" the e-mail address has been updated to giquestion@crab.org.

3. Section 5.12, Page 29: The following sentence was added to the end of this section: All palliative radiation therapy alone must be completed at least 14 days prior to registration.

4. Section 5.13, Page 29: The definitions for reproductive potential and effective contraception have been added for clarification.

5. Section 7.3, Page 30: In the Arm 1 table under “Route”, “over 1 hr” has been removed from the 5-FU IV bolus line. The following was added to the ** footnote at the bottom of the table: “…the dosage may be reduced to 20 mg/m^2 or…”.

6. Section 8.4b, Page 36: In the “NOTE”, the reference to Sections 8.4d-8.4k has been corrected to Sections 8.4e-8.4f.

7. Model Consent Form, Page 64: "over one hour" has been removed from the sixth sentence under the Arm 1 heading.

8. Model Consent Form, Page 68: “Decreased number of a type of white blood cell (lymphocyte)” has been removed from the Less Likely section for Arm 1 as it is already listed in the Likely section.

Replacements are included for those pages listed above. Attach this memorandum to your copy of the protocol, insert the replacement pages, and forward to your Institutional Review Board (IRB) for review.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Jacqueline K. Benedetti, Ph.D.
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Distribution Date: March 15, 2012
CTEP Submission Date: March 1, 2012

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TO: ALL SWOG GROUP MEMBER, CCOP, AND AFFILIATE MEDICAL ONCOLOGISTS; CTSU

FROM: Kimberly F. Kaberle, Protocol Coordinator

RE: **S1201,** "A Randomized Phase II Pilot Study Prospectively Evaluating Treatment for Patients Based on ERCC1 (Excision Repair Cross-Complementing 1) for Advanced/Metastatic Esophageal, Gastric or Gastroesophageal Junction (GEJ) Cancer." Study Coordinators: Drs. S Iqbal and H-J Lenz.

REVISION #1

Study Coordinator: Syma Iqbal, M.D.
Phone: 323/865-3907
E-mail: iqbal@usc.edu

IRB Review Requirements

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- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #1

The above referenced protocol has been revised as follows:

1. Title page: The version date has been updated.

2. Section 15.1a.1, Page 53: A sentence has been added to the end of this section to include submission of slides in the event that a tumor block cannot be released. 15.1a.1a and 15.1a.1b have been added to include the specific slides that are required if a tumor block cannot be submitted.

3. Section 15.1b, Page 53: "or slides" has been added after "block" in the last sentence of the paragraph.

4. Section 15.1d.2c, Page 54: “or slides are” has been added after “block” in the second sentence of the paragraph. The alignment of this paragraph has been corrected.

5. Section 15.2a.2, Pages 55-55a: “or slides” has been added after “tumor block”.

   Page 55a was added to prevent extensive repagination.

Replacements are included for those pages listed above. Attach this memorandum to your copy of the protocol, insert the replacement pages, and forward to your Institutional Review Board (IRB) for review.

This memorandum serves to notify the NCI and SWOG Statistical Center.

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Distribution Date: February 15, 2012
E-mailed Date: February 8, 2012

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TO: ALL SWOG GROUP MEMBER, CCOP, AND AFFILIATE MEDICAL ONCOLOGISTS; CTSU

FROM: Kimberly F. Kaberle, Protocol Coordinator

RE: **S1201,** "A Randomized Phase II Pilot Study Prospectively Evaluating Treatment for Patients Based on ERCC1 (Excision Repair Cross-Complementing 1) for Advanced/Metastatic Esophageal, Gastric or Gastroesophageal Junction (GEJ) Cancer." Study Coordinators: Drs. S Iqbal and H-J Lenz.

STATUS NOTICE

Study Coordinator: Syma Iqbal, M.D.
Phone: 323/865-3907
E-mail: iqbal@usc.edu

IRB Review Requirements

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- ( ) Study closure due to new risk information

( ) Expedited review allowed

( ) No review required

ACTIVATION

The study referenced above is now open for participation. The entire protocol is attached for your use.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Jacqueline K. Benedetti, Ph.D.
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Rodney Sutter

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

Activated February 8, 2012

SWOG

A RANDOMIZED PHASE II PILOT STUDY PROSPECTIVELY EVALUATING TREATMENT FOR PATIENTS BASED ON ERCC1 (EXCISION REPAIR CROSS-COMPLEMENTING 1) FOR ADVANCED/METASTATIC ESOPHAGEAL, GASTRIC OR GASTROESOPHAGEAL JUNCTION (GEJ) CANCER

NCT #01498289

STUDY CHAIRS:

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IND Exempt Agents:
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Docetaxel (Taxotere®) (RP56976) (NSC-628503)
Irinotecan (CPT-11) (NSC-616348)
Leucovorin Calcium (NSC-3590)
Oxaliplatin (Eloxatin®) (NSC-266046)

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NRG/NRG Oncology

NCIC-CTG/NCIC Clinical Trials Group

SWOG/SWOG

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA19103 Fax: 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org For more information, call the CTSU Help Desk at 888-823-5923 or the Regulatory Help Desk at 866-651-CTSU.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Online Data Submission: Institutions participating through CTSU are required to submit and amend their data electronically via Online Data Submission. Access the SWOG Workbench using your CTSU userid and password at the following url: https://crawb.crab.org/TXQWB/ctsulogon.aspx. Exceptions: Data items that are not available for online submission (operative and pathology reports, patient completed forms, scan reports, etc.) may be submitted by fax at 800-892-4007. Do not submit data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.

For patient eligibility questions contact the SWOG Data Operations Center by phone or email:

206-652-2267
giquestion@crab.org

For treatment or toxicity related questions contact the Study PI of the Coordinating Group.

For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail:

CTSU General Information Line:
888-823-5923
ctsucontact@westat.com

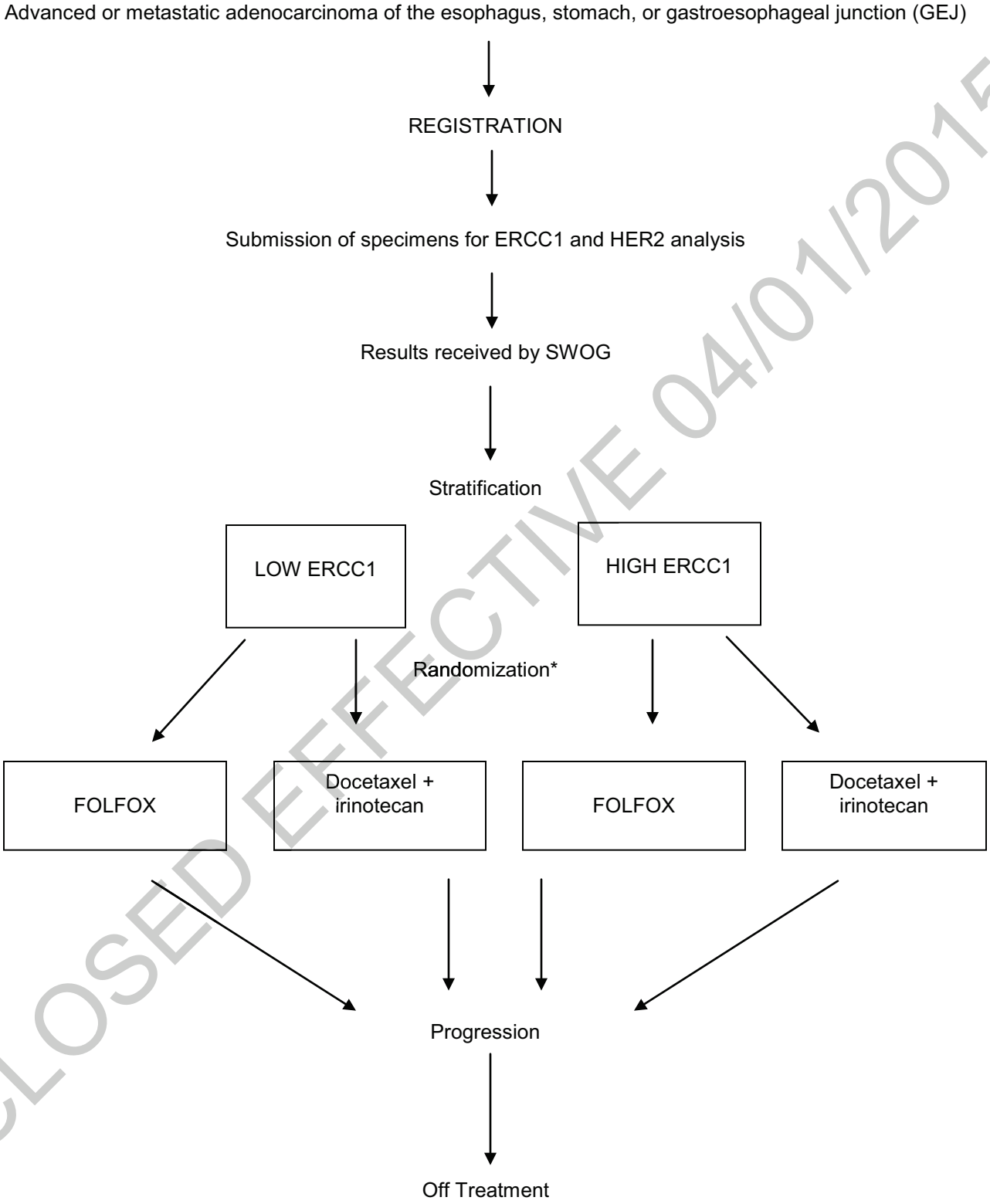
All calls and correspondence will be triaged to the appropriate CTSU representative.

For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website:

https://www.ctsu.org > education and resources tab > CTSU Operations Information >CTSU Regulatory and Monitoring Policy

The CTSU Web site is located at https://www.ctsu.org

SCHEMA



* Sites will be informed via e-mail of patient's treatment assignment (see Section 15.1).

1.0 OBJECTIVES

1.1 Primary Objectives

a. To assess progression-free survival in high-ERCC1 patients with advanced or metastatic cancer of the esophagus, stomach, or GEJ treated with FOLFOX compared to those treated with irinotecan plus docetaxel.

b. To assess progression-free survival in low-ERCC1 patients with advanced or metastatic cancer of the esophagus, stomach, or GEJ treated with FOLFOX compared to those treated with irinotecan plus docetaxel.

c. To assess progression-free survival in low-ERCC1 patients with advanced or metastatic cancer of the esophagus, stomach, or GEJ treated with FOLFOX compared to high-ERCC1 patients treated with FOLFOX.

d. To assess overall survival and toxicities in each of the two treatment arms in this group of patients.

1.2 Other Objectives

a. To assess the response probability (confirmed and unconfirmed, complete and partial responses) in the subset of patients with measurable disease in each of the two treatment arms.

b. To explore whether there is evidence of interaction between treatment arm and ERCC1 expression in this group of patients.

c. To bank tissue and blood for future translational medicine studies.

1. To explore the relationship of ERCC-1 and ERCC-2 single nucleotide polymorphism (SNP) genotypes with clinical outcome in these patients.

2. To explore the association between germline variations in these SNPs and ERCC-1 mRNA expression in these patients.

2.0 BACKGROUND

Treatment Overview of Inoperable Gastric Cancer

In 2010 there were 37,640 cases of gastric and esophageal cancer diagnosed in the United States with over 25,000 deaths. *(1)* Most patients with upper GI cancers are diagnosed with advanced disease. Even patients who have curative surgical approaches have a high incidence of recurrence. *(1)* Many chemotherapeutic drugs have demonstrated single-agent activity in advanced disease, including fluoropyrimidines, platinums, CPT-11, taxanes and adriamycin. Combinations have been shown to be more effective than single agent chemotherapy. Although response rates with cytotoxic combinations range from 30 to 50%, there can be significant toxicity associated with these regimens, and median survival remains largely between 6 and 9 months, with progression free survival in the 4 to 5 month range. Newer combination targeted therapies have offered some increased benefit to a small population. Given the limitations of traditional therapies and promising preliminary data with targeted therapeutics, novel agents are being investigated. Nevertheless, there is no clear standard regimen for this disease. There are data regarding identification of potential markers of response and survival to chemotherapeutic treatment with fluorouracil and platinum compounds, which may help tailor treatment and rationally choose agents based on individual tumors.

ERCC1 (Excision Repair Cross-Complementing 1)

The nucleotide excision repair (NER) pathway is a recognized DNA repair pathway that has been identified to repair bulky, helix-distorting DNA lesions caused by UV light or chemicals, including platinum compounds. The cytotoxic effect of platinum compounds is based on the formation of these bulky instrastrand platinum-DNA adducts and removal of these adducts from genomic DNA is mediated by the NER pathway. *(2)* Recognition and repair of the platinum-induced damage results in platinum resistance. Critical in this pathway is the ERCC1 gene (and protein) and low expression has been associated with platinum sensitivity. Several studies across tumor types have evaluated ERCC1 mRNA levels and potential response to outcome in patients treated with platinum compounds.

ERCC-1 and Primary Gastric Cancer (Cisplatin + 5-FU)

ERCC1 has shown a statistically significant relationship to response and survival in patients with advanced gastric cancer. *(3)* In a retrospective evaluation of patients with gastric cancer patients eligible for preoperative cisplatin and infusional 5-FU, cDNA derived from the primary gastric cancer before chemotherapy was used was evaluated to assess ERCC1 mRNA levels by PCR. Thirty-three of 38 tumor samples were assessable for response. Of the patients responding (17), 13 (76%) were less than or equal to 5.8 X 10^{-3}/β actin and 4 were greater, p=0.003. The median survival for the patients with ERCC1 mRNA levels ≤ 5.8 x 10-3 had not been reached at the time of publication vs. 5.4 months (p=0.03) for those with levels above this value. The median TS mRNA level also separated responsive vs. resistant tumors; 3.7 x 10-3 was a cut-off determined. In an evaluation of both TS mRNA and ERCC1, 11 of 13 patients (85%) responded, p=0.003. *(3)*

ERCC-1 and Esophageal Adenocarcinoma (Oxaliplatin and 5-FU)

The SWOG neoadjuvant esophageal cancer trial, **S0356** tested a preoperative treatment regimen consisting of oxaliplatin Days 1, 15 and 29 with protracted-infusion 5-FU (PI-5-FU) administered continuously Days 8-43 with 4,500 cGy external beam radiation (EBRT). *(4)* Surgical resection took place four to six weeks after the completion of therapy. The PCR rate was 28.5% and median overall survival was just under three years. Progression free survival was 20 months. Of the 90 patients evaluable for this trial, 53 specimens (58.8%) were analyzed for ERCC1 as well as several other genes of interest. ERCC-1 mRNA levels within the primary tumor had a statistically significant inverse relationship to two-year overall survival (37 vs. 67%, p=0.04) and two-year progression free survival (17 % vs. 72%, p<0.002). The cut off level was 1.66, consistent with the previously reported 1.7. No other gene expression or polymorphism tested in **S0356** had a statistically significant relationship to overall or progression free survival. *(5)* (Accepted for publication in JCO)

ERCC-1 and NSCLC (Non-Small-Cell Lung Cancer) (Cisplatin Doublet)

Cobo and colleagues evaluated patients with NSCLC and prospectively assigned chemotherapy based on quantitative assessment of ERCC1. In 444 patients with metastatic NSCLC, RNA was isolated from pretreatment biopsies and quantitative real time reverse transcriptase PCR assays were performed to determine ERCC1 mRNA expression. Patients were randomly assigned in a 1:2 ratio to either control or genotypic experimental arm before ERCC1 assessment was done. The control arm was docetaxel and cisplatin; in the experimental/genotypic arm, patients with low ERCC1 levels received docetaxel plus cisplatin and patients with high ERCC1 levels received docetaxel and gemcitabine (a non-platinum compound). Of the 346 assessable for response, 53 (39.3%) patients had a response in the control arm and 107 (50.7%) patients had a response in the experimental/genotypic arm, (p=0.02). Response rate was the primary endpoint of the study. Patients who were assigned chemotherapy based on ERCC1 had significantly higher response rates than the control group making this the first clinical trial demonstrating that assigning therapy using gene expression could increase the benefit of chemotherapy for patients with NSCLC. Although there was no significant difference in PFS or OS, the primary endpoint of the trial was RR. *(6)* This study demonstrated the feasibility of pursuing such a design.

ERCC-1 and Colorectal Cancer (Oxaliplatin and 5-FU)

In patients with colorectal cancer, Shirota et al. showed that gene expression of TS and ERCC1 are associated with response and survival in patients treated with 5-FU and oxaliplatin. *(7)* They evaluated 50 patients with Stage IV colorectal cancer and found gene expression of ERCC1 and TS independently correlated with outcome to treatment with FOLFOX. Patients with high ERCC1 had lower response rates and median overall survival compared with those with low ERCC1. *(7)*

Further, Grimminger recently published TS and ERCC-1 mRNA expression from patients with metastatic colorectal cancer who participated in CONFIRM-1, treatment with PTK787 with FOLFOX4. To validate established cutoff levels of ERCC1, 122 samples of patients with metastatic colorectal cancer were evaluated. They demonstrated ERCC-1 was associated with overall survival and the ERCC1 level of 1.73 was the cutoff. *(8)*

ERCC1 Established Cut-Off

Table 1: ERCC1 gene expression levels associated with clinical outcome in lung, colorectal and gastric cancer clinical trials.

Clinical Study	ERCC1 Threshold for Platin Sensitivity	Percent Patients with Low ERCC1	Benefit	Ref
NSCLC: GILT (Platin Doublets)	ERCC1<1.7	53	RR=53%	*6*
NSCLC: MADeIT (Platin Doublets)	ERCC1<1.44	50	RR=44%, Increased Survival	*9*
CRC: FOLFOX	ERCC1<1.7	80	Increased Survival and Response	*7*
CRC: FOLFOX Validation	ERCC1<1.7	80	Increased Survival	*10*
CRC: CapeOX	ERCC1<3.4	91	Increased TTF	*11*
Gastric: 5-FU/Cis	ERCC1<1.46	50	Increased Survival	*3*
Gastric: FOLFOX	ERCC1<2.2	80	Increased Survival	*12*
Gastric: Platin (S-1/Oxaliplatin)	ERCC1<1.85	67	Increased RR and Survival	*13*
Esophageal:DCF	---	38	NS for RR	*14*
Esophageal	ERCC1<1.1	36	Increased RR	*15*
Esophageal	ERCC1<3.0	99	Increased OS	*16*
Esophageal: 5FU/Oxali	ERCC1<1.66	55	Increased 2 yr PFS and OS	*5*

In defining a threshold for ERCC-1 expression that imparts resistance to platinum-based chemotherapies, a review of studies in gastric, colon, ovarian, non-small cell lung, and head/neck cancers showed that the median level of ERCC-1 mRNA expression was typically between 1.4–1.8 × 10–3 (relative to expression of β-actin). Patients harboring tumors with ERCC-1 mRNA levels of approximately 2.2 do not appear to derive benefit from platinum-based chemotherapy,

suggesting a resistance threshold between 1.4 and 2.2. The threshold for sensitivity to platinum based chemotherapy shows that patients harboring tumors with mRNA expression levels of ERCC1 ≥ 2.2 and in one study 3.4, do not appear to derive benefit from platinum based chemotherapy. Further, these studies support the hypothesis that high levels of ERCC1 predict resistance to platinum based chemotherapy. Later studies have consistently identified lower ERCC1 levels as correlating with outcome. The variation in reports of ERCC1 may be attributed to current data offering better techniques in evaluating the tissue, the addition of microdissection, primers used, etc. suggesting a resistance threshold between 1.4 and 2.2. Further, these studies support the hypothesis that high levels of ERCC1 predict resistance to platinum based chemotherapy. Later studies have consistently identified lower ERCC1 levels as correlating with outcome. The variation in reports of ERCC1 may be attributed to current data offering better techniques in evaluating the tissue, the addition of microdissection, primers used, etc. Furthermore, the trials reported in upper GI tumors have been single arm studies that have noted the association between ERCC1 and clinical outcome. Most of these are retrospective evaluations. This could be another possible explanation for the variability and potential inconsistencies in significance with RR, PFS and/or OS. While they suggest that ERCC1 shows resistance, investigators cannot distinguish between ERCC1 being associated with resistance or just with clinical outcome itself, that is a prognostic marker. This is part of the justification for going forward with this trial randomizing patients with ERCC1 high and low to either both regimens. Table 1 outlines currently published data for ERCC1 and the correlation with outcome. Lastly, these cutoff values have been established and corroborated over numerous analyses of samples at Response Genetics, Inc.

ERCC1 and ERCC2 SNP as predictor of outcome in patients with platinum based chemotherapy.

ERCC1 and ERCC2 proteins are major components of the NER complex, acting as the rate-limiting enzymes in the NER pathway. Several common and putatively functional single nucleotide polymorphisms (SNPs) of ERCC1 and ERCC2 have been identified, of which ERCC1 rs11615 and rs3212986 SNPs (C118T and C8092A) have some effects on ERCC1 mRNA expression, whereas ERCC2 rs1799793 and rs13181 SNPs [Asp312Asn (G>A) and Lys751Gln (T>G), respectively] SNPs are associated with suboptimal DNA repair capacity. *(17-19)* Previous studies have suggested that ERCC1 is a promising predictive marker for response to the platinum-based chemotherapy because of its low expression associated with increased chemotherapeutic sensitivity. *(20)* Therefore, these ERCC1 and ERCC2 SNPs may be useful prognostic markers for treatment with platinum agents. In a recent meta-analysis, ERCC1 rs11615 T allele was a biomarker of low objective response, a short PFS, and OS in Asian patients, whereas ERCC2 rs13181 G allele showed significant or marginally significant association with low objective response, a short PFS, and OS in overall patients, Caucasians, and colorectal cancer subgroups. Although some single studies may have influenced the significance of the pooled results, the association tendency was obvious with or without these studies. The consistent changes of 3 parameters strongly suggested that ERCC1 rs11615C>T and ERCC2 rs13181T>G both had an effect on oxaliplatin-based chemotherapy and that objective response could be a useful surrogate of survival in oxaliplatin-treated gastric and colorectal cancer patients. These results could be reasonably explained by the biological significance of these 2 SNPs. The rs11615 T allele of ERCC1 polymorphism was found to be associated with high mRNA expression of the corresponding gene, whereas the rs13181 G allele of ERCC2 polymorphism was found to be associated with a low number of X-ray–induced chromatid aberrations. *(18,21)* Functional studies confirmed a substantial influence of the ERCC1 rs11615C>T and ERCC2 rs13181T>G SNPs on the phenotype of NER capacity, and possessing the TT genotype of ERCC2 rs13181T>G SNP was associated with the risk of suboptimal DNA repair up to 7-fold, compared with the GG/GT genotypes. *(7,17,18,22,23)* Hence, patients carrying the ERCC1 rs11615 T or ERCC2 rs13181 G allele may have higher DNA repair capacity that could effectively reduce the anticancer effect of oxaliplatin, leading to poor prognosis of these patients. The meta-analysis showed that ERCC1 rs11615C>T and ERCC2 rs13181T>G SNPs might be useful prognostic factors for assessing clinical outcomes of oxaliplatin-based chemotherapies (FOLFOX or XELOX) in gastric and colorectal cancer. In this proposal, investigators will evaluate ERCC1 and ERCC2 SNPs and a potential association to correlate these SNPs with ERCC1 intratumoral mRNA.

Current treatment of advanced upper GI tumors

The current standard chemotherapy regimens for advanced gastric/gastroesophageal/ esophageal cancers have limited efficacy as summarized in Table 2. Current efforts in ongoing clinical trials are focusing on new drug combinations and the addition of novel, targeted therapies. Although, the addition of some of these newer therapeutics has added potential benefit to chemotherapy, many of these studies have shown conflicting outcomes and/or addition of toxicity and significant cost.

Table 2: Current Regimens

Combination	Response Rate (%)	Median TTP (Months)	Median OS (Months)
FAM (80)	9-42		5.6-6
FP (91-'99)	27-45	4.5	9.0-10.6
FAMTX (82-99)	21-63		6.1-10
ECF (96-2001)	42-71	5.0	8.6-9.0
Cis/Irin	41-58	4.8	9.0
DI	45	4.6	8.2
DC (99-05)	26	3.7-5.0	10.5
DCF (03-05)	43	5.6-5.9	9.6
CAPOX (06)	65	4	6.4
CAP/D (06)	39	4.2	9.0
S-1/cis (04-06)	49	4.9	10.6

Both FOLFOX and the combination of irinotecan and docetaxel have been evaluated for patients with previously untreated advanced gastric cancer and GE junction tumors in Phase II studies. Louvet and colleagues reported a response rate of 45% with FOLFOX. *(24)* Time to progression (TTP) was 6.2 months with an overall survival (OS) of 8.6 months. Al-Batran and colleagues reported a randomized clinical trial in metastatic gastroesophageal patients, reporting PFS for FLO (5-FU/LV/Oxaliplatin) of 5.8 months with OS 10.7 months. *(1)* Further, Enzinger and colleagues recently presented a randomized phase II comparing FOLFOX, ECF and IC (with cetuximab [C]) showing higher responses for ECF-C and FOLFOX-C, with the FOLFOX combination being better tolerated. Park et al. evaluated the combination of irinotecan and docetaxel in 48 untreated advanced or metastatic gastric cancer. This group reported a response rate of 45%, TTP 4.5 months and OS of 8.2 months. *(25)* These results are similar to what has been reported with other regimens. (Table 2)

Van Cutsem and colleagues evaluated fluoropyrimidines and platinum based chemotherapy in combination with trastuzumab in patients with HER2 positivity. HER2 overexpression has been demonstrated in approximately 20 to 25% of patients in vitro and in vivo. Trastuzumab blocks HER2 activation by blocking the extracellular domain cleavage and activates antibody-dependent cellular cytotoxity. With the addition of trastuzumab to chemotherapy, they demonstrated an overall survival of 13.8 months with trastuzumab vs. 11.1 months for 5-FU/cisplatin alone. *(26)* The hazard ratio was 0.74, demonstrating statistical superiority for the HER2 receptor inhibitor. Trastuzumab reduced the risk of death by 26% when combined with chemotherapy. *(26)* Given the unclear relationship between HER2, ERCC1, and outcome, HER2 positive patients will be excluded from this study.

This study will evaluate the utility of ERCC1 in upper GI tumors. Based on data from previous clinical trials, including SWOG trials, validated technology will be used to assess ERCC1 gene expression and evaluate ERCC1 levels with FOLFOX and irinotecan/docetaxel in patients with metastatic esophageal, gastroesophageal, or gastric cancer. Despite some inconsistencies with ERCC1 and association with outcome (study specific), there is enough data to suggest that this marker may help identify those patients that will benefit from platinum based therapy. This study

will assess the role of ERCC1 in patient treatment. The evaluation of patients is based on the genotypic marker ERCC1 (as measured by mRNA levels) as follows: ERCC1 status will be determined and patients within each subset (low or high ERCC1) will be randomized to FOLFOX or irinotecan/docetaxel. This will allow comparative evaluations of the each regimen based on ERCC1 status i.e, FOLFOX with high or low and CD based on high or low ERCC1. An evaluation of ERCC1 and ERCC2 SNPs will also be explored. If this marker is validated in a prospective setting, a validation randomized Phase III will need to be done to potentially incorporate ERCC1 into standard of care. If the marker is not validated prospectively, as to its predictive value, it may be that the reported conflicts in the literature are related to a greater impact of ERCC1 as a prognostic marker. Tailoring a chemotherapeutic regimen based on molecular profiling would represent a major step forward in gastric, GE junction, and esophageal cancer therapy and it would represent a paradigm shift in current clinical practice potentially allowing for maximal benefit from treatment and decreasing exposure to ineffective drugs.

Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

Ethnic Category	Females	Males	Total
Hispanic or Latino	16	32	48
Not Hispanic or Latino	59	118	177
Total Ethnic	75	150	225
Racial Category			
American Indian or Alaskan Native	1	1	2
Asian	6	11	17
Black or African American	15	32	47
Native Hawaiian or other Pacific Islander	0	0	0
White	53	106	159
Racial Category: Total of all Subjects	75	150	225

3.0 DRUG INFORMATION

For information regarding Investigator Brochures, please refer to SWOG Policy 15.

For this study, all drugs are commercially available; therefore, Investigator Brochures are not applicable to these drug/s. Information about commercial drugs is publicly available in the prescribing information and other resources.

3.1 5-Fluorouracil (5-FU) (NSC-19893)

a. Description

1. 5-FU is a fluorinated pyrimidine, which has been modified from the naturally occurring product uracil by the addition of a fluoride at position 5.
2. Molecular Formula: $C_4H_3FN_2O_2$
3. Molecular Weight: 130.1g/mol

b. Pharmacology

Mechanism of Action: 5-FU's primary mode of action is the inhibition of thymidylate synthase which is necessary for both the synthesis and repair of DNA. The agent exhibits activity in different phases of the cell cycle based on mode of administration. After bolus exposure of 5-FU s-phase cytotoxicity is noted. After 24 hours of continuous intravenous infusion G-1 phase cytotoxicity has been demonstrated.

c. Pharmacokinetics

1. Absorption: Oral 5-FU is incompletely absorbed from the GI tract with highly variable rates of bioavailability reported between 0 and 80%. Topical absorption is also minimal with only 2.4% of active drug being absorbed from the 5% commercial cream.

2. Distribution: 5-Fluorouracil has wide ranging distribution to both tissue and extracellular fluid. Volume of distribution has been reported between 13-27 liters after IV bolus administration.

3. Metabolism: The metabolism of 5-FU is well known and occurs primarily in the liver via non-linear kinetics. The rate limiting step of hepatic breakdown is the conversion of 5-fluorouracil to 5-6 dihydrofluorouracil via dihydropyrimidine dehydrogenase (DPD). Patients with known DPD deficiency should not be given 5-FU.

4. Elimination: the elimination half life of 5-FU after IV bolus administration has been reported to occur within 6-22 minutes. Small amounts of unchanged 5-FU are eliminated via the kidney and biliary systems.

d. Adverse Effects

1. Human:
   - CNS: confusion, disorientation, euphoria, nystagmus, headache, encephalopathy, and peripheral neuropathy
   - Opthalmic: lacrimal duct stenosis, visual changes, lacrimation, and photophobia, excessive nasal discharge, reddening of the eyes, blurring of the vision
   - Gastrointestinal: stomatitis, esophagopharyngitis, nausea, vomiting, anorexia, diarrhea, gastrointestinal ulceration and bleeding
   - Cardiovascular: cardiomyopathy, ischemic chest pain, myocardial ischemia, diaphoresis, thrombophlebitis, electrocardiogram changes.
   - Dermatologic: maculopapular rash, alopecia, dry skin, fissuring, hand-foot syndrome, nail changes, rash, photosensitivity and vein pigmentation. onycholisis, dystrophy, pain and thickening of the nail bed, transverse striations, half and half nail changes, loss of nail, paronychial inflammation, and hyperpigmentation
   - Hematologic: leucopenia, agranulocytosis, anemia, epistaxis, pancytopenia, and thrombocytopenia
   - Immunologic: allergic reactions, anaphylaxis

2. Pregnancy and lactation: 5-FU is classified as pregnancy category D. Teratogenic effects have been demonstrated in animals, however no well controlled studies in humans have been performed. In addition, no adequate data is available on the use of 5-FU while breast feeding. Women are advised to use formula if remaining on treatment.

3. Drug interactions:

DRUG CLASS	EXAMPLES	OUTCOME
Blood thinning agents	NSAIDS, platelet inhibitors, salicylates, strontium-89 chloride, thrombolytics, warfarin	Increased risk of hemorrhage
Antifolates	Dapsone, trimethoprim, pyrimethamine	Increased antifolate toxicity
Hydantoins	Phenytoin, fosphenytoin, ethotoin	Altered levels of hydantoin serum levels monitor closely
Growth factors	G-CSF, GM-CSF, PEG-G-CSF	Increased bone marrow suppression if used outside of recommended timelines
Vaccines	Any live vaccine ie. rotavirus	Potential for infection with live virus
Cardiac glycosides	Digoxin	Altered absorption due to GI toxicity. Monitor levels closely
Cytochrome p450 2C9 metabolized agents	Ramelteon, bosentan,	Increased levels of co-administered agent use alternative if possible
----------	Dipyridamole	Inhibition of DPD function and increased 5-FU toxicity
nitroimidazoles	Metronidazole, Tinidazole	Increased 5-FU levels and toxicity
----------	Tamoxifen	Increased risk of thromboembolism

e. Administration (Dosing): See treatment plan (Section 7.3)

f. Storage/Stability

1. Compatibility: Store unopen vials at room temperature and protect from light. May be diluted in NS or D_5W.

2. 5-FU is a cytotoxic drug and appropriate procedures for handling, preparing and administering the drug should be followed.

3. When diluted in NS or D_5W to a concentration of 1.5 mg/ml in either glass or polyvinyl chloride containers 5-FU is stable for 8 weeks at room temperature. In ethylene vinyl chloride pumps, 5-FU 10 mg/ml in NS or D_5W is stable for 28 days at 4—35 degrees C.

g. How Supplied

1. 5-FU is available as an IV solution for injection. The concentration is 50 mg/ml

2. 5-FU is commercially available and should be purchased by a third party. This drug will no longer be supplied by the NCI.

3. Drug accountability will not be required for 5-FU as it is commercially available.

3.2 Docetaxel (Taxotere®) (RP56976) (NSC-628503)

a. Description

1. Docetaxel is a semisynthetic antineoplastic agent extracted from the needles of the European yew tree (Taxus baccata).

2. Molecular Formula: $C_{43}H_{53}NO_{14}•3H_2O$

3. Molecular Weight: 861.9 g/mol

b. Pharmacology

Mechanism of Action: Docetaxel is a member of the taxane class of antimicrotubule agents. Docetaxel promotes the assembly of microtubules and stabilizes their formation by inhibiting depolymerization. This stabilization creates a microtubule which is non-functional. Cell death is promoted by the disruption of normal cell shape, motility, attachment, and intracellular transport. Docetaxel is cytotoxic predominately in the s-phase of the cell cycle

c. Pharmacokinetics

1. Absorption: studies of oral docetaxel have demonstrated a bioavailability of 8% +/- 6%.

2. Distribution: in vitro studies demonstrated that docetaxel is approximately 94% protein bound, primarily to alpha-1-acid glycoprotein, albumin, and lipoproteins. Docetaxel has a volume of distribution of 113L and widely distributed to all tissues except the CNS.

3. Metabolism: Docetaxel is primarily metabolized in the liver by cytochrome P450 3A4 and 3A5 isoenzymes. The metabolism results in one major and three minor metabolites. All four metabolites are oxidation products of the tert-butyl group attached to the C13-side chain.

4. Elimination: docetaxel elimination follows a three compartment model with an initial distribution half-life of 3 to 5 minutes, an intermediate elimination half-life of 36 to 60 minutes, and a terminal half-life of 10 to 18 hours. Approximately 6% of unchanged drug is eliminated by the kidney in 24 hours, with the majority (80%) of excretion occurring in feces at 7 days.

d. Adverse Effects

1. Human toxicity:

- CNS: asthenia, paresthesia, dysesthesia, pain, periphereal motor neuropathy, myalgia, arthralgia
- Opthalmic: Conjunctivitis, Epiphora
- Gastrointestinal: colitis, diarrhea, GI hemorrhage, nausea and vomiting, stomatitis

- Cardiovascular: cardiac dysrythmia, edema, congestive heart failure, hypotension, myocardial ischemia, phlebitis, syncope, vasodilatation, DVT
- Hepatic: elevated bilirubin, SGOT, SGPT, and alkaline phosphatase are common. Rare instances of hepatic coma, and hepatitis have been reported.
- Respiratory: pleural effusion, pulmonary embolism
- Hematologic: Anemia, neutropenia, leukopenia, thrombocytopenia. Rare cases of AML, and MDS have been reported.
- Dermatologic: Alopecia, nail disorders, dry skin. Cutaneous reactions, including localized erythema of the extremities with edema followed by desquamation, have been reported with docetaxel use. In addition, Hand foot syndrome, injection site reactions, extravasation, rash and pruritis have been reported.
- Immunologic: hypersensitivity, anaphylaxis, lymphedema

2. Pregnancy and Lactation: Docetaxel is classified as FDA pregnancy risk category D. There are no data concerning the effects in pregnant women. In animal studies, docetaxel is embryotoxic and fetotoxic. Females of childbearing potential should be instructed to avoid becoming pregnant during therapy. It is unknown whether docetaxel is excreted in breast milk therefore patients should be instructed to avoid breast feeding during treatment.

3. Drug interactions:

Drug Class	Examples	Outcome
Blood thinning agents	NSAIDs, platelet inhibitors, high dose salicylates, strontium-89 chloride, and thrombolytic agents	Increased risk of hemorrhage
Cytochrome P450 3A4 metabolized agents	Aprepitant, fosaprepitant, carbamazepine, etravirine, imatinib, nefazodone, voriconazole, conivaptan, ketoconazole, sorafenib, quinupristin/dalfopristin, macrolides	Altered levels of docetaxel monitor closely
MDR-p glycoprotein inhibitors	Cyclosporine, nilotinib,	Possible enhanced toxicity of docetaxel
Growth factors	Filgrastim, sargramostim, pegfilgrastim	Increased bone marrow suppression if used outside of recommended timelines
Vaccines	Any live vaccine ie. rotavirus	Potential for infection with live virus
Cardiac glycosides	Digoxin	Altered absorption due to GI toxicity. Monitor levels closely
Anthracyclines	Doxorubicin, epirubicin	Potential sequence related increase in docetaxel
----------	Thalidomide	Increased risk of VTE

e. Administration (Dosing): See treatment plan (Section 7.3)

f. Storage and Stability

1. Store between 2-25°C (36-77°F). Retain in the original package to protect from bright light. May use D5W or NS for administration.
2. Docetaxel is a cytotoxic drug and appropriate procedures for handling, preparing and administering the drug should be followed. Use only non-DEHP bags and tubing for administration.
3. The reconstituted solution may be used immediately or stored either in the refrigerator or at room temperature for up to 8 hours.

g. How Supplied

1. Docetaxel is available as a lyophilized powder, and solution for injection.
2. This drug is commercially available for purchase by a third party. It will not be supplied by the NCI.
3. Drug accountability will not be required for docetaxel as it is commercially available.

3.3 Irinotecan (CPT-11) (NSC-616348)

a. Description

1. Irinotecan is a water-soluble derivative of camptothecin (CPT), a cytotoxic plant alkaloid isolated from the Chinese tree Camptotheca acuminata.
2. Molecular Formula: $C_{33}H_{38}N_4O_6$•HCl•3H2O
3. Molecular Weight: 677.2 g/mol

b. Pharmacology

Mechanism of Action: irinotecan and its metabolite SN-38, work by inhibiting topoisomerase I. Topoisomerase I relieves the torsional strain in the DNA helix during replication and RNA transcription by inducing single-strand breaks. By binding with the topoisomerase I—DNA complex, irinotecan or SN-38 prevents the relegation of the single-strand breaks. Irreversible DNA damage occurs when a DNA replication fork encounters the irinotecan or SN-38/topoisomerase I complexes resulting in double-strand DNA breaks. Camptothecins are highly S-phase specific in their activity due the requirement of DNA synthesis.

c. Pharmacokinetics

1. Absorption: NA
2. Distribution: Protein binding of irinotecan is 30-70 percent, whereas SN-38 shows a higher 95% protein binding. Both irinotecan and its metabolite are primarily bound to albumin. Volume of distribution of irinotecan has been found to be 110-234 L/m^2.

3. Metabolism: Irinotecan is metabolized primarily in the liver by carboxylesterase to SN-38, and via hepatic cytochrome P450 (CYP) 3A4 to aminopentane carboxylic acid (APC). SN-38 is conjugated to form a glucuronide metabolite by the enzyme UDP-glucuronosyl transferase 1A1 (UGT1A1). Genetic polymorphisms exist in the enzyme UGT1A1, leading to different levels of exposure and toxicity among patients. In addition, both irinotecan and SN-38 undergo plasma hydrolysis between their active (lactone) and inactive forms (carboxylate). Finally, a small amount of irinotecan is metabolized by the intestinal wall.

4. Ellimination: 10-25% of irinotecan is recovered unchanged in urine whereas only small amounts of SN-38 have been found. Clearance is approximately 13.5 L/hr/m^2. In addition, irinotecan has approximately 25% biliary excretion.

d. Adverse Effects

1. Human:
   - Neurologic: Asthenia, confusion, dizziness, headache, insomnia, somnolence
   - Gastrointestinal: abdominal pain, constipation, diarrhea (early and late onset), flatulence, indigestion, mucositis, loss of appetite, stomatitis, nausea and vomiting
   - Cardiovascular: dysrhythmias, ischemia, edema, flushing, hypotension, vasodilatation, and mechanical cardiac dysfunction
   - Hepatic: elevated AST, ALT, bilirubin and alkaline phosphatase. Non-specific hepatotoxicity has also been reported
   - Musculoskeletal: backache, pain
   - Respiratory: cough, dyspnea, rhinitis, pneumonia, and pneumonitis
   - Dermatologic: acral erythema, alopecia, rash, sweating, and extravasation
   - Endocrine: dehydration, weight loss
   - Hematologic: anemia, eosinophilia, neutropenia, leukopenia, thrombocytopenia, and thromboembolic disorder
   - Immunologic: fever, shivering, hypersensitivity, and anaphylaxis have been reported

2. Pregnancy and Lactation: Irinotecan is not recommended for use during pregnancy. It carries an FDA pregnancy risk category D and may cause fetal harm. Irinotecan is embryotoxic in animals; however, there are no data concerning use in pregnant humans. Teratogenic effects in animals like rats and rabbits include a variety of external, visceral, and skeletal abnormalities. Breast feeding should be avoided while on irinotecan as the drug is known to be excreted in breast milk.

3. Drug Interactions:

Drug Class	Examples	Outcome
UGT1A1 inhibitors	**Atazanavir***, Sorafenib	Increased exposure to SN-38
CYP 3A4 inhibitors	**Ketoconazole***, nilotinib, aprepitant, fosaprepitant, telithromycin	Increased levels of irinotecan
CYP 3A4 inducers	**St. John's Wort*,** carbamazepine, rifampin, rifabutin, pheytoin, barbituates, etravirine, lopinavir	Decreased levels of irinotecan
Diuretics	Conivaptan,	Increased risk of volume depletion
Growth factors	G-CSF, GM-CSF, PEG-G-CSF	Increased bone marrow suppression if used outside of recommended timelines
Blood thinning agents	NSAIDS, platelet inhibitors, salicylates, strontium-89 chloride, thrombolytics, warfarin	Increased risk of hemorrhage
Vaccines	Any live vaccine ie. **Rotavirus***	Potential for infection with live virus
Cardiac glycosides	Digoxin	Altered absorption due to GI toxicity. Monitor levels closely
----------	Citalopram	Increased risk of myopathy and rhabdomyolysis
----------	Succynlcholine	Prolongation of neuromuscular blockade

***DENOTES CONTRAINDICATED DRUG**

e. Administration (Dosing): See treatment plan (Section 7.3)

f. Storage/Stability

1. Store at 15-30ºC (59-86ºF). Protect from light. Keep both the vial and protective backing in the manufacturer's original packaging until just before use. Irinotecan may be Diluted in D_5W (preferred) or NS injection to a final concentration of 0.12—2.8 mg/ml.

2. irinotecan is a cytotoxic drug and appropriate procedures for handling, preparing and administering the drug should be followed

3. Prepared irinotecan is physically and chemically stable for up to 24 hours at room temperature and room lighting. However, because of the possible microbial contamination during preparation, an admixture prepared with D_5W or NS should be used within 6 hours of preparation if kept at room temperature. Solutions prepared with D_5W, stored at refrigerated temperatures and protected from light are physically and chemically stable for 48 hours. It is recommended that infusion solutions prepared with NS not be refrigerated.

g. How Supplied

1. Irinotecan is supplied as a liquid for injection

2. This drug is commercially available for purchase by a third party. This drug will not be supplied by the NCI.

3. Drug accountability will not be required for irinotecan as it is commercially available.

3.4 Leucovorin Calcium (NSC-3590)

a. Description

1. Leucovorin is a mixture of the diastereoisomers of 5-formyl derivative of tetrahydrofolic acid. The active component is the (-)-L-isomer known as Citrovorum factor.

2. Molecular Formula: $C_{20}H_{21}CaN_7O_7$

3. Molecular Weight: 511.51 g/mol

b. Pharmacology

Mechanism of Action: During normal processes, thymidylate synthetase forms a noncovalent ternary complex with deoxyuridylate (dUMP) and the reduced folate cofactor of leucovorin 5,10-methylenetetrahydrofolate (mTHF). The reduced folate facilitates the association and disassociation of the complex and the formation of thymidylate (dTMP) and dihydrofolate. Fluorouracil inhibits thymidylate synthetase through the covalent binding of 5-fluorodeoxyuridine monophosphate (FdUMP) and mTHF. The binding of FdUMP is dependent upon the intracellular concentration of mTHF. Since l-leucovorin is metabolized to mTHF, it increases and stabilizes the binding of FdUMP to thymidylate synthetase, thus increasing the cytotoxic effects of fluorouracil.

c. Pharmacokinetics

1. Absorption: Oral bioavailability of leucovorin is concentration dependent and severely reduced with doses greater than 25 mg. Studies have produced bioavailabilities of 97% 75%, and 37% for doses of 25 mg, 50mg and 100mg respectively.

2. Distribution: Leucovorin is rapidly converted to mTHF and distributed widely to tissues including the CNS. Distribution is however slowed in the presence of methotrexate as this agent competes with bodily tissues for leucovorin, and a higher percentage of unchanged drug is excreted in the urine when methotrexate is present.

3. Metabolism: Through the intravenous route the active isomer of leucovorin, l-leucovorin, is primarily metabolized through hepatic means to mTHF. The d isomer is not metabolized nor biologically active. By the oral route leucovorin is converted to mTHF primarily by the intestinal mucosa.

4. Elimination: the d isomer is primarily excreted unchanged in the urine while the active form is extensively metabolized by intestinal and hepatic means. Leucovorin has a half life of approximately 6 hours.

d. Adverse Effects

1. Human toxicity:
   - Gastrointestinal: Toxicity has been studied in combination with 5FU where diarrhea, dehydration and stomatitis are all more common with the combination.
   - Immunologic: hypersensitivity and anaphylaxis have been reported
   - Endocrine: hypocalcemia

2. Pregnancy and Lactation: Leucovorin is classified as FDA pregnancy risk category C. No adequate human studies have examined the effects of this drug on the fetus. It is not known if leucovorin is excreted into breast milk, and therefore mothers receiving the agent should consider alternative modes of feeding.

3. Drug Interactions:

Drug Class	Examples	Outcome
Anti-metabolites	5FU, capecitabine, floxuridine	Enhanced toxicity
Anti-folates	Methotrexate	Antagonistic effect if not sequenced properly
Anti-convulsants	Phenyntoin, primidone, fosphenytoin, barbituates	Decreased efficacy of anti-convulsant monitor closely

e. Administration (Dosing): See treatment plan (Section 7.3)

f. Storage/Stability

1. Compatibility Information: leucovorin may be dilute in D5W, D10W, NS, Ringer's, or lactated Ringer's solution.

2. Drug handling and compatibility: leucovorin is not considered as hazardous substance and as such may be prepared in a laminar flow hood using aseptic technique.

3. Store dry powder, reconstituted solution and tablets at controlled room temperature. Protect from light. When reconstituted with Bacteriostatic Water for Injection, the resulting solution must be used within seven days. If reconstituted with Sterile Water for Injection, use immediately and discard any unused portion. Diluted injections are stable for 24 hours.

g. How Supplied

1. Leucovorin is provided as both a powder and liquid for injection.

2. Leucovorin is commercially available, and should therefore be purchased by a third party. This drug will NOT be supplied by the NCI.

3. Drug accountability will not be required for leucovorin as it is commercially available.

4. Drug handling and compatibility: leucovorin is not considered as hazardous substance and as such may be prepared in a laminar flowhood using aseptic technique. Leucovorin will be commercially provided and so drug accountability records will not be required for this agent.

3.5 Oxaliplatin (Eloxatin®) (NSC-266046)

a. Description

1. Oxaliplatin is a third generation platinum analog. Oxaliplatin contains a bulky carrier ligand, 1,2-diaminocyclohexane (DACH), not present in either cisplatin or carboplatin.

2. Molecular Formula: $C_8H_{14}N_2O_4Pt$

3. Molecular Weight: 397.3 g/mol

b. Pharmacology

Mechanism of Action: Oxaliplatin is a non-cell cycle specific, alkylating antineoplastic agent that inhibits DNA synthesis through the formation of Crosslinks between the N7 positions of two adjacent guanines (GG), adjacent adenine-guanines (AG), and guanines separated by an intervening nucleotide (GNG). These crosslinks inhibit DNA replication and transcription.

c. Pharmacokinetics

1. Absorption: NA

2. Distribution: oxaliplatin has a protein binding of 70-95% with longer in vitro exposure leading to higher protein binding rates. In addition, it has been demonstrated approximately 37% of platinum is taken up by erythrocytes. Steady state volume of distribution is approximately 35L.

3. Metabolism: Oxaliplatin is rapidly metabolized in plasma primarily by biotransformation. No unchanged oxaliplatin is found 2 hours after administration. Oxaliplatin demonstrates no cytochrome P450 metabolism. 17 known metabolites of oxaliplatin have been identified, monochloro DACH platinum, dichloro DACH platinum, and mono and diaquo DACH platinum, are cytotoxic.

4. Elimination: Platinum is predominately excreted through the kidney with a clearance of 9-17 L/hour. Elimination kinetics are triphasic with alpha, beta, and gamma half-lives of approximately .3, 15.5, and 321 hours respectively. A very small (2%) amount of platinum is excreted in the feces.

d. Adverse Effects:

Refer to package insert or manufacturer website for the most complete and up to date information on contraindications, warning and precautions, and adverse reactions.

Adverse Events with Possible Relationship to Oxaliplatin (CTCAE 4.0 Term) [n= 1141]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia		
	Disseminated intravascular coagulation	
	Febrile neutropenia	
	Hemolysis	
		Thrombotic thrombocytopenic purpura
CARDIAC DISORDERS		
	Atrial fibrillation	
	Atrial flutter	
	Paroxysmal atrial tachycardia	
	Sinus bradycardia	
	Sinus tachycardia	
	Supraventricular tachycardia	
	Ventricular arrhythmia	
	Ventricular fibrillation	
	Ventricular tachycardia	
EAR AND LABYRINTH DISORDERS		
	Hearing impaired	
	Middle ear inflammation	
EYE DISORDERS		
	Conjunctivitis	
	Dry eye	
	Eye disorders - Other (amaurosis fugax)	

EYE DISORDERS (contd.)		
	Eye disorders - Other (cold-induced transient visual abnormalities)	
	Eyelid function disorder	
	Papilledema	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Ascites	
	Colitis	
	Constipation	
Diarrhea		
	Dry mouth	
	Dyspepsia	
	Dysphagia	
	Enterocolitis	
	Esophagitis	
	Flatulence	
	Gastritis	
		Gastrointestinal disorders – Other (pneumatosis intestinalis)
	Gastrointestinal hemorrhage[2]	
	Gastrointestinal necrosis[3]	
	Gastrointestinal ulcer[4]	
	Ileus	
	Mucositis oral	
Nausea		
	Pancreatitis	
	Small intestinal obstruction	
Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
	Edema face	
	Edema limbs	
Fatigue		
	Fever	
	Gait disturbance	
	General disorders and administration site conditions - Other (Hepato-renal syndrome)	

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS (contd)		
	Injection site reaction	
	Non-cardiac chest pain	
HEPATOBILIARY DISORDERS		
		Cholecystitis
	Hepatic failure	
	Hepatobiliary disorders - Other (hepatic enlargement)	
	Hepatobiliary disorders - Other (veno-occlusive liver disease)	
IMMUNE SYSTEM DISORDERS		
	Allergic reaction	
INFECTIONS AND INFESTATIONS		
	Infection[5]	
INVESTIGATIONS		
	Activated partial thromboplastin time prolonged	
Alanine aminotransferase increased		
	Alkaline phosphatase increased	
Aspartate aminotransferase increased		
	Blood bilirubin increased	
	Creatinine increased	
	GGT increased	
	INR increased	
	Lymphocyte count decreased	
	Neutrophil count decreased	
Platelet count decreased		
	Weight gain	
	Weight loss	
	White blood cell decreased	

METABOLISM AND NUTRITION DISORDERS		
	Acidosis	
	Anorexia	
	Dehydration	
	Hyperglycemia	
	Hyperuricemia	
	Hypoalbuminemia	
	Hypocalcemia	
	Hypoglycemia	
	Hypokalemia	
	Hypomagnesemia	
	Hyponatremia	
	Hypophosphatemia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Bone pain	
	Myalgia	
	Trismus	
NERVOUS SYSTEM DISORDERS		
	Ataxia	
	Depressed level of consciousness	
	Dizziness	
	Dysgeusia	
	Dysphasia	
	Extrapyramidal disorder	
	Headache	
	Intracranial hemorrhage	
	Ischemia cerebrovascular	
	Nerve disorder[6]	
	Nervous system disorders - Other (multiple cranial nerve palsies)	
	Peripheral motor neuropathy	
Peripheral sensory neuropathy		
	Seizure	
PSYCHIATRIC DISORDERS		
	Anxiety	
	Confusion	
	Depression	
	Insomnia	

RENAL AND URINARY DISORDERS		
		Acute kidney injury
	Hematuria	
	Renal hemorrhage	
	Urinary frequency	
	Urinary retention	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
	Hematosalpinx	
	Ovarian hemorrhage	
	Prostatic hemorrhage	
	Spermatic cord hemorrhage	
	Testicular hemorrhage	
	Uterine hemorrhage	
	Vaginal hemorrhage	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
		Adult respiratory distress syndrome
	Allergic rhinitis	
	Bronchopulmonary hemorrhage	
	Bronchospasm	
	Cough	
	Dyspnea	
	Hiccups	
	Pneumonitis	
	Pulmonary fibrosis	
	Sinus disorder	
	Voice alteration	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia	
	Dry skin	
	Hyperhidrosis	
		Palmar-plantar erythrodysesthesia syndrome
	Pruritus	
	Rash maculo-papular	
	Urticaria	

VASCULAR DISORDERS		
	Flushing	
	Hot flashes	
	Hypertension	
	Hypotension	
	Phlebitis	
	Thromboembolic event	
	Vascular disorders - Other (hemorrhage with thrombocytopenia)	

[1] This table will be updated as the toxicity profile of the agent is revised.

[2] Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Doudenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[3] Gastrointestinal necrosis includes Anal necrosis, Esophageal necrosis, Gastric necrosis, Pancreatic necrosis, Peritoneal necrosis, and Rectal necrosis under the GASTROINTESTINAL DISORDERS SOC.

[4] Gastrointestinal ulcer includes Anal ulcer, Colonic ulcer, Duodenal ulcer, Esophageal ulcer, Gastric ulcer, Ileal ulcer, Jejunal ulcer, Rectal ulcer, and Small intestine ulcer under the GASTROINTESTINAL DISORDERS SOC.

[5] Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[6] Nerve disorder includes Abducens nerve disorder, Accessory nerve disorder, Acoustic nerve disorder NOS, Facial nerve disorder, Glossopharyngeal nerve disorder, Hypoglossal nerve disorder, IVth nerve disorder, Oculomotor nerve disorder, Olfactory nerve disorder, Trigeminal nerve disorder, and Vagus nerve disorder under the NERVOUS SYSTEM DISORDERS SOC.

[7] Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

Also reported on oxaliplatin trials but with the relationship to oxaliplatin still undetermined:

CARDIAC DISORDERS - Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Pericardial effusion
EYE DISORDERS - Eye pain
GASTROINTESTINAL DISORDERS - Gastrointestinal perforation7
INJURY, POISONING AND PRCEDURAL COMPLICATIONS – Injury to superior vena cava, Vascular access complication
INVESTIGATIONS - Cardiac troponin I increased; Lipase increased; Serum amylase increased

METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Tumor lysis syndrome
MUSCOLOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness
NERVOUS SYSTEM DISORDERS – Syncope
RESPIRATORY, THORARIC AND MEDIASTINAL DISORDERS – Hypoxia
VASCULAR DISORDERS - Visceral arterial ischemia

Note: Oxaliplatin in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent

1. Pregnancy and Lactation: Oxaliplatin may cause fetal harm when administered to a pregnant woman (FDA pregnancy risk category D). In animal studies, oxaliplatin at doses less than one-tenth the recommended human dose based on body surface area caused developmental mortality and adversely affected fetal growth (decreased fetal weight, delayed ossification). If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be counseled regarding the potential risks to the fetus. Females of childbearing potential should avoid becoming pregnant while receiving treatment with oxaliplatin. It is unknown whether oxaliplatin is excreted in breast milk. Therefore alternative means to feeding, or delaying treatment should be considered.

2. Drug Interactions:

Drug Class	Examples	Outcome
Blood thinning agents	NSAIDS, platelet inhibitors, salicylates, strontium-89 chloride, thrombolytics, warfarin	Increased risk of hemorrhage
Growth factors	G-CSF, GM-CSF, PEG-G-CSF	Increased bone marrow suppression if used outside of recommended timelines
Vaccines	Any live vaccine ie. rotavirus	Potential for infection with live virus
----------	Zalcitabine	Increased risk of neuropathy

e. Administration (Dosing): See treatment plan (Section 7.3)

f. Storage/Stability

1. Compatibility: Oxaliplatin is incompatible in a solution with alkaline medications or diluents (such as basic solutions of 5-FU) and must not be mixed with these or administered simultaneously through the same infusion line. The infusion line should be flushed with D_5W prior to administration of any conconminant medications. Only D5W is acceptable for dilution. Aluminum needles or iv sets should not be used as degradation of platinum may occur.

2. Special Handling: oxaliplatin is a cytotoxic drug and appropriate procedures for handling, preparing and administering the drug should be followed.

3. Store the intact vials at controlled room temperature. Excursions permitted to 15°C to 30°C (59°F to 86°F), not exceeding 30°C. Reconstituted solution: in 5% Dextrose or Water for Injection in the original vial, the solution may be stored for up to 48 hours between 2°C to 8° C (36°F-46°F). Infusion solution: after dilution in 5% Dextrose in Water, the shelf life is 24 hours at 2°C to 8°C (36°F-46°F).

g. How Supplied

1. Oxaliplatin is commercially available, and should therefore be purchased by a third party. This drug will NOT be supplied by the NCI.

2. Drug accountability will not be required for oxaliplatin as it is commercially available.

4.0 STAGING CRITERIA

Staging criteria are not applicable to this study.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the Prestudy Form and submit to the Data Operations Center in Seattle (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. If Day 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.

SWOG Patient No. _____

Patient's Initials (L, F,M) _____

5.1 Disease Related Criteria

_____ a. Patients must have unresectable advanced or metastatic histologically or cytologically confirmed adenocarcinoma of the esophagus, stomach, or gastroesophageal junction (GEJ). Patients must not have received treatment for metastatic or unresectable disease or have brain metastases.

_____ b. Patients must have measurable and/or non-measurable disease, as defined in Section 10.1. CT scans or MRIs used to assess measurable disease must have been completed within 28 days prior to registration. CT scans or MRIs used to assess non-measurable disease must have been completed within 42 days prior to registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form (RECIST 1.1).

_____ c. Patients who have had HER-2 expression testing prior to registration to this study must be HER-2 negative. If HER-2 expression has not been tested prior to registration to this study, tissue specimen must be submitted for HER-2 expression (see Section 15.1a.1c). If the specimen is HER-2 positive (or if HER-2 could not be evaluated), the patient will not be randomized.

_____ d. Patients must have completed any prior neoadjuvant and adjuvant therapy for resectable disease at least 180 days prior to registration.

5.2 Specimen Submission

_____ a. Patients must have tumor available for submission to assess ERCC-1 (see Section 15.1). If ERCC-1 or HER-2 (if not already performed) cannot be evaluated from the submitted specimen, sites will be notified and the patient will not be randomized.

_____ b. Patients must be given the opportunity to consent to the optional submission of whole blood, leftover tissue (from ERCC-1 and HER-2 testing), and additional tissue (if available) for future research as outlined in Section 15.1 and 15.2.

SWOG Patient No. _____

Patient's Initials (L, F,M) _____

5.3 Clinical/Laboratory Criteria

_____ a. Patients must have a Zubrod performance status of 0-1. (See Section 10.4)

_____ b. Patients must have adequate hematologic function as evidenced by all of the following within 28 days prior to registration: hemoglobin ≥ 9 g/dL; ANC ≥ 1,500/mcL; platelets ≥ 100,000/mcL.

_____ c. Patients must have adequate hepatic function as evidenced by all of the following within 28 days prior to registration: total bilirubin ≤ 1.5 mg/dL regardless of whether patients have liver involvement secondary to tumor; AST and ALT both ≤ 3 x Institutional Upper Limit of Normal (IULN) unless the liver is involved with tumor, in which case both AST and ALT must be ≤ 5 x IULN.

_____ d. Patients must have adequate kidney function as evidenced by at least ONE of the following:

- Serum creatinine < 1.5 mg/dL within 28 days prior to registration.
- Calculated creatinine clearance > 60 ml/min. The serum creatinine value used in the calculation must have been obtained within 28 days prior to registration.

Calculated creatinine clearance = $\frac{(140 - \text{age}) \times \text{wt (kg)} \times [0.85 \text{ (if female)}]}{72 \times \text{creatinine (mg/dL)}}$

_____ e. Prestudy history and physical must be obtained within 28 days prior to registration.

_____ f. Patients must not have motor or sensory neuropathy > Grade 1 using CTCAE Version 4.0.

_____ g. Patient must have no plans to receive concurrent chemotherapy, hormonal therapy, radiotherapy, immunotherapy or any other type of therapy for treatment of cancer while on this protocol treatment. All palliative radiation therapy alone must be completed at least 14 days prior to registration.

_____ h. Due to the possibility of harm to a fetus or nursing infant, patients must not be pregnant or nursing. Women and men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

_____ i. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for five years.

SWOG Patient No. _____

Patient's Initials (L, F,M) _____

5.3 Clinical/Laboratory Criteria (contd.)

_____ j. Prestudy history and physical must be obtained within 28 days prior to registration.

5.4 Regulatory Criteria

_____ a. All patients or their legally authorized representative must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

_____ b. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

6.0 STRATIFICATION FACTORS

Patients will be randomized using a dynamic balancing algorithm (*27*) with stratification based on:

a. ERCC1 expression based on results from Response Genetics (see Section 15.1): high (≥ 1.7) vs. low (< 1.7).

b. Site of disease: esophageal vs. gastric/GEJ.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Iqbal at 323/865-3907 and Dr. Lenz at 323/865-3955. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

7.1 Premedication and Supportive Care

Premedication associated with standard drug administration and supportive care (including anti-diarrheals, antibiotics, diuretics or other medications) may be given according to institutional standards.

7.2 ERCC-1 and HER-2 Determination

Tissue specimens submitted at registration will be used to determine ERCC-1 expression and HER-2 status (see Section 15.1). Once ERCC-1 expression and HER-2 status results have been received at the SWOG Statistical Center, HER2-negative patients will be randomized to one of the treatment arms described in Section 7.3. Once the randomization has been completed, patient treatment assignment and HER-2 status will be emailed to the contact people identified by the registering institution during the specimen submission process (see Section 15.1e). If ERCC-1 expression or HER-2 status (if not already performed) cannot be determined, or if the patient is HER2-positive, sites will be informed and the patient will not be randomized. Turnaround time from specimen submission to notification of treatment assignment will be 7-10 calendar days.

7.3 Treatment

Arm 1: FOLFOX

Patients assigned to Arm 1 will receive the following treatment until meeting one of the criteria in Section 7.4.

Agent	Dose	Route	Day	Schedule*
Oxaliplatin	85 mg/m^2	IV over 2 hr	1	q 14 days
Leucovorin Calcium **	400 mg/m^2	IV over 2 hr	1	q 14 days
5-FU	400 mg/m^2	IV bolus	1	q 14 days
5-FU	2,400 mg/m^2	IV over 46-48 hours via CADD pump	1-2	q 14 days

* Note: One cycle = 14 days
** In the event of a leucovorin calcium shortage, the dosage may be reduced to 20 mg/m^2 or 200 mg/m^2 racemic levoleucovorin may be substituted. Leucovorin may be infused concurrently with oxaliplatin (via separate infusion lines).

Arm 2: Irinotecan + Docetaxel

Patients assigned to Arm 2 will receive the following treatment until meeting one of the criteria in Section 7.4.

Agent	Dose	Route	Day	Schedule *
Irinotecan ***	65 mg/m^2	IV over 90 minutes	1, 8	q 21 days
Docetaxel	30 mg/m^2	IV over 30 ** minutes	1, 8	q 21 days

* Note: One cycle = 21 days
** Initial dose of docetaxel should be given IV over 60 minutes.
*** Administer irinotecan prior to docetaxel

7.4 Criteria for Removal from Protocol Treatment

a. Progression of disease or symptomatic deterioration (as defined in Section 10.2).

b. Unacceptable toxicity.

c. Treatment delay for any reason > 4 weeks.

d. The patient may withdraw from the study at any time for any reason.

7.5 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.6 Follow-Up Period

All patients randomized to a treatment will be followed until death or 3 years after registration, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Considerations

a. No dose re-escalations are permitted. If the patient experiences toxicity requiring a dose reduction, the dose will remain lowered for subsequent cycles.

b. Where several toxicities with different grades or severity occur at the same time, the dose modification applied should be the greatest reduction applicable.

c. For toxicities that are considered by the investigator to be unlikely to develop into serious or life-threatening events (e.g., alopecia, altered taste, etc.), treatment will be continued at the same dose without reduction or interruption. In addition, no dose reductions or interruptions will be required for anemia (non-hemolytic) as it can be satisfactorily managed by transfusions.

d. The maximum dose delay for any reason is 4 weeks.

e. Doses omitted during a cycle will not be made up.

8.3 Dose Delay/Modification for FOLFOX

a. Dose Levels for Treatment Modifications

Agent	Starting Dose	Level -1	Level -2*
Oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2
Leucovorin calcium	400 mg/m^2	No dose adjustments allowed	No dose adjustments allowed
5-FU bolus	400 mg/m^2	320 mg/m^2	240 mg/m^2
5-FU infusion	2,400 mg/m^2	2,000 mg/m^2	1,600 mg/m^2

* Patient must be removed from the specified agent if further reduction is indicated beyond the -2 level.

When, at the beginning of a treatment cycle, treatment delay related to oxaliplatin treatment alone is indicated, 5-FU treatment may continue. If treatment delay is related to 5-FU, all treatment should be delayed. Treatment should only be restarted when the requirements for restarting 5-FU are met.

The dose modifications described below for 5-FU should be applied to both the 5-FU bolus and the 5-FU infusion.

b. Neutrophil Count or White Blood Cell Decreased

Toxicity Grade	Dose Modification	
	Oxaliplatin	5-FU
3 - 4	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at next lowest dose level.	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at next lowest dose level.
Febrile neutropenia Grade 3 -4	Hold treatment. Check weekly. When resolves to grade 1 with no fever continue at next lowest dose level.	Hold treatment. Check weekly. When resolves to grade 1 with no fever continue at next lowest dose level.

c. Platelet Count Decreased

Toxicity Grade	Dose Modification	
	Oxaliplatin	5-FU
2*	Hold treatment. Check weekly. When completely resolved, continue at same dose level.	Hold treatment. Check weekly. When completely resolved, continue at same dose level.
3 - 4	Hold treatment. Check weekly. When completely resolved, continue at next lowest dose level.	Hold treatment. Check weekly. When completely resolved, continue at next lowest dose level.

* After 2nd occurrence reduce both oxaliplatin and 5-FU.

d. Diarrhea, despite optimal anti-diarrheal treatment

Toxicity Grade	Dose Modification	
	Oxaliplatin	5-FU
2 - 3	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at same dose level.	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at next lowest dose level
4	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at next lowest dose level.	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at next lowest dose level

e. Mucositis

Toxicity Grade	Dose Modification	
	Oxaliplatin	5-FU
2	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at same dose level.	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at same dose level.
3 - 4	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at same dose level.	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at next lowest dose level.

f. Allergic Reactions

Toxicity Grade*	Dose Modification	
	Oxaliplatin	5-FU
3 - 4	Discontinue oxaliplatin	No dose modification. If hypersensitivity reaction continues after discontinuing oxaliplatin, remove from protocol treatment.

* For Grade 1 or 2 acute allergic reactions, pre-medication 30 minutes prior to oxaliplatin administration is recommended with dexamethasone 20 mg IV, diphenhydramine 50 mg IV, and one of the following: ranitidine 50 mg IV or famotidine 20 mg IV or equivalent. If an allergic reaction persists into the next cycle, administer 50 mg dexamethasone PO 12 hours and 6 hours prior to administration of oxaliplatin.

g. Palmar-plantar Erythrodysesthesia Syndrome

Toxicity Grade	Dose Modification	
	Oxaliplatin	5-FU
3 - 4	No dose modification	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at next lowest dose level.

h. Cough, Dyspnea, Hypoxia or Pneumonitis

Toxicity Grade	Dose Modification	
	Oxaliplatin	5-FU
3 - 4	Hold treatment until interstitial lung disease is ruled out, then resume treatment at same dose level.	No dose modification

i. Paresthesia or Peripheral Sensory Neuropathy – Dose modifications for oxaliplatin only

Toxicity Grade	Duration of Toxicity		Persistent between cycles
	1 - 7 days	> 7 days	
Grade 1	No dose modification	No dose modification	No dose modification
Grade 2	No dose modification	No dose modification	Next lowest dose level for oxaliplatin
Grade 3	Next lowest dose level for oxaliplatin	Next lowest dose level for oxaliplatin	Discontinue
Peripheral Sensory Neuropathy - Grade 4	Discontinue	Discontinue	Discontinue

j. Laryngopharyngeal Dysesthesia

This toxicity may be induced or exacerbated upon exposure to cold. Patients on oxaliplatin should not receive cold drinks or ice chips on Day 1 of each cycle as this may exacerbate oral or throat dysesthesias, as well as laryngopharyngeal dysesthesia.

Oxaliplatin: Hold oxaliplatin and evaluate patient's oxygen saturation via a pulse oximeter. If normal, reassurance such as an anxiolytic agent or benzodiazepine should be considered. The patient should be observed in the clinic until the episode has resolved. The oxaliplatin infusion may then be continued at 1/3 the rate.

Because this syndrome may be associated with the rapidity of oxaliplatin infusion, subsequent doses of oxaliplatin should be administered as 6-hour infusions (instead of the normal 2-hour infusion).

k. Other Non-Hematologic Toxicities

Note: Alopecia, anorexia, and nausea or vomiting that can be controlled by antiemetics do not require dose modifications.

Toxicity Grade	Dose Modification	
	Oxaliplatin	5-FU
3 or Grade 4 fatigue	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at next lowest dose level.	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at next lowest dose level.
4 (other than fatigue)	Hold treatment. Check weekly. If **asymptomatic**, when resolves to ≤ Grade 1, continue at next lowest dose level. If **symptomatic** (e.g. electrolytes), stop drug.	Hold treatment. Check weekly. If **asymptomatic**, when resolves to ≤ Grade 1, continue at next lowest dose level. If **symptomatic** (e.g. electrolytes), stop drug.

8.4 Dose Delay/Modification for Docetaxel and Irinotecan

a. Dose Levels for Treatment Modification

Agent	Starting Dose	Level -1	Level -2
Docetaxel	30 mg/m^2	25 mg/m^2	20 mg/m^2
Irinotecan	65 mg/m^2	50 mg/m^2	35 mg/m^2

Patients must be removed from the specified agent if further reduction is indicated beyond the -2 level. Patients may continue on one agent if the other is discontinued.

b. General Considerations

Some patients will develop toxicity and require omission of Day 8 dose. In these patients, the investigator should start the next cycle as scheduled with dose reductions as appropriate.

NOTE: There are two different dose adjustment schedules in Sections 8.4e-8.4f: (1) adjustment at the beginning of a new cycle, based on labs on the scheduled day of treatment, and upon maximum toxicity encountered in the previous cycle, and (2) adjustment on treatment days during a cycle.

c. Neutrophil Count or White Blood Cell Decreased

Toxicity Grade	Dose Modification	
	Irinotecan	Docetaxel
3 - 4	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at next lowest dose level.	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at next lowest dose level.
Febrile neutropenia Grade 3-4	Hold treatment. Check weekly. When resolves to Grade 1 with no fever continue at next lowest dose level.	Hold treatment. Check weekly. When resolves to Grade 1 with no fever continue at next lowest dose level.

d. Platelet Count Decreased

Toxicity Grade	Dose Modification	
	Irinotecan	Docetaxel
2*	Hold treatment. Check weekly. When completely resolved, continue at same dose level.	Hold treatment. Check weekly. When completely resolved, continue at same dose level.
3 - 4	Hold treatment. Check weekly. When completely resolved, continue at next lowest dose level.	Hold treatment. Check weekly. When completely resolved, continue at next lowest dose level.

* After 2nd occurrence reduce both irinotecan and docetaxel.

e. Diarrhea, despite optimal anti-diarrheal treatment

Toxicity Grade	Dose Modification	
	During a cycle of Therapy	At Start of Subsequent Cycle of Therapy*
2*	Reduce irinotecan by one dose level; maintain docetaxel dose level	Hold irinotecan until resolution. to Grade 1 then reduce by one dose level; maintain docetaxel dose level.
3	Omit irinotecan and docetaxel doses; when resolved to ≤ Grade 2, reduce irinotecan by one dose level, maintain docetaxel dose level	Hold irinotecan and docetaxel doses; when resolved to ≤ Grade 2, reduce irinotecan by one dose level; maintain docetaxel dose level
4	Omit irinotecan and docetaxel doses; when resolved to ≤ Grade 2, reduce irinotecan and docetaxel by one dose level	Hold irinotecan and docetaxel doses; when resolved to ≤ Grade 2, reduce irinotecan and docetaxel by one dose level

* After 2nd occurrence reduce another dose level.

f. Mucositis

Toxicity Grade	Dose Modification	
	During a Course of Therapy	At Start of Subsequent Course of Therapy
3	Maintain irinotecan dose level; omit docetaxel dose until resolved to ≤ Grade 1, then reduce by one dose level	Hold irinotecan and docetaxel doses until resolved to ≤ Grade 1, then maintain irinotecan dose level and reduce docetaxel by one dose level
4	Omit irinotecan and docetaxel doses until resolved to ≤ Grade 1, then reduce doses by one dose level	Hold irinotecan and docetaxel doses until resolved to ≤ Grade 1, then reduce docetaxel dose by one dose level

g. Peripheral Neuropathy

	Docetaxel	Irinotecan
Grade 3-4	Hold until grade 1 and reduce 1 dose level.	Maintain dose

h. Docetaxel Allergic Reactions

Severity of Symptom	Treatment Guidelines
Allergic Reaction Grade 1	Consider decreasing the rate of infusion until recovery from symptoms; stay at bedside and monitor patient, then complete docetaxel infusion at the initial planned rate.
Allergic Reaction Grade 2	Interrupt docetaxel infusion. Give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV; monitor patient until symptoms resolve. Resume docetaxel infusion after resolution of symptoms; depending on physician assessment, docetaxel infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate (e.g. infuse at 8 hour rate for 5 minutes, then at 4 hour rate for 5 minutes, then at a 2 hour rate for 5 minutes, then finally, resume at the 1 hour rate). Depending on intensity of reaction, additional oral or IV premedication with an antihistamine should also be given for the **next cycle** of treatment, and the rate of infusion should be decreased initially, then increased back to the recommended 1-hour infusion rate (as described above).
Allergic Reaction Grade 3 Or Anaphylaxis Grade 3	Immediately discontinue docetaxel infusion. Utilize same treatment guidelines as those described above for moderate reactions.
Allergic Reaction Grade 4 or Anaphylaxis Grade 4	Discontinue docetaxel and continue irinotecan.

8.5 G-CSF

G-CSF, pegylated G-CSF, or GM-CSF may be utilized per ASCO guidelines (http://jop.ascopubs.org/cgi/content/full/2/4/196).

8.6 Dose Modification Contacts

For treatment or dose modification questions, please contact Syma Iqbal, M.D. at 323/865-3907 or Heinz-Josef Lenz, M.D. at 323/865-3955.

8.7 Adverse Events Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

9.1 ARM 1: FOLFOX

		Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7		Cycle 8		Cycle 9		Cycle 10		Cycle 11		Cycle 12		Ω	%
REQUIRED STUDIES	PRE	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	F/U prior to	F/U after
	STUDY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	prog	prog
PHYSICAL ∑																											
History and Physical Exam	X~	X		X		X		X		X		X		X		X		X		X		X		X		X	X
Weight and Performance Status	X	X		X		X		X		X		X		X		X		X		X		X		X		X	
Disease Assessment	X						X						X						X						X	X	
Toxicity Notation		X		X		X		X		X		X		X		X		X		X		X		X			
LABORATORY ∑																											
CBC/Differential/Platelets	X	X		X		X		X		X		X		X		X		X		X		X		X			
Serum creatinine/ Calculated creatinine clearance	X																										
Serum bilirubin	X	X		X		X		X		X		X		X		X		X		X		X		X			
AST and ALT	X	X		X		X		X		X		X		X		X		X		X		X		X			
SPECIMEN SUBMISSION																											
ERCC1 and HER2 £	X																										
Tissue for banking β	X																										
Blood β	X																										
X-RAYS AND SCANS ¥																											
CT or MRI for disease assessment	X						X						X						X						X	X	
TREATMENT ∑																											
Oxaliplatin δ		X		X		X		X		X		X		X		X		X		X		X		X			
Leucovorin δ		X		X		X		X		X		X		X		X		X		X		X		X			
5-FU α		X		X		X		X		X		X		X		X		X		X		X		X			

Click here for Footnotes for Calendar 9.1

FOOTNOTES for Calendar 9.1

Note: Forms are found in Section 18.0. Forms submission guidelines are found in Section 14.0.

∑ Protocol treatment and parameters will continue at these intervals until progression of disease or until patient has met any of the guidelines in Section 7.4.

£ Required tissue submission for patients. See Section 15.1 for additional information.

δ To be given on Day 1 of each cycle.

α To be given on Days 1-2 of each cycle.

β Optional submission for patients. See Section 15.2 for additional information.

Ω After off treatment prior to disease progression, scans for disease assessment and physical assessments (with lab tests performed at the discretion of the treating investigator) should take place every 6 weeks until progression.

% After off treatment following disease progression, physical assessments (with lab tests performed at the discretion of the treating investigator) should take place every 3 months for three years from the time of registration.

~ Prestudy history and physical exam must be obtained within 28 days.

9.2 Arm 2: Irinotecan/docetaxel

		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6			Ω	%
REQUIRED STUDIES	PRE	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	F/U Prior to Prog	F/U After Prog
	STUDY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
PHYSICAL ∑																					
History and Physical Exam	X ~	X			X			X			X			X			X			X	X
Weight and Performance Status	X	X			X			X			X			X			X			X	
Disease Assessment	X						X						X						X	X	
Toxicity Notation		X			X			X			X			X			X				
LABORATORY ∑																					
CBC/Differential/Platelets	X	X	X		X	X		X	X		X	X		X	X		X	X			
Serum creatinine/ Calculated creatinine clearance	X	X	X		X	X		X	X		X	X		X	X		X	X			
Serum bilirubin	X	X	X		X	X		X	X		X	X		X	X		X	X			
AST and ALT	X	X	X		X	X		X	X		X	X		X	X		X	X			
SPECIMEN SUBMISSION																					
ERCC1 and HER2 £	X																				
Tissue for banking β	X																				
Blood β	X																				
X-RAYS AND SCANS ¥																					
CT or MRI for disease assessment	X						X						X						X	X	
TREATMENT ∑																					
Irinotecan δ		X	X		X	X		X	X		X	X		X	X		X	X			
Docetaxel δ		X	X		X	X		X	X		X	X		X	X		X	X			

Click here for Footnotes.

FOOTNOTES for Calendar 9.2.

Note: Forms are found in Section 18.0. Forms submission guidelines are found in Section 14.0.

∑ Protocol treatment and parameters will continue at these intervals until progression of disease or until patient has met any of the guidelines in Section 7.4.

£ Required tissue submission for patients. See Section 15.1 for additional information.

B Optional submission for patients. See Section 15.2 for additional information.

δ To be given on Day 1 and 8 of each cycle. See Section 7.2.

Ω After off treatment prior to disease progression, scans for disease assessment and physical assessments (with lab tests performed at the discretion of the treating investigator) should take place every 6 weeks until progression.

% After off treatment following disease progression, physical assessments (with lab tests performed at the discretion of the treating investigator)should take place every 3 months for three years from the time of registration.

¥ Scans will continue at this interval until progression of disease, even if the patient is removed from protocol treatment before progression.

~ Prestudy history and physical exam must be obtained within 28 days.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

This study will use the RECIST 1.1 guidelines. *(28)*

10.1 Measurability of lesions

a. **Measurable disease**

Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should by performed with breath-hold scanning techniques, if possible.

2. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

4. Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition simple cysts.

5. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

10.2 Objective status at each disease evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as *target* lesions at baseline. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as *non-target* lesions. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR):** Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable:** Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.2e).

Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.

2. No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**. Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. Objective status notes:

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).
2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.
3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.
4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.
5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.
6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.
7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.3 Best Response. This is calculated from the sequence of objective statuses

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

h. Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 Performance Status: Patients will be graded according to the Zubrod Performance Status Scale

POINT DESCRIPTION

0 Fully active, able to carry on all pre-disease performance without restriction.

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.

2 Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.

3 Capable of limited self-care, confined to bed or chair more than 50% of waking hours.

4 Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.5 Progression-Free Survival

From ate of registration to date of first documentation of progression or symptomatic deterioration (as defined in above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last contact

10.6 Overall Survival

From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

11.0 STATISTICAL CONSIDERATIONS

11.1 Accrual

The accrual rate is anticipated to be approximately 6 patients per month based on **S0356** and **S0413**. Based on previous trials in this patient population, we anticipate enrolling 225 patients in order to have 200 eligible patients randomized in this study. It is not known how many patients will be HER-2 positive after registration. If this is a considerable number, it may be necessary to enroll additional patients until 200 eligible patients have been randomized.

11.2 ERCC-1 Evaluation and Stratification

Patient specimens will be evaluated for ERCC-1 levels. ERCC-1 will be defined as 'high' if it is 1.7 or greater, and 'low' if below 1.7. Patients within each ERCC-1 subset will be randomized to either FOLFOX or irinotecan and docetaxel. Patients for whom ERCC-1 expression level cannot be measured will not be randomized.

Based on previous data, it is anticipated that roughly 50% of patients will fall into each of the ERCC-1 subgroups, such that 200 total eligible patients will yield approximately 100 patients in each subgroup. Since outcomes within ERCC1-based subgroups have not been well described in the historical data, we have conducted power calculations over a range of potential outcomes and effect sizes. These are presented for the comparisons within both the low and high ERCC-1 subgroups in Table 3 below. To the extent that the observed breakdown of eligible, randomized patients into ERCC-1 based subgroups differs from the expected 50:50 split, actual power for each comparison will differ slightly from the estimates below.

11.3 Primary Objectives and Analyses

The primary hypothesis is that high-ERCC-1 patients treated with irinotecan plus docetaxel will have superior PFS to those treated with FOLFOX. Based on a log-rank test, there will be 80% or greater power to detect hazard ratios of 1.55 or greater over a wide range of potential medians (Table 3), based on a 10% one-sided test, 3 years of accrual, and 2 years of follow-up. There will also be 80% or greater power to detect hazard ratios of 1.55 or greater over a similarly wide range of potential medians for the secondary hypothesis that low-ERCC-1 patients treated with FOLFOX will have superior PFS to those treated with irinotecan plus docetaxel.

Table 3, Power to detect various hazard ratios based on 100 patients per comparison, 10% one-sided type 1 error. For high-ERCC-1 patients, hypothesized outcomes on the FOLFOX and irinotecan plus docetaxel arms are represented in the first and second columns, respectively. For low-ERCC-1 patients, the order is reversed.

Median PFS, months (inferior arm)	Median PFS, months (superior arm)	Hazard Ratio	Power, %
3.0	4.65	1.55	81
	4.8	1.6	85
	5.1	1.7	91
	5.4	1.8	95
4.0	6.2	1.55	80
	6.4	1.6	84
	6.8	1.7	90
	7.2	1.8	94
5.0	7.75	1.55	79
	8	1.6	83
	8.5	1.7	89
	9	1.8	93
5.5	8.5	1.55	79
	8.8	1.6	83
	9.35	1.7	89
	9.9	1.8	93

Based on a 10% one-sided test, there will be 80% or greater power to detect hazard ratios of 1.55 or greater over a wide range of potential medians for the comparison between ERCC-1 high and low patients treated with FOLFOX.

11.4 Other Analyses

Secondary endpoints include overall survival, response rate, and toxicity. With 100 eligible patients in each arm, overall survival at a particular timepoint, and rates of response and of specific toxicities can be estimated to within +/- 10% (95% confidence interval). Any toxicity occurring with at least 5% probability is likely to be seen at least once (>99% chance).

Investigators will also explore whether there is evidence of interaction between ERCC-1 expression and treatment arm. For example, based on a 10% 2-sided test, 3 years of accrual, and 2 years of follow-up, there will be 92% power to detect an interaction if the hazard ratio comparing FOLFOX to irinotecan plus docetaxel among high-ERCC1 patients is 1.55 AND that among low ERCC-1 patients is 0.65. If there is no treatment effect in one ERCC-1 subgroup (i.e., hazard ratio is 1), then the power to detect this interaction is only 46%.

The association between ERCC-1 and ERCC-2 germline polymorphisms and progression-free survival will also be explored. If adequate blood specimens for genotyping are received from 80% of randomized patients, and if, for example, the dominant allele is present in 70% of patients, then within each treatment arm a 10% two-sided logrank test will have at least 80% power to detect a hazard ratio of 1.85 or greater over a wide range of potential medians for the comparison between homozygous recessive patients. For the analysis including both treatment arms, under the same assumptions the logrank test (stratified by treatment arm) will have at least 80% power to detect a hazard ratio of 1.55 or greater. If the homozygous recessive genotype occurs in less than 30% of patients, then power for these tests will be more limited.

Finally, the association between ERCC-1 mRNA expression and ERCC-1 and ERCC-2 germline polymorphisms will be explored using the Mantel-Haenszel chi square test for trend.

11.5 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of the SWOG, 3 SWOG members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistical Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for recommendations regarding possible termination and/or early reporting of the study.

12.0 DISCIPLINE REVIEW

There will be no discipline review for this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must begin treatment within 5 working days after receiving randomization assignment.

13.2 Investigator/Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) or by calling the PMB at 301/496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinic site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

Oncology Patient Enrollment Network (OPEN) will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Cooperative Group Credit

f. Credit Investigator

g. Patient Initials

h. Patient's Date of Birth

i. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

j. Country of Residence

k. ZIP Code

l. Gender (select one):
- Female Gender
- Male Gender

m. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

n. Method of Payment (select one):
- Private Insurance
- Medicare

- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

o. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration procedures

a. All site staff (SWOG and CTSU Sites) will use OPEN to enroll patients to this study. OPEN is a web-based application and can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designee. Site staff should refer to Section 5.0 to verify eligibility.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

- The study site is listed as "approved" in the CTSU RSS.

c. Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user ID and password) used for the CTSU members' web site.

- To perform registrations, the site user must have been assigned the 'Registrar' role on the SWOG or CTSU roster:

1. If you are a SWOG member, to perform registrations on SWOG protocols you must have an equivalent 'Registrar' role on the SWOG roster. Role assignments are handled through SWOG.

2. If you are not a SWOG member, to perform registrations on SWOG protocols you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

d. Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.5 Exceptions to SWOG registration policies will not be permitted

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

Late registrations (after initiation of treatment) will not be accepted.

13.6 Patients Not Randomized

Patients who register to this study, but are not randomized (see Sections 7.2 and 15.1e) will not require follow-up, whereas all patients who are randomized to receive either FOLFOX or irinotecan plus docetaxel should be followed regardless of whether they receive the assigned treatment (in accordance with the intent-to-treat principle).

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirements

Data must be submitted according to the protocol requirements for **ALL** patients randomized to treatment, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3a for details.

14.3 Data Submission Procedures

a. SWOG institutions must submit data electronically via the Web by using the SWOG CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Next, click on the *Data Submission* link and follow the instructions. For new users, the link to a "Starter Kit" of help files may be found by clicking on the **Starter Kit** link at the Members' logon page.

To submit data via the web the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed, and
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to submit data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page). For other difficulties with the CRA Workbench, please email technicalquestion@crab.org.

b. If you need to submit data that are not available for online data submission, the only alternative is via facsimile. Should the need for this occur, institutions may submit data via facsimile to 800/892-4007 or 206/342-1680 locally. Please do not use cover sheet for faxed data. Please make sure that each page of all faxed data include the SWOG patient number, study ID and patient initials.

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to the CTSU Participation Table on page 4.

14.4 Data Submission Overview and Timepoints

a. ON THE SAME DAY AS REGISTRATION:

Submit tissue specimen for ERCC-1 expression and (if not already done) HER-2 testing (see Section 15.1).

Submit pathology report including HER-2 status (if known) with specimen to Response Genetics, Inc. (see Section 15.1).

b. WITHIN 7 DAYS OF REGISTRATION:

Submit pathology report including HER-2 status (if known). (NOTE: This is to be submitted to the Data Operations Center in Seattle. This submission is in addition to the pathology report submission to Response Genetics, Inc. that is required by Section 15.1b.)

c. WITHIN 7 DAYS AFTER RECEIVING RANDOMIZATION ASSIGNMENT:

Submit radiology reports from all scans performed to assess disease at baseline.

Baseline Tumor Assessment (RECIST 1.1)

S1201 Prestudy Form

d. WITHIN 28 DAYS AFTER RECEIVING RANDOMIZATION ASSIGNMENT:

Submit blood, if patient consents (see Section 15.2)

Submit additional tissue for banking if patient consents (see Section 15.2)

e. WITHIN 7 DAYS AFTER EVERY CYCLE ON TREATMENT:

S1201 Treatment Form

S1201 Adverse Event Form

f. WITHIN 7 DAYS AFTER EVERY DISEASE ASSESSMENT (INCLUDING BOTH ON TREATEMENT AND OFF TREATMENT PRIOR TO DISEASE PROGRESSION) (see Section 9.0):

Follow-Up Tumor Assessment Form

Radiology reports

g. WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

Follow-Up Tumor Assessment Form (RECIST 1.1)

Follow-Up Form – if patient is already off treatment

Off Treatment Notice – if patient is still on treatment

Radiology Reports

h. WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT:

Off Treatment Notice

S1201 Treatment Form

S1201 Adverse Event Form

i. AFTER OFF TREATMENT, EVERY 3 MONTHS FOR THREE YEARS:

Follow-Up Form

j. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death **and a final S1201** Treatment Form (if the patient was still on protocol treatment) or Follow-Up Form (if the patient was off protocol treatment) documenting death information.

15.0 SPECIAL INSTRUCTIONS

15.1 Specimens for ERCC-1 and HER-2 testing (required for patient)

a. The following specimen must be submitted on the same day as registration (see Section 5.2a). Collection instructions are outlined in Section 15.1b and submission instructions are outlined in Section 15.1d. With additional patient consent, any material remaining after ERCC-1 and HER-2 testing will be forwarded to the SWOG Solid Tumor Repository for banking.

1. Tumor block: optimal tumor area of 5mm^2 or larger (minimum of 3 mm^2 required). (Copy of pathology report must be included.) In the event that a tumor block cannot be released, the following slides must be submitted:

    a. Ten (fifteen preferred) charged slides with 10-micron tissue sections mounted on each slide from paraffin embedded tissue block. (NOTE: Do not use coverslip or bake slide)

    b. One coverslipped H & E stained slide with 5-micron tissue section.

    c. If HER-2 testing was not performed prior to registration, submit, in addition to the above, four 4-micron tissue sections on regular glass slides. Do not bake, deparafffinize, stain or coverslip slides.

    Note: Cytological specimens are not acceptable.

b. Specimen Collection Instructions

Obtain biopsy according to institutional standards. The tissue sample should be fixed in formalin for 8-24 hours and then paraffin embed the sample according to institutional procedures. Ship the paraffin embedded block or slides to Response Genetics (see Section 15.1e).

c. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

d. SHIPPING SAMPLES

1. Specimen Tracking System

    a. All repository submissions for patients registered by SWOG institutions and affiliates must be entered and tracked using the SWOG Online Specimen Tracking System (SpecTrack).

    b. SWOG members may log onto SpecTrack via the CRA Workbench using their SWOG roster ID number and password.

    c. SpecTrack laboratory IDs are used to identify the laboratories to which specimens are shipped. Under "Specimen Specific Questions", sites must enter patient's HER2 status, as well as contact information for the people who will receive the randomized treatment assignment (see Section 15.1e).

    d. **All specimens must be logged via this system; there are no exceptions.**

e. To report technical problems with SpecTrack, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org.For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page. For further assistance, contact the Data Operations Center at 206-667-2267 to be routed to the Data Coordinator.

g. In the online specimen tracking system, the appropriate SWOG laboratory for submission of tissue samples for ERCC1 testing is identified as follows:

Lab #175: Response Genetics, Inc.
1640 Marengo Street, 4th Floor
Los Angeles, CA 90033
Phone: 323/224-3900
Contact: Nathalie Kertesz

2. Submission to Response Genetics Inc.

Specimens must be shipped Monday through Thursday and at least two days prior to major U.S. holidays. Once the specimen has been logged in using the SWOG Specimen Tracking System, sites must send an email to S1201@responsegenetics.com with the following information:

a. On subject line: **S1201**, Principal Investigator Name, and SWOG Site number
b. In body of e-mail: List the specimens being sent with patient number and date of birth
c. In body of email: FedEx tracking number

Be sure the Pathology Report Label is on the patient's pathology report and place the pathology report and shipment packing list in a plastic bag. Ensure the block or slides are labeled with the SWOG patient ID. Ship overnight by FedEx. Specimens must be shipped according to the following IATA shipping regulations:

d. The specimen must be wrapped in absorbable material.

e. Place the specimen in an AIRTIGHT container (must have a primary and secondary container, ex a Saf-T-Pak).

f. Place packaged specimen in an appropriate shipping container (ex. FedEx box or clinical pack).

g. Mark the outside shipping container with an "Exempt Human Specimen" label.

e. Institutions will be notified by e-mail with the patient's treatment assignment (FOLFOX or docetaxel + irinotecan) within approximately 10 calendar days after specimen submission. If an e-mail with the patient's treatment assignment has not been received within 10 calendar days of submitting the specimen, please contact the SWOG Data Operations Center at 206/652-2267.

NOTE: Treatment assignment will be e-mailed to the contact persons identified in the Specimen Tracking System. At the time of data entry into the Specimen Tracking System, under "Specimen Specific Questions", sites must enter the e-mail address of a contact person and a back-up contact person who are responsible for receiving the treatment assignment notification.

15.2 Translational medicine and Banking

Specimens for correlative studies and banking (submitted to the SWOG Specimen Repository-Solid Tissue, Myeloma and Lymphoma Division, Lab #201) (optional for patient):

a. With patient's consent specimens must be obtained at the following times and submitted no later than 28 days after randomization (see Section 9.0):

1. Obtain one purple-top tube of blood prior to first dose of chemotherapy. Once the purple top tube of blood is collected, it should be stored in the refrigerator and sent at room temperature the same or next day.

2. Any available tissue at baseline after submission of the tumor block or slides for ERCC-1 and HER-2 testing.

b. Additional specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp), or via the link on the **S1201** protocol abstract page on the SWOG website (www.swog.org).

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. See also Appendix 18.1 for general and background information about expedited reporting.

b. Reporting methods

This study requires that expedited adverse event reporting use the CTEP's Adverse Event Reporting System (CTEP-AERS). The NCI's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

In the rare event when internet connectivity is disrupted an electronic report MUST be submitted immediately upon re-establishment of internet connection.

c. When to report an event in an expedited manner

When the adverse event requires expedited reporting, submit the report within 10 calendar days of learning of the event.

d. Other recipients of adverse event reports

The Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must also be reported according to local policy and procedures.

e. Expedited reporting for commercial agents

Commercial reporting requirements are provided in Table 16.1. The commercial agents used in Arm 1 of this study are 5-fluorouracil, leucovorin calcium, and oxaliplatin. The commercial agents used in Arm 2 of this study are docetaxel and irinotecan. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1: Expedited reporting requirements for adverse events experienced by patients on both study arms within 30 days of the last administration of the commercial agent(s). All of the agents used in the study are commercial agents.

ATTRIBUTION	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted via NCI CTEP-AERS within 10 calendar days of learning of the event[b].

[a] This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

[b] Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210-614-0006.

f. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Fetal Death** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle

after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions** SOC.

3. **Death Neonatal** Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

   A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects/htm

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18.0 APPENDIX

18.1 Determination of Expedited Reporting Requirements

18.2 ERCC-1 Methods

18.3 HER-2 Methods

18.4 SNPs Methods

18.1 Determination of Expedited Adverse Event Reporting Requirements

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. Expedited adverse event reporting principles and general guidelines follow; specific guidelines for expedited adverse event reporting on this protocol are found in Section 16.1.

All serious adverse events determined to be reportable to the Institutional Review Board responsible for the oversight of the patient must be reported according to local policy and procedures. Documentation of this reporting should be maintained for possible inspection during quality assurance audits.

Steps to determine if an adverse event is to be reported in an expedited manner (*This includes all events that occur while on treatment or within 30 days of the last dose of protocol treatment.*)

Step 1: Determine whether the patient has received an investigational agent, commercial agent, or a combination of investigational and commercial agents.

An investigational agent is a protocol drug administered under an Investigational New Drug Submission (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- ***Concurrent administration*:** When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- ***Sequential administration*:** When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm with sequential administration all expedited reporting of adverse events should follow the guidelines for the type of agent being given. For example, if the patient begins the study on the investigational agent(s), then all expedited reporting of adverse events should follow guidelines for the investigational agent(s). Once the patient begins receiving the commercial agent(s) then all expedited reporting of adverse events should follow the guidelines for commercial agent(s).

Step 2: Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov). Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms.

Step 3: Grade the event using the NCI CTCAE version specified in the protocol for reporting serious adverse events.

Step 4: Determine if the adverse event is Expected or an Exception to Expedited Reporting. **Expected** events are those that have been previously identified as resulting from administration of the agent and are listed in one of the following:

- The current NCI SPEER (Specific Protocol Exceptions to Expedited Reporting) for treatments using agents provided under an NCI-held IND, or an equivalent listing for treatments using agents provided under a Non-CTEP-held IND; located in Section 3.0 of the protocol.
- For treatments using commercial agents, the current CAEPR (Comprehensive Adverse Event and Potential Risks), ASAEL (Agent Specific Adverse Event List), or other list of expected toxicities located in Section 3.0 of the protocol, or the drug package insert.
- Exception to Expedited reporting located in Section 16.1f of the protocol.

An adverse event is considered **unexpected,** for expedited reporting purposes only, when either the type of event or the severity of the event is **not** listed in one of the areas outlined above.

Step 5: Determine whether the adverse event involved hospitalization or a prolongation of hospitalization (≥ 24 hours).

Step 6: Additionally, for commercial drugs, determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite. Consult the appropriate table for expedited reporting criteria for commercial agent(s).

NOTE: Any event that occurs more than 30 days after the last dose of study agent and is attributed (possible, probable, or definite) to the study agent(s) must be reported according to the instructions above and as outlined in the appropriate table in Section 16.1.

18.2 ERCC1 Methods

Manual micro-dissection using a light microscope will be performed on all tumor samples to ensure > 80% tumor cells is dissected. RNA isolation from paraffin-embedded samples will be performed according to a proprietary procedure defined by Response Genetics. After RNA isolation, cDNA will be prepared from each sample. Quantitation of the ERCC1 gene and an internal reference (β-actin) cDNA will be performed using a fluorescence-based real-time detection method (ABI PRISM 7900HT Sequence detection System [TaqMan®] Applied Biosystems, Foster City, CA). The polymerase chain reaction mixture consists of primer, probe, AmpliTaq Gold Polymerase, the dNTP mixture and the TaqMan Buffer. A reference dye is added to a final reaction volume which is 20 µL (all reagents from Applied Biosystems, Foster City, CA).

All samples will be amplified in triplicate for each gene. For each sample, parallel TaqMan polymerase chain reactions will be performed for the ERCC1 gene and the β-actin reference gene to normalize the gene expression for ERCC1. The obtained ratio between the values provides relative gene expression levels for ERCC1.

18.3 HER2 Methods

FISH*

In situ hybridization is a technique that allows the visualization of specific nucleic acid sequences within a cellular preparation. Specifically, DNA fluorescence in situ hybridization involves the precise annealing of a single standard, fluorescently-labeled DNA probe to complementing target sequences. The hybridization of the probe with the cellular DNA site is visible by direct detection using fluorescent microscopy. The probes are pre-mixed and pre-denatured in hybridization buffer for ease of use. Unlabeled blocking DNA is also included with the probes to suppress sequences contained within the target loci that are common to other chromosomes.

The PathVysion Kit is designed for detection of Her2/neu gene amplification in formalin-fixed, paraffin-embedded human tissues specimens by FISH. The DNA is denatured to single-stranded form and subsequently allowed to hybridize with the PathVysion probes. Following hybridization, the unbound probe is removed by a series of washes and the nuclei are counterstained with DAPI (4,6 diamidino-2-phenylindole), a DNA-specific stain that fluoresces blue. Hybridization of the PathVysion probes is viewed by using a fluorescent microscope equipped with appropriate excitation and emission filters allowing visualization of the intense orange and green fluorescent signals. Enumeration of the LSI HER-2/neu and CEP 17 signals is conducted by microscopic examination of the nucleus, which yields a ratio of the HER-2/neu gene to chromosome 17 copy number.

*Excerpt from Abbott PathVysion HER-2 DNA Probe Package Insert

18.4 SNPs Methods

Methods: Taqman assays

The polymorphisms in ERCC-1/2 are single nucleotide polymorphisms and will be assessed using Taqman assays. For the Taqman assay, the genomic DNA fragment of interest is PCR amplified. Included in the reaction are two hybridization probes complementary to either the wild type or the variant allele. The two probes are labeled with different reporter dyes and a quencher dye. Hybridization conditions are chosen such that the probes do not anneal when there is a mismatch; e.g., the wild type primer does not anneal to the variant PCR fragment and *vice versa*. During PCR amplification, the 5' exonuclease activity of Taq polymerase cleaves the 5' reporter dye from a probe that annealed to the template. The instrument measures the fluorescence generated by the reporter dye released from the wild type and variant probes. In samples that are homozygous either for wild type or for the variant, signal from only one probe is detected. For heterozygous samples, signal from both probes is detected. The advantages of using an ABI PRISM 7900 for genotyping are a decreased sensitivity to PCR artifacts (non-specific amplification), reduction of the number of procedures required and the potential error associated with them, and the fact that lower amounts of genomic DNA template can be used. Taqman assays are validated by genotyping 100-200 individuals using both the Taqman assay and an alternate assay, usually RFLP or sequencing. A Taqman assay is considered validated if there are no discrepancies between the two assays.

Quality control

This study will use several approaches to minimize contamination and monitor quality control in the conduct of the genotyping assays: 1) all reagents are prepared with dedicated or disposable vessels, solutions, and pipettes and 2) positive displacement pipettes or air-displacement pipettes with aerosol-resistant tips are used for reaction assembly and sample analysis. To detect contamination, each batch of samples includes one blank, containing all reagents, but no DNA. Taqman assays also include control DNAs with known genotypes. The accuracy of the genotyping assays will be tested by repeating the assay for 15% of randomly chosen samples. *For Taqman assays, an additional 10% of samples will be genotyped using either an RFLP method or sequencing.* If discrepancies are found, the assay results will be carefully investigated and potential reasons for discrepancies will be explored. Assays will be repeated a third time. If no clear result can be obtained, the sample will be sequenced and all assays will be repeated if necessary.

Informed Consent Model for S1201

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

This model informed consent form has been reviewed by the DCTD/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the SWOG Operations Office for approval before a patient may be registered to this study.

Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the SWOG Operations Office.

Readability Statistics:	
Flesch Reading Ease	65.8 (targeted above 55)
Flesch-Kincaid Grade Level	7.8 (targeted below 8.5)

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form) and SWOG.

  "SWOG" must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to SWOG. This includes consent forms for studies where all patients are registered directly through the SWOG Data Operations Office, all intergroup studies for which the registration is being credited to SWOG (whether the registration is through the SWOG Data Operations Office or directly through the other group), as

well as consent forms for studies where patients are registered via CTSU and the registration is credited to SWOG.

- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This model for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is titled: "Taking Part in Cancer Treatment Research Studies". This pamphlet may be ordered on the NCI Web site at *https://cissecure.nci.nih.gov/ncipubs* or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

S1201, "A Randomized Phase II Pilot Study Prospectively Evaluating Treatment for Patients Based on ERCC1 (Excision Repair Cross-Complementing 1) for Advanced/Metastatic Esophageal, Gastric, or Gastroesophageal Junction (GEJ) Cancer"

NOTE to sites: As described in Sections 5.1c, 5.2a, and 15.1, sites must submit tissue specimens for ERCC1 and HER-2 analysis prior to randomization. (4/28/14)

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have advanced esophageal, gastric, or gastroesophageal junction cancer.

Why is this study being done?

The purpose of this study is to find out what effects (good and bad) a targeted therapy (specific treatment that is based on certain genes found in tumor cells) approach has on you and your esophageal, gastric, or gastroesophageal junction cancer.

This research is being done because we currently do not have advanced knowledge of which patients will benefit from which type of chemotherapy.

How many people will take part in the study?

About 225 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study …

A sample of your tissue will be sent to an outside lab. The lab will look at genes in your tissue called ERCC1 and HER2 (if not already done). The results from the ERCC1 test will put you into one of two groups that randomly assign one of two treatments explained below. You and your physician will not find out the results of the ERCC-1 testing. Your tissue must be HER2

negative in order for you to be able to participate in this study. If your tissue is HER2 positive, your study doctor will tell you. In that case, you cannot receive treatment on this study, but your doctor will provide alternative treatment options.

ERCC1 and HER2 are genes that may be found in your tumor and could affect how your tumor will respond to treatment or guide your doctor to choose what may be the best treatment for your cancer. Currently, standard therapy uses the HER2 gene to determine whether or not to add a drug that targets this gene to your chemotherapy. This study will see how patients with different amounts of ERCC1, but without HER2, do with two different chemotherapy treatments (FOLFOX or irinotecan plus docetaxel). Because doctors do not know if the HER2 and ERCC1 genes interact with each other, patients who have the HER2 gene in their tumor will not be able to participate in this study.

Your tissue will be sent to the following laboratory: Response Genetics, Inc., in Los Angeles, California.

You will also need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- History and physical exam
- CT or MRI scan
- Blood tests for blood counts, kidney function, and liver function.

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will have one of the following treatments.

You will be "randomized" into one of the study arms described below. Randomization means that you are put into an arm by chance. A computer program will place you in one of the study arms. Neither you nor your doctor can choose the arm you will be in. You will have an equal chance of being placed in either arm.

Arm 1

If you are assigned to Arm 1, you will receive the drugs oxaliplatin, leucovorin, and 5-FU (FOLFOX). All drugs will be given into a vein. First, you will receive oxaliplatin over a 2-hour period. After that, you will receive leucovorin over a 2-hour period. (Or, your doctor may choose to give you oxaliplatin and leucovorin at the same time.) This will be followed by an injection of 5-FU. *(4/26/12)* Then you will receive another dose of 5-FU spread out over a 46-hour period. The drugs will be given to you once every 2 weeks. (Each two-week period is called a "cycle".)

The 46-hour 5-FU infusion will require placement of a special central venous catheter. This will be a tube placed into a large vein in your chest. This tube can be of two basic types: (1) It can

come out through your skin or (2) be attached to a small chamber with all of the device under your skin. In most patients, these can be placed under local anesthesia in an operating room. In most patients, these can remain indefinitely. However, you may need to be in the hospital for one day to have the catheter put in. 5-FU will be given through this catheter, and blood samples can be taken from the catheter so you may not have to be stuck with a needle. The placement of this catheter carries a small risk of infection, bleeding and penetration of your lung. The risk of infection and bleeding may be reduced by the strict attention to the care of the catheter. Your doctor will teach you how to care for the catheter. The catheter may be removed easily at any time that it is no longer necessary.

Arm 2
If you are assigned to Arm 2, you will receive the drugs irinotecan and docetaxel. Both of these drugs will be given into a vein. First, you will receive irinotecan over a 90-minute period. There you will receive docetaxel over a 30-minute period. The drugs will be given to you once each week for two weeks and then you will have a week without treatment. (Each three-week period is called a "cycle".) The initial docetaxel dose is given over 60 minutes.

Both Groups
You will need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

- Physical exam – once every cycle
- Blood tests for blood counts – For patients in Arm 1, once every cycle. For patients in Arm 2, this will be done during Week 1 and 2 of each cycle.
- Blood tests for kidney and liver function – For patients in Arm 1, once every cycle. For patients in Arm 2, this will be done during Week 1 and 2 of each cycle.
- X-rays and scans – every 6 weeks

When I am finished taking the study drugs...

Your study doctor will continue to follow your health status every three months for a maximum of three years. The follow-up evaluation tests that are standard of care include a medical history, physical examination, performance status, blood tests, and x-rays or scans to see whether your cancer has progressed. Your study doctor may wish to see you more often than this.

How long will I be in the study?

You will be asked to continue taking the study drugs as long as your disease does not get worse and the side effects are not too severe. You will have follow-up exams every 3 months for up to 3 years. It is up to your doctor what tests are done during the follow-up exams.

Can I stop being in the 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 treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up 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 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 treatment. 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.

Arm 1

Risks and side effects related to the combination of oxaliplatin, leucovorin, and 5-FU include those which are:

Likely:

- **Decreased number of a type of white blood cell (lymphocyte)**
- **Lack of enough red blood cells (anemia)**
- **Diarrhea**
- **Nausea or the urge to vomit**
- **Vomiting**
- **Constipation**
- **Fatigue or tiredness**
- **Loss of appetite**
- **Sore (ulcer) somewhere in the digestive tract**
- **Hair loss**
- **Skin sensitivity when exposed to light**
- **Inflammation (swelling and redness) or damage to the tissue surrounding where a drug was injected**
- **Dry skin**
- **Skin rash with the presence of macules (flat discolored area) and papules (raised bump)**

- **Increased blood level of a liver enzyme (ALT/SGPT)**
- **Increased blood level of a liver enzyme (AST/SGOT)**
- **Decreased number of a type of blood cell that helps to clot blood (platelet)**
- **Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning**
- **Tingling of hands and feet followed by pain, redness and swelling**
- **Numbness in mouth and throat made worse by cold weather or drinks**
- **Belly pain**

Less likely:

- **Fingernail changes**
- **Changes in mood**
- **Difficulty sleeping or falling asleep**
- **Abnormal blood clotting and/or bleeding**
- **Fever associated with dangerously low levels of a type of white blood cell (neutrophils)**
- **Destruction of red blood cells**
- **Abnormally fast irregular heartbeat involving the upper chambers of the heart (atria)**
- **Abnormally fast regular heartbeat involving the upper chambers of the heart (atria)**
- **Period of very rapid and regular heartbeats that begins and ends suddenly**
- **Slow heartbeat; regular rhythm**
- **Fast heartbeat; regular rhythm**
- **Fast heartbeat usually originating in an area located above the ventricles**
- **Irregular heartbeat resulting from an abnormality in the one of the lower chambers of the heart (ventricle)**
- **Ventricular fibrillation: irregular heartbeat that involves the lower chambers of the heart (ventricles) that results in uncoordinated contraction of the heart; life threatening and potentially fatal, needing immediate attention**
- **Rapid heartbeat of one of the lower chambers (ventricle) of the heart; regular rhythm but potentially life-threatening, needs immediate attention**
- **Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.**
- **Uncontrolled eye movements, changes in vision, watering eyes**
- **Hearing loss**
- **Inflammation (swelling and redness) to the middle ear**
- **Inflammation (swelling and redness) of the conjunctiva (the outermost layer of the eye and the inner surface of the eyelids). Commonly called "pink eye".**
- **Dry eye**
- **A situation in which one has temporary blindness of one eye, due to a blockage (or decreased blood flow) in the blood vessels leading to that eye**
- **Temporary vision problems caused by the cold**

- **Problem with eyelid**
- **Swelling around the nerve responsible for sight**
- **Fluid collection in the abdomen**
- **Inflammation (swelling and redness) of the large bowel (colon)**
- **Dry mouth**
- **Heartburn**
- **Difficulty swallowing**
- **Inflammation (swelling and redness) of the small and large bowel**
- **Inflammation (swelling and redness) of the esophagus (gullet or the tube that goes from mouth to stomach through which food passes)**
- **Excess passing of gas**
- **Inflammation (swelling and redness) of the stomach lining**
- **Bleeding in some organ(s) of the digestive tract**
- **Death of tissue somewhere in the digestive tract**
- **Partial or complete blockage of the small and/or large bowel. Ileus is a functional rather than actual blockage of the bowel.**
- **Irritation or sores in the lining of the mouth**
- **Inflammation (swelling and redness) of the pancreas**
- **Blockage of the small bowel**
- **Stiffening of muscles**
- **Cough**
- **Chills**
- **Infection**
- **Swelling of the face**
- **Swelling of the arms and/or legs**
- **Numbness, tingling**
- **Fever**
- **Limp or difficulty walking**
- **A condition in which both the liver and kidneys fail**
- **Chest pain not heart-related**
- **Liver failure**
- **Increase in size of the liver**
- **A condition in which there is blockage of the veins of the liver; leads to liver damage**
- **Test that shows a problem in blood clotting**
- **Increased blood level of a liver or bone enzyme (alkaline phosphatase)**
- **Increased blood level of a liver pigment (bilirubin) often a sign of liver problems**
- **Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)**
- **Increased blood level of a liver enzyme (GGT)**
- **Increased INR (measure of the ability of the blood to clot properly) which increases the risk of bleeding**
- *(deleted 4/26/12)*
- **Decreased number of a type of white blood cell (neutrophil/granulocyte)**

- **Weight gain**
- **Weight loss**
- **Decrease in the total number of white blood cells (leukocytes)**
- **More acid than normal in the blood**
- **Dehydration (when your body does not have as much water and fluid as it should)**
- **Increased blood sugar level**
- **Increased blood level of uric acid, a waste material from food digestion**
- **Decreased levels of a blood protein called albumin**
- **Decreased blood level of calcium**
- **Decreased blood sugar level**
- **Decreased blood level of potassium**
- **Decreased blood level of magnesium**
- **Decreased blood level of sodium**
- **Decreased blood level of phosphate**
- **Joint pain**
- **Back pain**
- **Bone pain**
- **Muscle pain**
- **Difficulty or limitation in ability to open mouth**
- **Loss of muscle coordination; awkward, uncoordinated walking; unsteadiness when walking**
- **Sleepiness**
- **Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)**
- **Taste changes**
- **Speech problems**
- **Restless, repetitive, or involuntary movements and rapid speech**
- **Headache or head pain**
- **Bleeding in the brain**
- **Stroke caused by decreased blood flow to the brain**
- **A malfunction of the nerves within the head and neck**
- **Paralysis of facial muscles due to problems with the nerves that supply them**
- **Weakness or paralysis (loss of muscle function) caused by damage to peripheral nerves (those nerves outside of brain and spinal cord)**
- **Convulsion or seizure**
- **Anxiety, feelings of dread or danger**
- **Confusion or other mental changes**
- **Feelings of sadness, worthlessness, thoughts of suicide or death (depression)**
- **Blood in the urine**
- **Bleeding in the kidney**
- **Need to urinate often**
- **Difficulty emptying the bladder**
- **Presence of blood in a fallopian tube (tube between ovary to uterus [womb])**
- **Bleeding in the ovary**

- **Bleeding in the prostate**
- **Bleeding in the spermatic cord (a structure resembling a cord that suspends the testis within the scrotum and contains the vas deferens [the tube that carries sperm] and other vessels and nerves)**
- **Bleeding in the testis**
- **Bleeding in the uterus (womb)**
- **Bleeding in the vagina**
- **Stuffy or runny nose, sneezing**
- **Bleeding from the lungs**
- **Sudden constriction of the small airways of the lung that can cause wheezing and shortness of breath**
- **Shortness of breath**
- **Hiccups**
- **Inflammation of the lungs that may cause difficulty breathing and can be life-threatening**
- **Scarring of the lungs that can cause coughing, shortness of breath, interfere with breathing**
- **Problem of the sinuses**
- **Voice change**
- **Excess sweating**
- **Itching**
- **Hives**
- **Sudden reddening of the face and/or neck**
- **Hot flashes**
- **High blood pressure**
- **Low blood pressure**
- **Inflammation (swelling and redness) of a vein; blood clot**
- **Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung**
- **Bleeding with a decreased number of blood cells that help to clot blood (platelets)**

Rare but serious:

- **Bleeding in your stomach or intestines**
- **Severe allergic reaction, which may cause difficult breathing, hives itching, low blood pressure and possibly death**
- **Condition in which the lens of the eye becomes cloudy**
- **Formation of blood clots in small blood vessels around the body that leads to a low platelet (a type of blood cell that helps to clot blood) count**
- **Gas in the intestinal (bowel) wall**
- **Inflammation (swelling and redness) of the gallbladder possibly associated with gallstones**
- **Sudden decrease of kidney function**

- **Severe potentially life-threatening damage to the lungs which can lead to fluid in the lungs**
- **Swelling and redness of the skin on the palms of the hands and soles of the feet**

Arm 2

Risks and side effects related to the combination of irinotecan and docetaxel include those that are:

Likely:

- **decrease in the number of white blood cells, red blood cells and platelets that may lead to an increased risk of infection, fatigue, bruising and bleeding**
- **nausea, vomiting**
- **diarrhea**
- **loss of appetite**
- **loss of hair**
- **skin sensitivity when exposed to sunlight**
- **dry skin, redness, rash**
- **brittle nails**
- **abdominal cramping**
- **generalized fatigue**
- **kidney damage**
- **abnormal liver function tests**
- **flushing or localized skin reactions**
- **swelling of the arms and legs**

Less likely:

- **soreness or painful sores in your mouth, throat or the tube from your mouth to your stomach**
- **tingling of hands and feet followed by pain, redness and swelling**
- **constipation**
- **low blood pressure during infusion**
- **high blood pressure that could be life-threatening**
- **slurred speech**
- **inflammation or infection of the bowel**
- **fever**
- **cough**
- **chills**
- **pain in your muscles or joints**
- **infection**
- **liver failure**
- **numbness, burning, tingling or prickling of skin**

- **seizure**
- **headache**
- **drowsiness**
- **anxiety/depression**
- **changes in taste**
- **inflammation of the eye**

Rare but serious:

- **dehydration**
- **serious infection starting from the bowel. This can cause death.**
- **scar tissue on the lungs that can cause coughing, shortness of breath, trouble breathing, or even death**
- **severe allergic reaction, which may cause difficulty breathing, hives with itching, low blood pressure and possibly death**
- **condition in which the lens of the eye becomes cloudy**
- **shortness of breath and dry cough**
- **fluid in the lung**
- **abnormal heart rhythm, fluid around the heart, congestive heart failure**
- **fluid retention,**
- **muscle weakness**
- **drug-related death**
- **abnormal bleeding and/or blood clots**
- **Very rare cases of myeloid leukemia or myelodysplasia**

Reproductive risks for all patients: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

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

Are there benefits to taking part in the study?

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

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

Your other choices may include:

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

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

Will my medical information be kept private?

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

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- *[List relevant organizations like local IRB, etc.]*
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials.
- SWOG
- Response Genetics, Inc.

A description of this study will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results of the study. You can search this web site any time.

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Oxaliplatin, leucovorin, 5-FU, docetaxel and irinotecan are commercially available and will be charged to you or your insurance.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/learningabout/payingfor/how-insurance-companies-decide. *(4/28/14)* You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about important new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at _____ (telephone number).

[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

Future Contact

I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

Yes **No**

Consent Form for Use of Specimens for Research

About Using Specimens for Research

You are going to or have had a biopsy (or surgery) to see if you have cancer. Your doctor will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue specimens that are left over from the biopsy or surgery, left over tissue from the ERCC-1 and (if applicable) HER-2 testing, and draw some blood (approximately two teaspoons before you begin treatment) for future research. If you agree, these specimens will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How are Specimens Used for Research" to learn more about specimen research.

The research that may be done with your specimens is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your specimens 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.

Things to Think About

The choice to let us keep the left over specimens 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 specimens 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 specimens. Then any specimens 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 SWOG 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 specimens are used for genetic research (about diseases that are passed on in families). Even if your specimens are used for this kind of research, the results will not be put in your health records.

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

Benefits

The benefits of research using specimens 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.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No." If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. **My specimens may be kept for use in research to learn about, prevent, treat or cure cancer.**

   Yes No

2. **My specimens may be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).**

   Yes No

3. **Someone may contact me in the future to ask me to allow other uses of my specimens.**

   Yes No

If you decide to withdraw your specimens from a SWOG Specimen Repository in the future, a written withdrawal of consent should be submitted through your study doctor to the SWOG Operations Office. Please designate in the written withdrawal whether you would prefer to have the specimens destroyed or returned to the study doctor.

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____
(or legally authorized representative) *(added 4/28/14)*

Date _____

Specimen Consent Supplemental Sheets

How are Specimens Used for Research?

Where do specimens come from?

A specimen may be from a blood sample or from bone marrow, skin, toenails or other body materials. People who are trained to handle specimens and protect donors' rights make sure that the highest standards of quality control are followed by SWOG. Your doctor does not work for SWOG, but has agreed to help collect specimens from many patients. Many doctors across the country are helping in the same way.

Why do people do research with specimens?

Research with specimens can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using specimens can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my specimen?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your specimen may look for genetic causes and signs of disease.

How do researchers get the specimen?

Researchers from universities, hospitals, and other health organizations conduct research using specimens. They contact SWOG and request samples for their studies. SWOG reviews the way that these studies will be done, and decides if any of the samples can be used. SWOG gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. SWOG will not send your name, address, phone number, social security number or any other identifying information to the researcher.

Will I find out the results of the research using my specimen?

You will not receive the results of research done with your specimen. This is because research can take a long time and must use specimen samples from many people before results are known. Results from research using your specimen may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your specimen, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to SWOG. If more information is needed, SWOG will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go to the researcher. The researcher will not know who you are.

How could the records be used in ways that might be harmful to me?

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research may not apply only to you, but to your family members too. For disease caused by gene changes, the information in one person's health record could be used against family members.

How am I protected?

SWOG is in charge of making sure that information about you is kept private. SWOG will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.

What if I have more questions?

If you have any questions, please talk to your doctor or nurse, or call our research review board at (Insert IRB's Phone Number).