ECOG-ACRIN
cancer research group
Reshaping the future of patient care

Operations Office
Located at the Frontier Science & Technology Research Foundation, Inc.

December 16, 2014

[redacted] MS RAC
[redacted]
Quality Assurance Section EPN Room 7000
CTEP, DCT, NCI
6130 Executive Boulevard
Rockville, MD 20852

Dear Ms. [redacted]

Enclosed is E5202, Update #6, *A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers.*

This update contains administrative and editorial changes only. We are submitting this update to the NCI and activating it within ECOG-ACRIN simultaneously.

The following revisions to the E5202 protocol were made in this update:

	Section	Change
1.	Cover Page	Updated NCI Update Date
2.	Global	Updated names, addresses, numbers, and forms relating to the move from ECOG-ACRIN PCO to ECOG-ACRIN CBPF.

The following revisions to the E5202 Informed Consent were made in this update:

	Section	Change
3.	Cover Page	Updated NCI Update Date

If you have any questions regarding this update, please contact [redacted] at [redacted] or (617) 632-3610.

Thank you.

Sincerely,

[redacted]
[redacted]

Enclosure
cc:
[redacted] MD
[redacted] MD
[redacted], MD
[redacted] MD
[redacted] DSc
[redacted] MD
[redacted] MD
[redacted] MD

[redacted] R.N.
[redacted]

00 Commonwealth Avenue, Boston, MA 02215 p: 617.632.3610 f: 617.632.2990 ecog-acrin.org

[redacted] MD
[redacted] MD
PhD,
PharmD
[redacted] PhD, PharmD
[redacted] MD

[redacted] R.Ph., MS, BCOP
PharmD

A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers

	STUDY CHAIR:	[redacted] III, MD
	STUDY CO-CHAIRS:	[redacted] MD
		[redacted] MD
	PATHOLOGY & LABORATORY CO-CHAIR:	[redacted] MD
	STUDY STATISTICIAN:	[redacted] DSc
	COMMUNITY CO-CHAIR:	[redacted], MD
Rev. 9/11	ECOG-ACRIN SURGERY CHAIR:	[redacted] MD
	GI COMMITTEE CHAIR:	[redacted] III, MD
Rev. 11/06	ACOSOG CO-CHAIR:	[redacted] MD
Rev. 11/06	SWOG CO-CHAIR:	[redacted] MD
Rev. 11/06, 8/09	NCIC-CTG CO-CHAIR:	[redacted] MD
Rev. 11/06	CALGB CO-CHAIR:	[redacted] MD
Rev. 12/08	DEVELOPMENTAL THERAPEUTICS CO-CHAIRS:	[redacted] PhD, PharmD [redacted] PhD, PharmD
Rev. 12/08, 8/09	PHARMACOGENETIC SUBCOMMITTEE CHAIR:	[redacted] MD

Version Date: April 30, 2014
NCI Update Date: December 16

Bevacizumab (NSC 704865, [redacted]) and oxaliplatin (NSC 266046) will be supplied by the NCI for this study.

The text of this protocol incorporates Addenda 1-8 and Update #1.

Rev. [redacted]

STUDY PARTICIPANTS

ALLIANCE / Alliance for Clinical Trials in Oncology*
SWOG / SWOG*
NCIC-CTG / NCIC Clinical Trials Group *
NRG / NRG Oncology Foundation, Inc

* This study is supported by the NCI Cancer Trials Support Unit (CTSU). Institutions not aligned with ECOG-ACRIN will participate through the CTSU mechanism. (Please see the Table of Contents and Appendix V for details.)

ACTIVATION DATE

August 4, 2005
Addenda #1-4 Prior to Activation
Addendum #5, January 11, 2006
Addendum #6, April 20, 2006
Addendum #7, 11/06
Update #1, 3/07
Addendum #8, 7/07 **ENTIRE DOCUMENT REVISED**
Update #2, 4/08
Update #3, 5/08
Addendum #9, 12/08
Update #4, 12/08
Addendum #10, 8/09
Addendum #11, 8/10
Addendum #12, 9/10
Update #5 – 9/11
Addendum #13, 7/14
Update #6 – 12/14

Table of Contents

STUDY CHAIR

[redacted], MD
Northwestern University
676 N. St. Clair; Suite 850
Chicago, IL 60611-2998
Phone: [redacted]
Fax: [redacted]
E-mail: [redacted]

STUDY CO-CHAIRS

[redacted] MD
University of Pennsylvania Cancer Center
12 Penn Tower
3400 Spruce Street, MAB103
Philadelphia, PA 19104-9104
Tel: [redacted]
Fax: [redacted]
E-mail: [redacted]

[redacted], MD
M.D. Anderson Cancer Center
1515 Holcombe Blvd. Box 85
Houston, TX 77030-7030
Tel: [redacted]
Fax: [redacted]
E-mail: [redacted]

Rev. 12/08
Rev. 12/08
Rev. 12/08
Rev. 12/08
Rev. 11/06, 7/07

STUDY CHAIR LIASON (SCL)

[redacted], RN, MS
Northwestern University
676 North St. Clair Suite 850
Chicago, IL 60611-2998
Phone: [redacted]
Fax: [redacted]
Email: [redacted]

STUDY CHAIR LIASON (SCL)

[redacted] ND, RN, CS-FNP, OCN
Northwestern University
676 North St. Clair Suite 850
Chicago, IL 60611-2998
Phone: [redacted]
Fax: [redacted]
E-mail: [redacted]

Rev. 11/06

ACOSOG CO-CHAIR

[redacted] MD
St. Michael Hospital
30 Bond Street, Suite 16 CCS-046
Toronto, ON, Canada M5B-1W8
Tel: [redacted]
Fax: [redacted]
Email: [redacted]

Rev. 11/06

SWOG CO-CHAIR

[redacted] Gold, MD
Swedish Cancer Institute
221 Madison Street
Seattle, WA 98104
Tel: [redacted]
Fax: [redacted]
Email: [redacted]

Rev. 11/06, 8/09

NCIC-CTG CO-CHAIR

[redacted] MD
Cross Cancer Institute
11560 University Avenue
Edmonton, AB Canada
T6G 1Z2
Tel: [redacted]
Fax: [redacted]
Email: [redacted]

Rev. 11/06

CALGB CO-CHAIR

[redacted], MD
[redacted]
Brigham and Women's Hospital
75 Francis Street
Boston, MA 02115
Tel: [redacted]
Fax: [redacted]
Email: [redacted]

Rev. 11/06, 12/14

PATHOLOGY COORDINATING CENTER CONTACT

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

Rev. 3/07

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

Institutions not aligned with ECOG-ACRIN will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://members.ctsu.org
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the ECOG-ACRIN. **Case report forms** (with the exception of patient enrollment forms) **and clinical reports** must be sent to ECOG-ACRIN unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.

Rev.

- **Data clarification forms and delinquency reports** will be sent directly to the enrolling site by ECOG-ACRIN. Please send data clarification form responses and delinquent data to ECOG-ACRIN and do not copy CTSU Data Operations. Please mail data clarification form responses and delinquent data directly to ECOG-ACRIN unless otherwise directed. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the ECOG-ACRIN data center.

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

Rev. 3/07

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, PA 19103 Phone – 1-888-823-5923 Fax – 215-569-0206	CTSU Patient Registration Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 Hours: 8:00 AM – 8:00 PM Eastern Time, Monday – Friday (excluding holidays) [For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.]	ECOG-ACRIN Operations Office – Boston, FSTRF 900 Commonwealth Avenue Boston, MA 02215 (ATTN: DATA). Phone # 617-632-3610 Fax # 617-632-2990 Data should be sent via postal mail (preferred), however fax is accepted. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
For patient eligibility or treatment-related questions: Contact the Study PI of the Coordinating Group.		

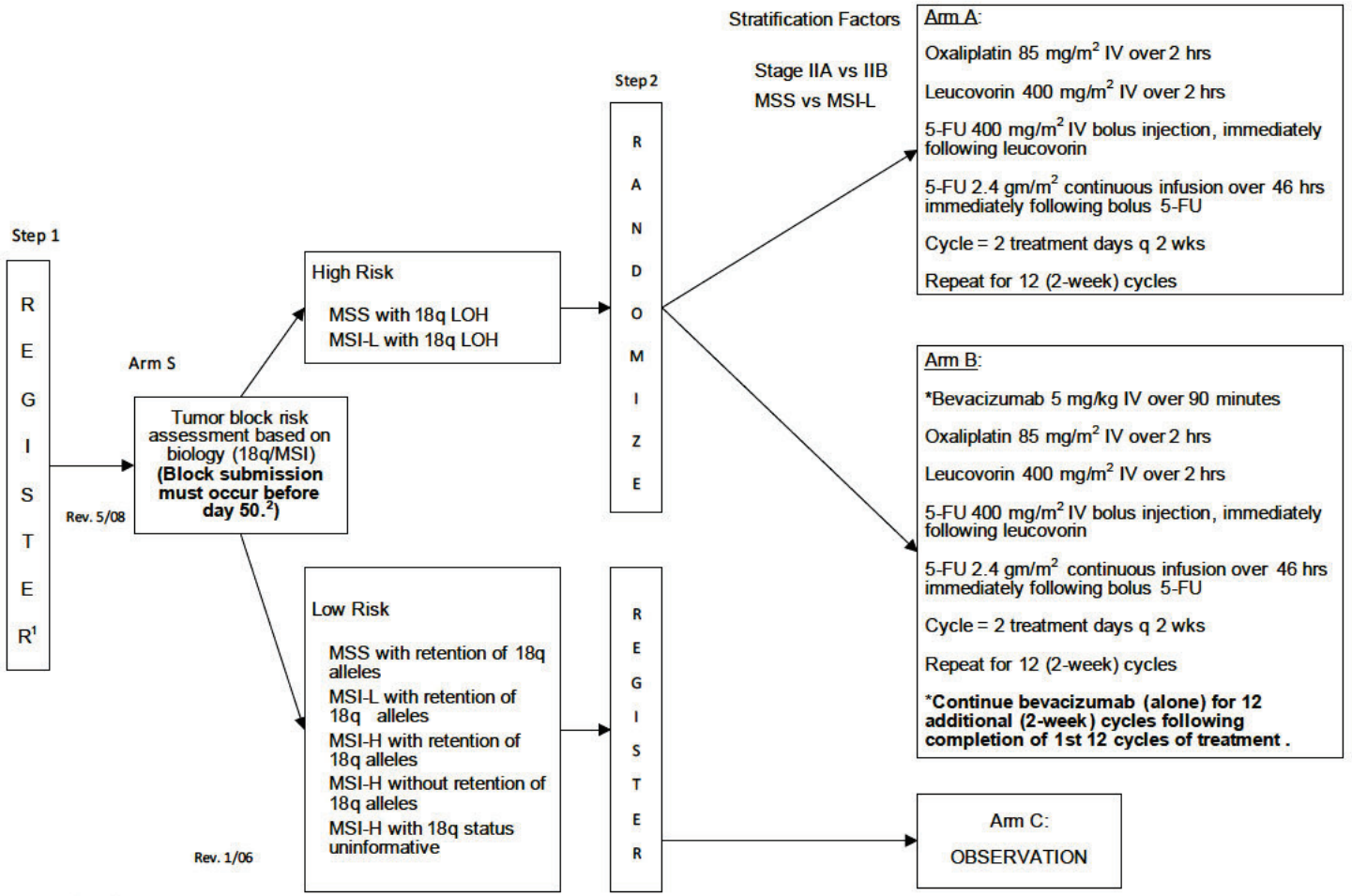
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

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

The CTSU Registered Member Web site is located at https://members.ctsu.org

CTSU logistical information is located in Appendix V.

Schema



Accrual Goal: 3,610

Cycle = 2 treatment days every 2 weeks
Dose calculations based on actual body weight at beginning of each cycle

1. Patients must begin adjuvant treatment (if randomized to Arm A or B) no less than 28 days and no more than 60 days after surgery, < 50 days optimal.
2. Tissue (tumor sample and normal mucosa sample) submission mandatory for randomization /registration prior to treatment assignment . Tissue should be submitted to the PCO post-operatively, but not later than day 50 to allow for tumor tissue molecular assessment . See section 10.

Rev. 11/06, 4/08

1. Introduction

1.1 Background

It is estimated that 130,000 new cases of colon cancer are diagnosed in the United States yearly. Of these, patients with Stage II colon cancer (tumor that has penetrated through the muscularis propria with negative lymph nodes, T_{3-4}, N_0, M_0) carry a 20-25% risk of recurrence. The Intergroup experience demonstrates minimal, if any, benefit of adjuvant therapy for stage II colon cancer patients perhaps in part because insufficient numbers of patients have been evaluated in past studies. Observation remains an appropriate option for these patients and is consistent with the 1990 consensus meeting held at the National Institutes of Health. There is a need to identify the subset of patients with stage II colon cancer who are at greatest risk to develop disease recurrence. ECOG and other data suggest that two groups of patients can be defined, high-risk vs. low-risk, based on 18q loss of heterozygosity (LOH) and microsatellite instability status (1). If these retrospective molecular observations hold true for patients with stage II colon cancer, it will be possible to more clearly define a low-risk group that would not require postoperative therapy. The focus for drug development would include the high-risk patients (18q LOH in microsatellite stable tumors and absence of the mutation of the gene for type II receptor for TGF-β1 in tumors with high levels of microsatellite instability).

Although the cure rates for patients with stage III colon cancer are clearly improved with 5-FU and leucovorin-based chemotherapy, patients with stage II colon cancer have received little, if any, benefit from adjuvant chemotherapy (2,3). In the recent Intergroup adjuvant trial, INT 0089, high-risk stage II patients (perforation or obstruction) achieved a 78% survival with adjuvant chemotherapy (4-6). It is unclear whether these patients, whose survival is comparable to the entire group of stage II patients, benefited from the adjuvant therapy or whether the stated risk factors were truly sufficient to alter survival. Since 20-25% of stage II patients will relapse, there is an expectation that these patients would potentially benefit from adjuvant therapy if they could be identified.

The ECOG retrospective data evaluating 18q where the DCC and other genes reside, MSI and integrity of the TGF β1-type II receptor suggest that it may be possible to identify a high-risk population who may not benefit from 5-FU-based therapy (1). Although the ideal trial for the high-risk stage II patients would include a no treatment observation arm, multiple focus groups, including patient representatives, have made it clear that a no treatment arm is unacceptable. Since the ECOG retrospective molecular data included a majority of patients who received a 5-FU-based regimen (e.g., 5-FU and leucovorin, the standard adjuvant regimen for stage III patients), a 5-FU –containing regimen would be an acceptable control arm for this trial.

Vascular endothelial growth factor (VEGF) has been identified as a crucial regulator of both normal and pathologic angiogenesis. Increased levels of VEGF expression have been found in most human tumors examined including tumors of the gastrointestinal tract. Inhibition of VEGF using an anti-VEGF monoclonal antibody blocks the growth of a number of human cancer cell lines in nude mice including the colorectal cancer cell lines, LS174T, HM-7, and LSLiM6. In addition,

the combination of anti-VEGF antibody and chemotherapy in nude mice injected with human cancer xenografts results in an increased antitumor effect compared with antibody or chemotherapy alone. Bevacizumab, a recombinant humanized version of a murine anti-human VEGF monoclonal antibody (rhuMAB VEGF), has been advanced into clinical development by Genentech, Inc.

Clinical development of bevacizumab began with two Phase I studies. Study AVF0737g, an open-label, dose-escalation study, evaluated the initial safety and pharmacokinetics of single-agent bevacizumab in subjects with advanced malignancies. In this study, 3 subjects experienced tumor-related hemorrhagic events; in two cases, the event was classified as serious. The pharmacokinetics of bevacizumab appeared to be linear for doses of $\geq$ 1 mg/kg, with a half-life of ~ 15 days. Study AVF0761g evaluated multiple does of bevacizumab in combination with one of three cytotoxic chemotherapy regimens (5-FU/leucovorin, carboplatin/paclitaxel, or doxorubicin) in subjects with advanced solid malignancies. No subjects in this study experienced serious bleeding. Co-administration of bevacizumab with cytotoxic chemotherapy did not appear to result in a change in the systemic concentrations of the cytotoxic agents. No antibodies to bevacizumab were detected in either study.

Study AVF0780g was a Phase II, multi-dose, randomized, multi-center clinical trial to evaluate the efficacy, safety and pharmacokinetics of bevacizumab combined with 5-FU/leucovorin in subjects with metastatic colorectal cancer (7). Subjects were randomized to three treatment arms: control (5-FU/leucovorin alone) 5 mg/kg bevacizumab plus 5-FU/leucovorin, or 10 mg/kg bevacizumab plus 5-FU/leucovorin. Bevacizumab was administered IV every 2 weeks until disease progression or for a maximum of 1 year. The primary efficacy endpoints were time to disease progression and best confirmed response (complete or partial response) rate as determined by an independent review group that was blinded to treatment assignment:

	Control (n=36)	5 mg/kg (n=35)	10 mg/kg (n=33)
Best Confirmed RR	6 (17%)	14 (40%, p=0.029)	8 (24%)
Median Time to Prog	5.2 mos.	9.0 mos. (p=0.005)	7.2 mos.
Median Survival	13.8 mos.	21.5 mos.	16.1 mos.

Subjects in the control arm who developed progressive disease had the option to cross over and receive single-agent bevacizumab. In all, 21 patients crossed-over and two achieved a partial response on single agent anti-VEGF in the cross-over phase.

During ASCO 2003, initial results from a randomized Phase III first-line trial of bevacizumab in combination with bolus IFL (irinotecan, 5-FU and leucovorin) were reported and then published in June 2004 (8, 13). A total of 925 patients were accrued with 813 patients randomized to IFL + placebo vs. IFL + bevacizumab given at a dose of 5 mg/kg every two weeks. A third group of patients (n=110) received 5-FU and leucovorin + bevacizumab. The following table summarizes the results.

	IFL/Placebo	IFL/BV	p-value
Randomized	411	402	

Median survival (mos)	15.6	20.3	< 0.001
PFS (mos)	6.24	10.6	< 0.001
ORR (CR+PR)	34.8%	44.8%	0.004
Duration of response (mos)	7.1	10.4	0.001
Grade ¾ bleeding*	2.5%	3.1%	
Any thromboembolism*	16.2%	19.4%	
Grade 3 proteinuria*	0.8%	0.8%	
Grade 3 hypertension*	2.3%	11%	

2. Uncorrected for differential time on therapy

Data for the 110 patients who received 5-FU, leucovorin and bevacizumab demonstrated an overall survival of 18.3 months, response rate of 40% and progression-free survival (PFS) of 8.5 months. Crossover to bevacizumab was disallowed for the placebo arm and 110 of 393 patients continued bevacizumab after progression on IFL. Fifty-three percent of patients received any second-line therapy in the control arm and 62% in the bevacizumab arm. Of these, 25% received oxaliplatin. Overall, the addition of bevacizumab to IFL was well tolerated. Only grade III hypertension, which was easily controlled with oral medications, was increased in the Phase III trial. Compared to the control arm, 22.4% vs. 8.3% experienced some increase in blood pressure. There was no difference in bleeding. Thrombotic events were noted in 19.4% vs. 16.2%. Sixty-day mortality was 4.9% vs. 3% in the control arm. There were six cases of bowel perforation noted in patients receiving bevacizumab, compared to none on the placebo arm.

Additional bevacizumab safety data were presented at ASCO 2003 by ECOG investigators (9). E3200 is a randomized Phase III trial evaluating the addition of bevacizumab to FOLFOX 4 compared to a bevacizumab alone arm. The dose of bevacizumab was 10 mg/kg and a total of 835 patients were randomized. Bevacizumab added to FOLFOX 4 did not substantially alter the regimen's toxicity profile, as presented in the table below.

	FOLFOX4+BEV N=75		**FOLFOX4 N=73**		**BEV N=75**	
	G3	G4	G3	G4	G3	G4
Hemorrhage	3%	0	0	0	3%	0
Thrombosis/embolism	4%	0	1%	0	1%	0
Hypertension	8%	1%	1%	0	7%	0
Neutropenia	n/a	8%	n/a	21%	0	0
Febrile neutropenia	1%	0	3%	0	0	0
Infection w/G3-4 neutropenia	0	1%	6%	1%	0	0
Diarrhea	11%	0	11%	0	1%	0
Vomiting	5%	0	1%	0	1%	0
Neuropathy (sensory)	4%	0	3%	0	0	0
Fatigue	8%	0	14%	1%	4%	1%
Worst grade	37%	11%	25%	23%	20%	9%

In the AVF2107 study, there was a 1% incidence of arterial thromboembolic events (ATE) (which include myocardial infarction, transient ischemia attack,

cerebrovascular accident/stroke and angina/unstable angina) in the IFL + placebo arm versus 3% in the IFL + bevacizumab arm. A pooled analysis of the rate of ATE from 5 randomized studies showed that treatment with bevacizumab increased the risk of these events two- or three-fold (up to 5%). Furthermore, certain baseline characteristics, specifically age > 65 years and prior ATE conferred additional risk.

At ASCO 2002 and 2003, the safety data and initial outcome data from the MOSAIC trial were presented and then published in June 2004 (10, 11, 14). This international, multicenter, randomized, Phase III study evaluated the effect of disease-free survival (DFS) of oxaliplatin and fluorouracil (5-FU)/leucovorin (LV) (FOLFOX4) compared with 5-FU/LV alone (LV5FU2) in the adjuvant setting in 2,246 stage II/III colon cancer patients. These patients, aged 18 to 75 years with completely resected colon cancer, were enrolled from October 1998 to January 2001 (1,123 in each arm). Additional entry criteria included treatment within 7 weeks of surgery; no prior radio-, chemo- or immunotherapy and an ECOG performance status (PS) ≤ 2 or a Karnofsky performance status (KPS) 60%. Patients were stratified according to study center, disease stage and bowel obstruction or tumor perforation. Patients were randomly scheduled to receive 12 cycles of therapy of either FOLFOX4 or LV5FU2 for 6 months of therapy. Patient characteristics were balanced in each arm with respect to gender, age, primary site, disease stage (40% stage II, 60% stage III), and performance status (KPS of 60%-100%). (11)

Single-agent dose modifications were as follows: Oxaliplatin was dose reduced for painful paresthesias or paresthesias with functional impairment; dose modifications of 5-FU were stipulated for grade 3/4 skin toxicity. Oxaliplatin and 5-FU doses were both reduced for grade 3/4 neutropenia, thrombocytopenia, diarrhea, stomatitis or other grade 3 drug-related toxicity. Treatment was discontinued in the event of cardiac toxicity, allergy or cerebellar toxicity. (10) Dose intensities were greater than 80% for both arms. Patients received a median of 12 cycles.

The primary end point, 3-year DFS, was 78.2% for FOLFOX4 vs. 72.9% for LV5FU2 (*P* =.002), with a 23% risk reduction in recurrence in patients treated with FOLFOX4 regardless of subset.

General toxicity results are presented in the first table and peripheral sensory neuropathy associated with FOLFOX4 is presented in the second table below. Toxicity was graded according to NCI Common Toxicity Criteria, version 1.

Toxicity by Percent of Patients, NCI Grade ≥ 3

NCI Grade ≥ 3	FOLFOX4 (n = 1,108)	LV5FU2 (n = 1,111)
Thrombocytopenia	1.7	0.4
Neutropenia	41.1*	4.7
Febrile neutropenia	1.8	0.2
Diarrhea	10.8	6.6
Stomatitis	2.7	2.2
Vomiting	5.8	1.4
Allergy	2.9	0.2
All-cause mortality	0.5	0.5

*Grade 4; 12.3%

**Peripheral Sensory Neuropathy in FOLFOX4 Arm
By Percent of Patients and Cycles**

Paresthesias (NCI grade)	FOLFOX4	
	Patients (%) (n = 1,106)	18 month follow-up (%) (n = 967)
Grade 1	48.2	19.8
Grade 2	31.6	3.4
Grade 3	12.4	0.5

Grade 3 sensory neuropathy was observed in 137 patients (12.4%) on the FOLFOX4 arm. One month after discontinuing treatment, > 60% of these patients had a partial or total recovery from grade 3 neuropathy. By 6 months, < 10% of these patients had grade 3 neuropathy and at 1-year follow-up, patients with grade 3 neuropathy decreased to 1.1% (11, 14).

Various modifications of the combination of oxaliplatin with 5-FU + LV regimens (FOLFOX1-FOLFOX7) have been evaluated[18-21]. The more recent modifications have simplified the schedule of administration and improved patient convenience without apparently compromising the efficacy of the regimen. Maindrault-Goebel et al reported on a phase II study of oxaliplatin (100 mg/m^2) and LV (400 mg/m^2) as a 2-hour infusion on Day 1 followed by bolus (400 mg/m^2) and a 46-hour infusion (2.4-3.0 g/m^2) of 5-FU every 2 weeks (FOLFOX6) as second-line treatment for metastatic colorectal cancer[19]. Sixteen of 60 patients treated had a partial response (27%) and an additional 45% had stable disease. Median PFS was 5.3 months and median survival was 10.8 months. Ryan et al evaluated biweekly oxaliplatin in combination with a modified FOLFOX6 regimen (oxaliplatin 85 mg/m^2 as a 2-hour infusion on Day 1 of each 2-week cycle, immediately followed by LV, 500 mg/m^2 as a 2-hour infusion followed by bolus 5-FU, 400 mg/m^2 and a 46-hour infusion of 5-FU, (total dose 2.4 g/m^2) in heavily pretreated patients with advanced colorectal cancer. Preliminary data showed a response rate of 7%[20]. Updated information reveals a response rate of 11% (5%-22%), all in patients who had received prior irinotecan. When only second-line patients were considered, the response rate was 25% (8-43%). Andre and coworkers reported preliminary results of the Optimox trial comparing first-line therapy of FOLFOX4 to FOLFOX7 at ASCO 2003[21]. FOLFOX7 uses an every 2-week schedule of LV 400 mg/m^2 and oxaliplatin 130 mg/m^2 followed by a 46-hour infusion of 5-FU 2400 mg/m^2. With 524 patients randomized, the ORR and PFS on the two arms were identical (ORR=59.8 and 63.1% and PFS=8.9 and 9.2 months). Toxicities with both regimens were similar with the exception that FOLFOX7 had significantly less grade 3/4 neutropenia and grade 3 neuropathy, but more grade 3/4 alopecia, thrombocytopenia and hand-foot syndrome, when compared with FOLFOX4. Finally, FOLFOX6 was compared directly with 5-FU + LV + irinotecan (FOLFIRI) in a randomized study conducted by Tournigand and coworkers[22]. These investigators found that the ORR and PFS associated with the first-line use of either regimen was nearly identical with response rate of 54 and 56% and PFS of 8 and 8.5 months, respectively. Taken together, these data suggest that the various modifications of the FOLFOX regimen result in similar clinical outcomes in patients with advanced colorectal cancer, although data concerning direct comparisons between the regimens is limited.

In E5202, we propose that beginning bevacizumab administration in combination with 5-FU, leucovorin and oxaliplatin will maximize its effects for the high-risk stage II patients.

1.2 Molecular Analysis for Risk Assessment/Treatment Assignment

The rationale for the molecular analysis is similarly compelling. The data generated in previous ECOG trials show that the specific abnormalities of individual tumors are an independent determinant of outcome. This important retrospective observation needs prospective validation, especially since the literature is conflicting at present with small studies purporting to show the relevance of several molecular markers, often asserting opposing prognostic influences.

The relationship between microsatellite instability and response to adjuvant chemotherapy is controversial. The studies of Elsaleh et al showed that patients with stage III colorectal cancer, whose tumor demonstrated MSI, derived greater benefit from adjuvant chemotherapy than microsatellite-stable cancers; whereas Ribic et al found that patients with microsatellite instability in their tumors did not benefit from adjuvant chemotherapy and showed a trend toward poor survival. A third study by the National Surgical Adjuvant Breast and Bowel Project in stage II and III patients showed that patients whose colon cancer had microsatellite instability and patients with microsatellite-stable cancers benefited equally from adjuvant chemotherapy (15, 16, 17).

This uncertainty was emphasized at a recent CTEP workshop to review the field: the ECOG results were discussed in detail at this workshop and the need for prospective validation agreed. The major markers to be studied are 18q, MSI and integrity of the TGF-β1 type II receptor. Clearly, provision will be made for analysis of additional markers in the future and, based on the use of the VEGF inhibitor, a retrospective analysis of outcome based on receptor expression and additional prognostic markers including those associated with 5-FU sensitivity/resistance. Validation of these markers would potentially provide the groundwork with which to investigate a role for individualized postoperative therapy and to tailor treatment to the specific tumor.

Forty percent of stage II patients will fall into the high-risk patient group, defined by a microsatellite-stable tumor with 18q LOH and 60% will fall into the low-risk group, defined by a tumor with high levels of microsatellite instability (MSI-H) or microsatellite stability with retention of 18q alleles. The molecular markers selected to distinguish high-risk vs. low-risk patient groups with stage II colon cancer were not selected based on any association to bevacizumab therapy. The molecular markers were selected based on clinical trial data of 5-FU-based chemotherapy in the adjuvant setting, and did not include bevacizumab as a component of therapy.

Rev. 8/09

The low-risk group of stage II patients will have a 5-year survival of approximately 90% whereas the high-risk stage II patients will have a 60% 5-year survival.

The addition of the anti-VEGF monoclonal antibody, bevacizumab, will improve survival in patients with high-risk stage II disease in combination with 5-FU, leucovorin and oxaliplatin compared to those high-risk patients randomized to receive 5-FU, leucovorin and oxaliplatin.

1.3 Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome:

Rev.

RPLS or clinical syndromes related to vasogenic edema of the white matter have been rarely reported in association with bevacizumab therapy (< 1%). Clinical presentations are variable and may include altered mental status, seizure and cortical visual deficit. HTN is a common risk factor and was present in most (though not all) patients on bevacizumab who developed RPLS. MRI scans are key to diagnosis and typically demonstrate vasogenic edema (hyperintensity in T2 and FLAIR images and hypointensity in T1 images) predominantly in the white matter of the posterior parietal and occipital lobes; less frequently, the anterior distributions and the gray matter may also be involved. RPLS should be noted in the differential diagnosis in patients presenting with unexplained mental status change, visual disturbance, seizure or other CNS findings. RPLS is potentially reversible, but timely correction of the underlying causes, including control of BP and interruption of the offending drug, is important in order to prevent progression to irreversible tissue damage.

1.4 Gastrointestinal Perforation/Fistula:

Rev.

GI perforations/fistula have been rarely reported but occurred at an increased rate in bevacizumab-containing therapies. The majority of such events required surgical intervention and some were associated with a fatal outcome. In the pivotal phase 3 trial in CRC (AVF2107), the incidence of bowel perforation was 2% in patients receiving IFL/bevacizumab and 4% in patients receiving 5-FU/bevacizumab compared to 0.3% in patients receiving IFL alone. GI perforation has also been reported in patients with gastric/esophageal cancer, pancreatic cancer, or comorbid GI conditions such as diverticulitis and gastric ulcer. GI perforation should be included in the differential diagnosis of patients on bevacizumab therapy presenting with abdominal pain or rectal/abdominal abscess.

1.5 On Study Guidelines

Rev. 7/07

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. It is important that at the time of Informed Consent, the patient understands both components of the trial and must be willing to accept the treatment assigned based on risk as determined by the microsatellite stability and 18q status.

1.6 NSABP C-08 and the AVANT B017920 Trial

Rev. 8/09

Two recent reports discussing the safety and efficacy from analyses of “NSABP C-08: A randomized phase III study of modified FOLFOX6 with or without bevacizumab for the adjuvant treatment of patients with stage II or III colon cancer” have been presented[23, 24]. Patients were randomized to receive either modified FOLFOX6 (oxaliplatin 85 mg/m^2, IV d1, leucovorin 400 mg/m^2 IV d1, 5-FU 400 mg/m^2 IV bolus d1, and 5-FU 2400 mg/m^2 CI over 46 hrs (d1+2) q14 d x 12 cycles) or mFOLFOX6 + bevacizumab (same mFOLFOX6 regimen + bevacizumab 5 mg/kg IV q 2 weeks x 1 year). The initial safety report of NSABP C-08 included 2,710 randomized patients demonstrating rates of grade 4 or 5

toxicities which were similar between the two arms, mFOLFOX 6 and mFOLFOX6 + bevacizumab (15.2% and 15%, respectively)[23]. The 6 month mortality rates were 0.96% and 0.9% respectively. The grade 3+ toxicities that were noted more frequently in the mFOLFOX + bevacizumab included hypertension (12% v 1.8%, respectively), wound complications (abdominal incisional hernia or infusion port dehiscence/inflammation; 1.7% v 0.3%, respectively), pain (11.1% v 6.3%, respectively), and proteinuria (2.7% v 0.8%, respectively). In addition, grade 2+ neuropathy was seen more frequently with mFOLFOX + bevacizumab (grade 2, 33% v 29%, respectively; grade 3, 16% v 14%, respectively; grade 4, < 1% each). There was, however, less thrombocytopenia in the mFOLFOX + bevacizumab arm (1.4% v 3.4%, respectively) and fewer allergic reactions (3.1% v 4.7%, respectively). Older patients experienced greater grade 4 and 5 toxicities regardless of treatment. Overall, it was felt that bevacizumab with modified FOLFOX6 was well tolerated in the adjuvant setting.

Efficacy results were reported at ASCO 2009 on 2,672 patients with stage II (24.9%) or stage III colon carcinoma[24]. Median follow up was 36 months. The results indicate that the addition of bevacizumab to mFOLFOX6 do not result in a statistically significant prolongation in the DFS (3 year DFS 75.5% v 77.4%, respectively, HR=0.89, p=0.15). The presentation also included an estimate of the DFS HR over time indicating that becazuimab reduced the risk of a DFS event during the interval from 0.5 to 1.0 year (year 1 HR = 0.6, p=0.0004; year 1.5 HR= 0.74, p=0.004;year 2 HR =0.81, p=0.02).

	N	Ev	3yDFS	P	Yr	1	1.5	2	2.5	3
mFF6	1338	312	75.5		**HR**	0.60	0.74	0.81	0.85	0.87
mFF6 + b	1334	291	77.4	0.15	**P**	0.0004	0.004	0.02	0.05	0.08

Data from the AVANT BO17920 trial are pending. There were 3,450 patients with stage II and III colon cancer accrued through this study between December 2004 and May 2007. The randomization is a comparison of FOLFOX4 v FOLFOX4 + bevacizumab v xelox + bevacizumab. The results of this study are expected within 1 year.

2. Objectives

2.1 Primary Objective

To demonstrate an improvement in 3-year disease-free survival for high-risk stage II colon cancer patients randomly assigned to 5-FU, leucovorin, oxaliplatin versus 5-FU, leucovorin, oxaliplatin and bevacizumab.

2.2 Secondary Objectives

2.2.1 To compare overall survival between the regimens.

2.2.2 To further define the toxicity profiles of the regimens.

2.2.3 To prospectively determine the impact of tumor biological characteristics on the survival of patients with stage II colon cancer.

2.2.4 Pharmacogenetic Ancillary Objective: To assess the association between oxaliplatin exposure, allelic variants in candidate genes, and neurotoxicity

3. Selection of Patients

Rev. 8/10

Applicable criteria in the following section must be met in order for a patient to be considered eligible for this study. Please carefully follow the instructions below and use the spaces provided to confirm a patient's eligibility.

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 four weeks later would be considered Day 28.

Rev. 7/07

NOTE: Because assignment to treatment Arms A/B and observation Arm C is based upon results of the risk assessment evaluating microsatellite instability and loss of heterozygosity at 18q, submission of tumor tissue and normal mucosa is pivotal to the completion of study. Your careful attention to submission time-points is crucial.

ECOG-ACRIN Patient No. _____

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

Physician Signature and Date _____

NOTE: All questions regarding eligibility should be directed to the ECOG-ACRIN Operations Office – Boston at (617) 632-3610.

NOTE: Institutions may use the eligibility checklist below as source documentation if it has been reviewed, signed and dated prior to registration/randomization by the treating physician.

3.1 Step 1: Initial Registration

Rev. 8/10

NOTE: During Step 1 initial registration, it is necessary to review requirements of Step 2 (3.2) to ensure that medical history and available post-operative laboratory values do not result in exclusion.

Rev. 8/10

3.1.1 The distal extent of the tumor must be ≥ 12 cm from the anal verge on endoscopy. If this distance was not confirmed on endoscopy pre-operatively, then the distal extent of the tumor must be ≥ 12 cm from the anal verge as determined by surgical examination. Colonoscopy should be performed postoperatively for those unable to have a preoperative colonoscopy to guarantee there are no synchronous lesions.

Distal extent of the tumor measures: _____

(If tumor is located beyond sigmoid colon and centimeter distance unavailable, include anatomic region of colon, e.g. right colon, transverse colon, hepatic flexure descending colon, cecum etc.)

Rev. 12/08

3.1.2 Patients must have paraffin-embedded tumor specimen available for evaluation of microsatellite instability and loss of heterozygosity at 18q, to determine high risk versus low risk. Tumor samples and normal mucosa will be shipped as specified in Section 10.2.

Rev. 7/07

3.1.2.1 High-risk patients will be randomized to treatment Arms A or B.

3.1.2.2 Low-risk patients will be registered to Arm C for observation. (Criteria noted in Sections 3.2.1 through 3.2.18 need not be met.)

Rev. 7/07
Rev.

NOTE: Every effort should be made to submit blocks (tumor and normal mucosa) to the PCO immediately. Blocks CANNOT be accepted after day 50 (post surgery) in order to allow for molecular assessment.

Date of surgery: _____ Date blocks sent to PCO: _____

Rev. 8/10

NOTE: Specific laboratory requirements for Step 2 must be obtained within 2 weeks prior to Step 2 randomization.

Rev. 7/07

3.1.3 Patients must not have synchronous tumors.

Rev. 7/07

3.1.4 Patients must not have appendiceal tumors.

Rev. 7/07

3.1.5 Patients must not have a history of inflammatory bowel disease (IBD).

Rev. 7/07, 12/08

3.1.6 Patients with hereditary non-polyposis colorectal cancer (HNPCC) are eligible.

Rev. 7/07

3.1.7 Patients must have no history of isolated, distant, or non-contiguous intra-abdominal metastases, *even if restricted*.

3.1.8 Patients must have histologically confirmed adenocarcinoma of the **colon** that meets the criteria below:

Rev. 12/08

Rev. 8/10

Stage II adenocarcinoma (pT3/pT4a/pT4b pN0 M0 according to the definitions of the American Joint Committee on Cancer, 7th Edition, 2010): The tumor invades through the muscularis propria into pericolic tissues (pT3), penetrates to the surface of the visceral peritoneum (pT4a), or directly invades other organs or structures (pT4b). Patients with mesenteric tumor deposits or satellites without identifiable residual lymph node in the absence of lymph node involvement are now designated pN1c, rather than pT3. Patients with such tumor deposits are not eligible for E5202.

Rev. 8/10

Appendix IV provides the AJCC 7th Edition (2010) TNM nomenclature and staging for colon cancer.

Stage: _____

Rev. 12/08

Patients must have had a complete resection (R0 resection).

R0 resection? Yes_____ No_____

3.1.9 Patients must have ≥ 8 lymph nodes evaluated and reported.

Number of lymph nodes evaluated and reported: _____

Rev. 11/06, 12/08

3.1.10 Patients must not have presented with clinical complete obstruction or perforation of the bowel.

3.1.11 Patients must not have had any systemic or radiation therapy initiated for this malignancy.

Rev. 12/08, 8/10

3.1.12 Patients must not have a previous or concurrent malignancy. Exceptions are made for patients who meet any of the following conditions:

- Non-melanoma skin cancer, in situ cervical cancer, or breast cancer in situ.
- Prior malignancy completely excised or removed and patient has been continuously disease free for > 5 years.

  Date of last evidence of disease: _____
- Patients with completely excised or removed breast cancer and disease free > 5 years, regardless of the continuation of hormonal therapy.

  Date of last evidence of disease: _____
- Patients with previous RT to the pelvic region will be ineligible.

Rev. 8/10

3.1.13 Patients must be ≥ 18 years old.

3.1.14 Patients must have ECOG performance status of 0-2.

3.2 Step 2: Randomization (High Risk Patients – Arms A and B only)

Rev. 8/10

NOTE: Each of the criteria below must be met within 2 weeks prior to RANDOMIZATION for eligibility purposes. Please refer to Section 7 for criteria that must be met within 2 weeks prior to TREATMENT. Plan accordingly to avoid repeating tests/assessments.

3.2.1 Within 2 weeks prior to randomization, postoperative absolute granulocyte count (AGC) must be ≥ 1500/mm_3 (or < 1500/mm_3, if in the opinion of the investigator, this represents an ethnic or racial variation of normal).

AGC count: _____ Date of test: _____

3.2.2 Within 2 weeks prior to randomization, the postoperative platelet count must be ≥ 100,000/mm^3.

Platelet count: _____ Date of test: _____

3.2.3 Within 2 weeks prior to randomization, there must be postoperative evidence of adequate hepatic function.

Bilirubin must be ≤ ULN unless the patient has a chronic grade 1 bilirubin elevation due to Gilbert's disease or similar syndrome due to slow conjugation of bilirubin.

ULN: _____ Bilirubin: _____ Date of test: _____

Alkaline phosphatase must be < 2.5 x ULN.

ULN: _____ Alk Phos: _____ Date of test: _____

AST must be < 1.5 x ULN.

ULN: _____ AST: _____ Date of test: _____

[Deleted in Addendum #9]

Rev. 11/06, 7/07, 12/08

3.2.4 Within 2 weeks prior to randomization, there must be postoperative evidence of adequate renal function.

Serum creatinine ≤ 1.5 x ULN.

ULN: _____ Creatinine: _____ Date of test: _____

Urine protein/creatinine (UPC) ratio of < 1.0. Patients with a UPC ratio ≥ 1.0 must undergo a 24-hour urine collection, which must be an adequate collection and must demonstrate < 1 gm of protein in order to participate. (See Appendix VIII).

Rev. 1/06

UPC rates: _____ Date of test: _____

3.2.5 Patients with any significant bleeding that is not related to the primary colon tumor within 6 months prior to study entry are not eligible.

Date of bleeding episode: _____

3.2.6 Patients with gastroduodenal ulcer(s) determined to be active by endoscopy are not eligible.

3.2.7 Patients with a history of hypertension must measure < 150/90 mmHg and be on a stable regimen of anti-hypertensive therapy.

BP measurement: _____

Anti-hypertensive therapy: _____

3.2.8 Patients must not have a serious or non-healing wound, skin ulcers or bone fracture.

3.2.9 [Deleted in Addendum #8]

Rev. 7/07

3.2.10 Patients experiencing clinically significant peripheral neuropathy at the time of step 2 randomization (defined in the NCI Common Terminology Criteria for Adverse Events version 4.0 [CTCAE 4.0] as grade 2 or greater neurosensory or neuromotor toxicity) are not eligible.

Rev. 9/11

3.2.11 Patients must not have had invasive procedures, defined as follows:

Major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to randomization

Yes: _____ No: _____ Date of procedure: _____

Core biopsy or other minor procedure, excluding placement of a vascular access device, within 7 days prior to randomization

Yes: _____ No: _____ Date of procedure:_____

or anticipate the need for major surgical procedure(s) during the course of the study.

3.2.12 Patients must begin adjuvant treatment no less than 28 days and no more than 60 days from surgery.

Date of surgery: _____

[NOTE deleted in Addendum #8]

Rev. 11/06, 7/07

3.2.13 Eligible patients of reproductive potential (both sexes) must agree to use an accepted and effective method of contraceptive during study therapy and for at least 3 months after the completion of bevacizumab.

Women must not be pregnant or breast-feeding because the study drugs administered may cause harm to an unborn fetus or breastfeeding child. All females of childbearing potential must have a serum pregnancy test to rule out pregnancy within 2 weeks prior to step 2 randomization.

Female of childbearing potential?: _____(Yes or No)

Date of serum pregnancy test: _____

3.2.14 Patients with PT (INR) > 1.5 are not eligible, unless the patient is on full-dose anticoagulants. If so, the following criteria must be met for enrollment:

The subject must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin or on a stable dose of low molecular weight heparin.

The subject must not have active bleeding or a pathological condition that is associated with a high risk of bleeding.

PT (INR) Measurement: _____

Stable dose warfarin/low molecular weight heparin:

Yes:_____ No: _____

Active bleeding : Yes: _____ No: _____

3.2.15 Patients with non-malignant systemic disease (cardiovascular, renal, hepatic, etc.) that would preclude any of the study therapy drugs are not eligible. Specifically excluded are the following conditions:

Rev. 1/06

Rev. 11/06

NYHA Class III or IV congestive heart failure

Yes: _____ No: _____

Current symptomatic arrhythmia

Yes: _____ No: _____

Any non-malignant systemic disease

Yes: _____ No: _____

3.2.16 Patients with a history of transient ischemic attack (TIA) or cerebrovascular accident (CVA) are not eligible.

- TIA? Yes: _____ No:_____
- CVA? Yes: _____ No:_____

3.2.17 Patients with a history of the following within twelve months of study entry are not eligible.

- Arterial thromboembolic events:

  Yes:_____ Date: _____ No: _____

- Unstable angina:

  Yes: _____ Date: _____ No: _____
- Myocardial Infarction:

  Yes: _____ Date: _____ No: _____

3.2.18 Patients with symptomatic peripheral vascular disease are not eligible.

Yes: _____ No: _____

3.2.19 Patients with psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude them from meeting the study requirements are not eligible.

3.2.20 Patients must not have a known allergy to platinum compounds.

Rev. 7/07

Known allergy to platinum compounds? Yes_____ No_____

3.3 Step 2: Registration (Low-Risk Patients – Arm C)

NOTE: Patients determined as low risk must be registered to Step 2.

Rev. 7/07

3.3.1 Patients determined to be low risk are eligible.

4. Registration/Randomization Procedures

Submitting Regulatory Documents

Before an ECOG-ACRIN Institution may enter patients, protocol specific regulatory documents must be submitted to the CTSU Regulatory Office at the following address:

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX: (215) 569-0206

Required Protocol Specific Regulatory Documents

1. **CTSU Regulatory Transmittal Form.**
2. **Copy of IRB Informed Consent Document.**

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

1. **A. CTSU IRB Certification Form.**
   Or

   HHS 310 Form.
   Or
   IRB Approval Letter

   NOTE: The above submissions must include the following details:

   - **Indicate all sites approved for the protocol under an assurance number.**
   - **OHRP assurance number of reviewing IRB**
   - **Full protocol title and number**
   - **Version Date**
   - **Type of review (full board vs. expedited)**
   - **Date of review.**
   - **Signature of IRB official**

The CTSU encourages you to link to the following RSS2.0 webpage so that more information on RSS2.0 as well as the submission forms can be accessed http://www.ctsu.org/rss2_page.asp. If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail CTSUContact@westat.com**.**

Rev.

Patients must not start protocol treatment prior to Step 2 randomization.

Rev. 7/07

Treatment must start within 7 days after randomization and no later than Day 60 post-operatively.

Observation for Arm C patients begins at Step 2 registration.

NOTE: Please refer to Appendix V for CTSU registration guidelines.

Institutions may register eligible patients to this study via the ECOG webpage 24 hours a day, 7 days a week, using the Web-based Patient Registration Program (https://webreg.ecog.org). If you need assistance or have questions, please telephone the Central Randomization Desk at the ECOG-ACRIN Operations Office – Boston 617-632-2022 Monday through Friday 9:00am-5:00pm (Eastern Time). Please note that a password is required to use this program. The following information will be requested:

4.1 Step 1 Registration

4.1.1 Protocol Number

4.1.2 Investigator Identification

4.1.2.1 Institution and affiliate name

4.1.2.2 Investigator's name

4.1.3 Patient Identification

4.1.3.1 Patient's initials and chart number

4.1.3.2 Patient's Social Security number

4.1.3.3 Patient demographics

4.1.3.3.1 Sex

4.1.3.3.2 Birth date (mm/yyyy)

4.1.3.3.3 Race

4.1.3.3.4 Ethnicity

4.1.3.3.5 Nine-digit ZIP code

4.1.3.3.6 Method of payment

4.1.4 Eligibility Verification

Rev. 8/10

Patients must meet all of the applicable eligibility requirements listed in Section 3. An eligibility worksheet is posted on the ECOG webpage. A confirmation of registration will be forwarded by the ECOG-ACRIN Operations Office – Boston.

4.1.5 Study Requirements

4.1.5.1 All patients must provide a signed and dated, written informed consent form.

Rev. 11/06, 7/07, 12/08

4.1.5.2 Two separate tissue blocks, one with **normal mucosa and one from the resection tumor** are to be submitted to the PCO no later than Day 50 post-operatively and within 5 working days of Step 1 registration, as outlined in Section 10. If only one block is available, it must contain both normal AND tumor tissue.

Rev. 4/06

Rev. 12/08

4.1.5.3 For patients participating in the "Pharmacogenetic Laboratory Studies", samples are to be submitted as outlined in Appendix XII. Submission of samples after registration/randomization to Step 2 is preferred.

Rev. 8/09

4.1.5.4 Pathology samples of recurrent tumor should be submitted for banking for future research studies as outlined in Section 10.3.

NOTE: ECOG-ACRIN requires that biological samples submitted from patients participating in E5202 be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). Any case reimbursements associated with sample submissions may not be captured if samples are not logged into STS. See Section 10.3

Rev. 7/07, 8/10

4.1.6 Instructions for Patients Who Do Not Register to Step 2 Registration/Randomization

Rev. 5/08

If a patient does not proceed to Step 2 registration/randomization, the baseline forms must still be collected (including source documents) and must be submitted according to the instructions in the E5202 Forms Packet. Document the reason the patient did not register/randomize to Step 2 on the E5202 Pre-Registration Form. Please note that follow-up data must be submitted according to the instructions in the E5202 Forms Packet for patients who had marker testing on their tumor (i.e., received a pathological risk status) and did not proceed to Step 2.

Rev. 1/06

4.1.7 Information for Medicare Patients

On 1/28/05, the Centers for Medicare and Medicaid Services (CMS – formerly HCFA) made a special decision to cover Medicare patients enrolled in E5202 and 8 other Cooperative Group cancer studies. ECOG-ACRIN wants to let you know about this (Coverage Decision No. CAG-00179N), so Medicare beneficiaries considering E5202, and their families, will know that most study-related costs will be covered by Medicare.

In the event sites encounter any problem obtaining Medicare reimbursement for services to a patient enrolled in E5202, your institution's Finance personnel may wish to refer the Medicare contractor to Coverage Decision No.CAG-00179N issued January 28, 2005, which approves coverage for E5202, among other cooperative group trials. The Decision Memo from CMS, the Center for Medicare and Medicaid Services of DHHS (formerly HCFA), can be found at www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=90.

4.2 Step 2: Randomization/Registration

Rev.

MD Anderson will notify (by fax) the submitting institution's CRA and the ECOG-ACRIN Randomization Desk at the ECOG-ACRIN Operations Office – Boston of the results of the risk assessment evaluated for microsatellite instability and loss of heterozygosity at 18q within 4 working days of receipt of the paraffin-embedded tumor specimens from the ECOG-ACRIN PCO.

Rev. 7/07

NOTE: Due to the complexity of MSI testing, some tumor specimens could require laser capture microdissection (LCM). This additional

procedure will delay the turnaround time for reporting results to the institution about one week or longer. The CRA will be notified of this delay.

Please do not call MD Anderson or the Pathology Coordinating Office for results, as testing data cannot be provided over the telephone. To request FAXed copies of the result reports, contact MD Anderson or the ECOG-ACRIN Operations Office – Boston.

- Patients with high risk will be randomized to Arms A or B.

  Rev.

  Randomization is accomplished via ECOG-ACRIN's standard permuted blocks within strata algorithm, stratifying on the stratification factors listed in 4.2.6 and balancing randomizations within main institutions. The strata are defined by the cross-classification of factor levels listed in 4.2.6.1 and 4.2.6.2 (four total strata).
- Patients with low risk will be registered to Arm C.

Patients must not start protocol treatment prior to step 2 randomization/registration.

Treatment for patients assigned to Arm A or Arm B must begin by Day 60.

Rev. 7/07

Institutions may register eligible patients to this study via the ECOG webpage 24 hours a day, 7 days a week, using the Web-based Patient Registration Program (https://webreg.ecog.org). If you need assistance or have questions, please telephone the Central Randomization Desk at the ECOG-ACRIN Operations Office – Boston at (617) 632-2022. Please note that a password is required to use this program. The following information will be requested:

4.2.1 Protocol Number

4.2.2 Investigator Identification

- 4.2.2.1 Institution and affiliate name
- 4.2.2.2 Investigator's name

4.2.3 Patient Identification

- 4.2.3.1 Patient's initials and chart number
- 4.2.3.2 Patient's Social Security number
- 4.2.3.3 Patient demographics
  - 4.2.3.3.1 Sex
  - 4.2.3.3.2 Birth date (mm/yyyy)
  - 4.2.3.3.3 Race
  - 4.2.3.3.4 Ethnicity
  - 4.2.3.3.5 Nine-digit ZIP code
  - 4.2.3.3.6 Method of payment

4.2.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3. An eligibility worksheet has been posted on the ECOG webpage. A confirmation of randomization/registration will be forwarded by the ECOG-ACRIN Operations Office – Boston.

4.2.5 Classification Factors

4.2.5.1 High risk for microsatellite instability and loss of heterozygosity at 18q.

- MSS with 18q LOH
- MSI-L with 18q LOH

4.2.5.2 Low risk for microsatellite instability and loss of heterozygosity at 18q.

- MSS with retention of 18q alleles
- MSI-L with retention of 18q alleles
- MSI-H with retention of 18q alleles
- MSI-H without retention of 18q alleles
- MSI-H with 18q status uninformative

Rev. 1/06

4.2.6 Stratification Factors

4.2.6.1 Stage IIA versus IIB

4.2.6.2 MSS versus MSI-L

4.2.7 Instructions for Patients Who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted according to the instructions in the E5202 Forms Packet. Document the reason for not starting protocol treatment after randomization on the E5202 Off-Treatment Form. Also report the date and type of the first non-protocol treatment that the patient received.

Rev. 7/07

Rev.4/06

5. Treatment Plan

5.1 Administration Schedule

Dose calculations are based on actual body weight at the beginning of each cycle. One cycle is two treatment days every 2 weeks. Drugs are administered in the order listed in the tables below.

Rev. 7/07

Administration of Cycle 2 may begin ± 2 days to accommodate patients' and clinics' schedules.

5.1.1 Arm A

Agent	Dose	Route	Treatment Administration
Oxaliplatin	85 mg/m²	IV infusion over 2 hours	Day 1
Leucovorin	400 mg/m²	IV infusion over 2 hours	Day 1
5-FU	400 mg/m²	IV bolus injection immediately following leucovorin	Day 1
5-FU	2.4 gm/m²	IV continuous infusion over 46 hours immediately following bolus 5-FU	Days 1 and 2

Repeated every 2 weeks for a total of 12 (2-week) cycles.

NOTE: Oxaliplatin and leucovorin can be administered simultaneously using Y-line tubing provided that the leucovorin has been diluted with 5% dextrose in water and NOT 0.9% sodium chloride because of the incompatibility of oxaliplatin and saline, as described in Section 8.2.7.

5.1.2 Arm B

Agent	Dose	Route	Treatment Administration
Bevacizumab[1]	5 mg/kg	IV infusion over 90 minutes[2]	Day 1
Oxaliplatin	85 mg/m²	IV infusion over 2 hours	Day 1
Leucovorin	400 mg/m²	IV infusion over 2 hours	Day 1
5-FU	400 mg/m²	IV bolus injection immediately following leucovorin	Day 1
5-FU	2.4 gm/m²	IV continuous infusion over 46 hours immediately following bolus 5-FU	Days 1 and 2

Repeated every 2 weeks for a total of 12 (2-week) cycles.

1. Bevacizumab will continue for 12 additional cycles following completion of chemotherapy. Patients will receive a total of 24 (2-week) cycles of bevacizumab.

2. Initial dose should be administered over a minimum of 90 minutes. If no adverse reactions occur, the second dose should be administered over a minimum of 60 minutes. Again, if no adverse reactions occur, the third and subsequent doses should be administered over a minimum of 30 minutes. Infusions should be run in via a volumetric infusion device. If infusion-related adverse reactions occur, subsequent infusions should be administered over the shortest period that is well tolerated.

   NOTE: Oxaliplatin and leucovorin can be administered simultaneously using Y-line tubing provided that the leucovorin has been diluted with 5% dextrose in water and NOT 0.9% sodium chloride because of the incompatibility of oxaliplatin and saline, as described in Section 8.2.7.

5.2 Adverse Event Reporting Requirements

Rev. 7/14

5.2.1 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 (please refer to the E5202 Forms Packet for the list of forms with directions for routine adverse event reporting). Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. The following sections provide information about expedited reporting.

5.2.2 Determination of reporting requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event; 3) the phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (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 arm 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.

Steps to determine if an adverse event is to be reported in an expedited manner:

Rev. 9/11

Step 1: *Identify the type of event:* The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized until September 30, 2011 for AE reporting. CTCAE version 4.0 will be utilized beginning October 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

Step 2: *Grade the event using the NCI CTCAE version 4.0*.

Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial).* Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event*. *Expected* events are those that have been previously identified as resulting from administration of the agent. 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:

- **Arm A** – the drug package insert or protocol
- **Arm B** – the current NCI Agent-Specific Adverse Event List for the investigational agent or package insert/protocol for the commercial agents

Rev. 1/06

Rev. 9/10

NOTE: The NCI Agent Specific Adverse Events List (ASAEL) is included in Section 5.3 of the protocol. The ASAEL is a list of events that should be considered 'expected' for adverse event reporting purposes. The ASAEL is presented in the last column of the Comprehensive Adverse Event and Potential Risks list (CAEPR) and identified with ***bold*** and ***italicized*** text.

Rev. 12/08, 8/10

Step 5: Review the "Additional instructions, requirements, and exceptions for protocol E5202" table in Section 5.2.6 and footnote b in Section 5.2.7 for protocol and/or ECOG-ACRIN specific requirements for expedited reporting of specific adverse events that require special monitoring.

NOTE: For general questions regarding expedited reporting requirements, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497.

5.2.3 Reporting methods

Arm A and B – This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to the AE Team at ECOG-ACRIN (617-632-3610), the NCI (301-897-7497) for Arm B and the FDA (1-800-FDA-1088) for Arm A.

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be faxed to ECOG-ACRIN (6176322990), Attention: AE within 48-72 hours. In addition, supporting or follow up documentation must be faxed to must be faxed to the NCI (301- 230-0159) for Arm B and the FDA (800-332-0178) for Arm A in the same timeframe.

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.2.4 When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Section 5.2.6). Please complete a 24-Hour Notification Report via the CTEP-AERS website (http://ctep.cancer.gov within 24 hours of learning of the event. The full CTEP-AERS report must be completed and submitted via CTEP-AERS within 5 calendar days.

Rev 1/06 4/06

If the CTEP-AERS system is down, a 24-hour notification call must be made to ECOG-ACRIN (617-632-3610) and to NCI (301-897-7497). Once the system is restored, a 24-hour Notification Report must be entered into the CTEP-AERS system by the original submitter of the report at the site.

When an adverse event requires expedited reporting, submit a full CTEP-AERS report within the timeframes outlined in Sections 5.2.6 and 5.2.7.

NOTE: Adverse events that meet the reporting requirements in Sections 5.2.6 or 5.2.7 and occur within 30 days of the last dose of protocol treatment must be reported on an expedited adverse event report form (using CTEP-AERS).

For any adverse events that occur more than 30 days after the last dose of treatment, only those that have an attribution of possibly, probably, or definitely AND meet the reporting requirements in Sections 5.2.6 or 5.2.7 must be reported on an expedited adverse event report form (using CTEP-AERS).

5.2.5 Other recipients of adverse event reports

Rev. 4/06. 11/06

DCTD, NCI will notify ECOG-ACRIN/pharmaceutical collaborator(s) of all Aes reported to FDA. Any additional written AE information requested by ECOG-ACRIN MUST be submitted to the NCI and ECOG-ACRIN.

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

5.2.6 Expedited reporting for investigational agents

Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of Investigational Agent (Bevacizumab) in this Study (Arm B) OR Within 30 Days of the Last Dose of Any Protocol Treatment.

Attribution	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

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

CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

CTEP-AERS 10 calendar day report:

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

[2] Although a CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table. Please see additional information below under section entitled "Additional instructions, requirements, and exceptions for protocol E5202"

March 2005

NOTE: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- Expedited AE reporting timelines:
  - **24 Hours; 5 calendar days** – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - **10 calendar days** – A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
    - Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates **hospitalization* (or prolongation of existing hospitalization)** must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
    - Any event that results in **persistent or significant disability/incapacity, congenital anomaly, or birth defect** must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND
    - Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

*Hospitalizations are defined as lasting 24 hours or longer and these events must be reported via CTEP-AERS.

Additional instructions, requirements and exceptions for protocol E5202

1. **Additional Instructions:**
   - With respect to determining the specific day by which the event must be reported, the day the reporter learns of the adverse event constitutes “Day 0”
   - For grade 2 and 3 unexpected events, CTEP-AERS reporting is only required if the event is related to the investigational agent(s); it is not required if the event is related only to the commercial agent(s) included in the protocol treatment.

     NOTE: For grade 3 unexpected events with hospitalization lasting ≥ 24 hours (or prolonged hospitalization), a CTEP-AERS report is required even if the event is unrelated to the investigational agent(s).
   - For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.
2. **ECOG-ACRIN and Protocol Specific expedited reporting requirements:**

   The adverse events listed below also require expedited reporting for this trial:

   ECOG-ACRIN specific expedited reporting requirements:
   - **Hospitalizations:** Any grade 1 or 2 adverse event which precipitates a hospitalization lasting ≥ 24 hours (or prolongs hospitalization) must be reported via CTEP-AERS within 10 calendar days of learning of the event regardless of the attribution and designation as expected or unexpected.

Protocol specific expedited reporting requirements:

Rev

➢ **Additional Events**: For this study, the adverse events listed below, regardless of attribution, require expedited reporting via CTEP-AERS within 10 calendar days of learning of the event:

- Hypertension ≥ grade 4
- Peripheral arterial ischemia ≥ grade 4

Rev. 9/10

- All thrombosis/thrombus/embolisms (including vascular access-related) ≥ grade 4
- Cardiac ischemia ≥ grade 4
- Hemorrhage ≥ grade 3
- CNS ischemia ≥ grade 4
- Perforation, GI ≥ grade 3
- Visceral arterial ischemia ≥ grade 4
- Proteinuria ≥ grade 3
- Fistula, GI ≥ grade 3
- Intra-abdominal abscess/infection ≥ grade 3
- Leak, GI ≥ grade 3
- Wound complication, non-infectious ≥ grade 3
- Veno-occlusive disease of the liver ≥ grade 1

Rev.

- All occurrences of **Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or Posterior Reversible Encephalopathy Syndrome (PRES)** and associated clinical presentations. [Please report under Neurology – Other (Leukoencephalopathy Syndrome)]

3. **Protocol specific expedited reporting exceptions:**

For study arm B, the adverse events listed below which occur during **combination chemotherapy (oxaliplatin, 5-FU, and leucovorin) and bevacizumab**, including hospitalizations for these events, **do not** require expedited reporting via CTEP-AERS. **Beginning 30 days following the last dose of chemotherapy and when a patient is receiving bevacizumab alone, these adverse events should be reported according to instructions in the table above:**

- Grade 3 - 4 leukocytes (total WBC) or neutrophils/granulocytes
- Grade 3 - 4 fatigue
- Grade 3 hand-foot reaction
- Grade 3 - 4 dehydration
- Grade 3 - 4 diarrhea (including associated electrolyte imbalances)
- Grade 3 - 4 dysphagia
- Grade 3 - 4 esophagitis
- Grade 3 – 4 mucositis (clinical exam or functional/symptomatic)
- Grade 3 - 4 nausea
- Grade 3 - 4 vomiting
- Grade 3 - 4 febrile neutropenia
- Grade 3 – 4 pain

5.2.7 Expedited reporting for commercial agents

Commercial reporting requirements are provided below. The commercial agents used in arm A of this study are 5-FU, Leucovorin, and Oxaliplatin.

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only – Arm A

Attribution	Grade 4		Grade 5[a]		ECOG-ACRIN and Protocol-Specific Requirements
	Unexpected	Expected	Unexpected	Expected	See footnote (b) for special requirements.
Unrelated or Unlikely			7 calendar days	7 calendar days	
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

A This includes all deaths within 30 days of the last dose of treatment regardless of attribution. **NOTE: Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event**.–

B Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported via CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

Additional Events: For this study, the adverse events listed below, regardless of attribution, require expedited reporting via CTEP-AERS within 7 calendar days of learning of the event: Protocol-specific expedited reporting requirements: The adverse events listed below, regardless of attribution, also require expedited monitoring for this trial:

- Hypertension ≥ grade 4
- Thrombosis/thrombus/embolism ≥ grade 4
- Hemorrhage ≥ grade 3
- Perforation, GI ≥ grade 3
- Proteinuria ≥ grade 3
- Intra-abdominal abscess/infection ≥ grade 3
- Wound complication, non-infectious ≥ grade 3
- All grade 4 unexpected events, with attribution of unrelated or unlikely
- Peripheral arterial ischemia ≥ grade 4
- Cardiac ischemia ≥ grade 4
- CNS ischemia ≥ grade 4
- Visceral arterial ischemia ≥ grade 4
- Fistula, GI ≥ grade 3
- Leak, GI ≥ grade 3
- Veno-occlusive disease of the liver ≥ grade 1
- All occurrences of **Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or Posterior Reversible Encephalopathy Syndrome (PRES)** and associated clinical presentations. [Please report under Neurology – Other (Leukoencephalopathy Syndrome)]

Rev.

5.2.8 Reporting second primary cancers

All cases of second primary cancers, including, acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN:

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**

1. Submit a completed Second Primary Form within 30 days to ECOG-ACRIN at

   ECOG-ACRIN Operations Office – Boston
   FSTRF
   900 Commonwealth Avenue
   Boston, MA 02215

2. Submit a copy of the pathology report to ECOG-ACRIN confirming the diagnosis.
3. If the patient has been diagnosed with AML/MDS, submit a copy of the cytogenetics report (if available) to ECOG-ACRIN

- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**

1. Submit a completed Second Primary Form within 30 days to ECOG-ACRIN at

   ECOG-ACRIN Operations Office – Boston
   FSTRF
   900 Commonwealth Avenue
   Boston, MA 02215

2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov

   Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy

3. Submit a copy of the pathology report to ECOG-ACRIN and NCI/CTEP confirming the diagnosis.
4. If the patient has been diagnosed with AML/MDS, submit a copy of the cytogenetics report (if available) to ECOG-ACRIN and NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

Rev. 1/06, 11/06, 2/08, 9/10, 7/14

5.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Bevacizumab (rhuMAb VEGF, NSC 704865)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Below is the CAEPR for bevacizumab (rhuMAb VEGF).

Version 2.1, May 4, 2010[1]

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term)			**EXPECTED AEs FOR CTEP-AERS REPORTING Agent Specific Adverse Event List (ASAEL)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	***Expected***
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia***
		Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)	
CARDIAC DISORDERS			
		Acute coronary syndrome	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	***Myocardial infarction***
	Supraventricular tachycardia		***Supraventricular tachycardia***
		Ventricular arrhythmia	
		Ventricular fibrillation	
EAR AND LABYRINTH DISORDERS			
	Vertigo		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain***
	Colitis		
	Constipation		***Constipation***
Diarrhea			***Diarrhea***
	Dyspepsia		***Dyspepsia***
		Gastrointestinal fistula[2]	
	Gastrointestinal hemorrhage[3]		***Gastrointestinal hemorrhage***[3]
		Gastrointestinal perforation[4]	
		Gastrointestinal ulcer[5]	
	Ileus		
	Mucositis oral		***Mucositis oral***
Nausea			***Nausea***
Vomiting			***Vomiting***

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue***
	Infusion related reaction		***Infusion related reaction***
	Non-cardiac chest pain		***Non-cardiac chest pain***
	Pain		***Pain***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction***
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[6]		***Infection[6]***
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Gastrointestinal anastomotic leak	
	Wound dehiscence		***Wound dehiscence***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased***
	Alkaline phosphatase increased		***Alkaline phosphatase increased***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased***
	Blood bilirubin increased		***Blood bilirubin increased***
	Cardiac troponin I increased		
	Neutrophil count decreased		***Neutrophil count decreased***
	Weight loss		***Weight loss***
	White blood cell decreased		***White blood cell decreased***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia***
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[7]		
	Myalgia		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness***
Headache			***Headache***
		Intracranial hemorrhage	***Intracranial hemorrhage***
		Ischemia cerebrovascular	***Ischemia cerebrovascular***
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
	Hematuria		***Hematuria***
	Proteinuria		***Proteinuria***
		Renal and urinary disorders - Other (Nephrotic Syndrome)	
		Renal and urinary disorders - Other (renal failure)	
		Urinary fistula	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
		Vaginal fistula	

	Vaginal hemorrhage		***Vaginal hemorrhage***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	
	Cough		***Cough***
	Dyspnea		***Dyspnea***
	Epistaxis		***Epistaxis***
	Hoarseness		***Hoarseness***
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)	
	Respiratory, thoracic, and mediastinal disorders - Other (rhinitis)		***Respiratory, thoracic, and mediastinal disorders - Other (rhinitis)***
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		***Pruritus***
	Skin and subcutaneous tissue disorders - Other (rash)		***Skin and subcutaneous tissue disorders - Other (rash)***
	Urticaria		***Urticaria***
VASCULAR DISORDERS			
Hypertension			***Hypertension***
	Thromboembolic event		***Thromboembolic event***
		Vascular disorders - Other (arterial thromboembolic event)[8]	

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Gastrointestinal fistula includes: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[3] Gastrointestinal hemorrhage includes: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[4] Gastrointestinal perforation includes: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, Small intestinal perforation, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[5] Gastrointestinal ulcer includes: Duodenal ulcer, Esophageal ulcer, Gastric ulcer and other sites under the GASTROINTESTINAL DISORDERS SOC.

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

[7] Metaphyseal dysplasia was observed in ***young patients who still have active epiphyseal growth plates.***

[8] Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke.

Also reported on Bevacizumab (rhuMAb VEGF) trials but with the relationship to Bevacizumab (rhuMAb VEGF) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura); Disseminated intravascular coagulation

CARDIAC DISORDERS - Pericardial effusion

GASTROINTESTINAL DISORDERS - Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Gait disturbance; Sudden death NOS

HEPATOBILIARY DISORDERS - Hepatic failure

INFECTIONS AND INFESTATIONS - Infections and infestations - Other (aseptic meningitis)

METABOLISM AND NUTRITION DISORDERS - Hyponatremia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone); Musculoskeletal and connective tissue disorder - Other (myasthenia gravis); Osteonecrosis of jaw

NERVOUS SYSTEM DISORDERS - Dysgeusia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure

PSYCHIATRIC DISORDERS - Confusion

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Pneumonitis; Pneumothorax; Pulmonary hypertension

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Skin ulceration

NOTE: Bevacizumab (rhuMAb VEGF) 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.

Rev. 12/08, 8/10, 9/10

Comprehensive Adverse Events and Potential Risks List (CAEPR) for Oxaliplatin (NSC 266046)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. They are developed and continuously monitored by the CTEP Investigational Drug Branch (IDB). The information listed in the CAEPR(s) below, as well as the other resources described in the 'Determination of reporting requirements' part of the Adverse Event Reporting section in this protocol, can be used to determine expectedness of an event when evaluating if the event is reportable via CTEP-AERS. Frequency is provided based on 1141 patients. Below is the CAEPR for oxaliplatin.

Version 2.2, March 11, 2010[1]

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 - 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)	
	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. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[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 perforation[7]

INJURY, POISONING AND PROCEDURAL 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

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness

NERVOUS SYSTEM DISORDERS - Syncope

RESPIRATORY, THORACIC 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.

5.4 Dose Modifications

Rev. 9/11

All toxicities should be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

The CTCAE version 4.0 is identified and located on the CTEP website at http://ctep.cancer.gov. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

Rev. 12/08

If dose-modifying toxicities last more than 3 weeks, contact Study Chair regarding continuation of treatment. According to the following tables, the final dose modification should be based upon the worst grade of toxicity experienced. If patients require dose reductions lower than level – 2, therapy with that particular agent will be discontinued. Any dose reduction is continued for all subsequent cycles.

NOTE: There are **no dose reductions for leucovorin**; the dose remains fixed at 400 mg/m^2 and without modification. In addition, there are **no dose reductions for bevacizumab**; the dose remains at 5 mg/kg and without dose modification.

5.4.1 Dose Modifications for Oxaliplatin and 5-FU Toxicity (Arms A and B)

NOTE: There are no dose reductions for leucovorin. The dose remains fixed at 400 mg/m^2. Leucovorin is discontinued only when 5-FU is discontinued.

NOTE: Patients on Arm A who require discontinuation of both 5-FU and oxaliplatin for toxicity will discontinue protocol therapy but will continue to be followed as indicated in Section 7.

NOTE: Patients on Arms A and B who require discontinuation of oxaliplatin may continue to receive 5-FU/leucovorin.

NOTE: Patients on Arm B who discontinue both 5-FU and oxaliplatin may continue to receive bevacizumab, provided patient experiences no bevacizumab-related toxicities.

Rev. 7/07

Dose Levels of Oxaliplatin, Leucovorin and 5-FU

	Starting Dose*	Dose Level – 1	Dose Level – 2
Oxaliplatin	85 mg/m²	65 mg/m²	50 mg/m²
Leucovorin	400 mg/m^2	400 mg/m^2	400 mg/m^2
5-FU Bolus	400 mg/m²	320 mg/m²	200 mg/m²
5-FU Infusion	2.4g/m²	2 g/m²	1.6 g/m² **

2 All patients will start cycle 1 with doses listed in “Starting Dose” column

** In the case of hand foot syndrome, the dose of infusional 5-FU may be further reduced by 20% as needed.

5.4.1.1 Non-Neurologic Toxicity (Oxaliplatin and 5-FU Toxicity)

The following table describes the recommended dose modifications at the start of each subsequent course of therapy. All dose modifications should be based on the worst preceding toxicity.

Rev. 7/07

Rev 9/11

Toxicity NCI CTCAE v4.0 Grade (Value)	NOTE: Dose modifications must be based on Aes observed during the cycle (column 2) and on the scheduled cycle day 1 (column 3). Dose modifications must be based on the AE requiring the greatest modification.	
	COLUMN 2 **Worst Interval Toxicity** **(Modifications for Aes that occurred during a cycle but DID NOT REQUIRE DELAY IN TREATMENT.)**	**COLUMN 3** **Day of Treatment** **(Modifications for Aes that require a DELAY IN TREATMENT.)**
No toxicity	Maintain dose level	Maintain dose level
Neutropenia (ANC) Grade 1 (ANC < LLN – 1500/mm³) Grade 2 (ANC <1499 – 1000/mm³) Grade 3 (ANC <999 – 500/mm³) Grade 4 (ANC < 500/mm³)	Maintain dose level Maintain dose level Reduce oxaliplatin one dose level Omit bolus 5-FU and reduce infusional 5-FU and oxaliplatin one dose level	If ANC < 1200 at start of cycle, hold and check weekly then treat based on worst interval toxicity. If ANC < 1200 after 4 weeks, discontinue therapy.
Thrombocytopenia[1] Grade 1 (PLT < LLN – 75,000/mm³) Grade 2 (PLT 74,999 – 50,000/mm³) Grade 3 (PLT 49,999 – 25,000/mm³) Grade 4 (PLT< 25,000/mm3)	Maintain dose level Maintain dose level Reduce bolus 5-FU and oxaliplatin by one dose level Omit bolus 5-FU; reduce infusional 5-FU one dose level; reduce oxaliplatin by two dose levels	If PLT < 75,000 at start of cycle, hold and check weekly then treat based on worst interval toxicity. If PLT < 75,000 after 4 weeks, discontinue therapy.
Other hematologic toxicities do not require dose modification; however red blood cell transfusion should be strongly considered for hemoglobin < 8 g/dl.		
Diarrhea Grade 1 Grade 2	Maintain dose level Maintain dose level Reduce both bolus 5-FU and infusional	Hold if any grade of diarrhea above baseline is present with the patient not taking anti-diarrheal agents within 24 hours of treatment. Reduce

Grade 3 Grade 4	5-FU one dose level Reduce both bolus and infusional 5-FU and oxaliplatin by one dose level	drugs per worst interval toxicity (column 2) upon resolution of diarrhea. If Grade ≥ 2 after 4 weeks, discontinue therapy.
Stomatitis Grade 1 Grade 2 Grade 3 Grade 4	 Maintain dose Maintain dose Reduce both bolus and infusional 5-FU one dose level Reduce both bolus and infusional 5-FU and oxaliplatin by one dose level	Hold until resolved then dose as follows: Maintain Dose Maintain Dose Reduce both bolus and infusional 5-FU one dose level Reduce both bolus and infusional 5-FU and oxaliplatin one dose level
Vomiting (despite antiemetics) Grade 1 Grade 2 Grade 3 Grade 4	 Maintain dose Maintain dose Reduce oxaliplatin one dose level Reduce both bolus and infusional 5-FU and oxaliplatin one dose level	Hold until resolved then doses as follows: Maintain Dose Maintain Dose Reduce both bolus and infusional 5-FU one dose level Reduce both bolus and infusional 5-FU and oxaliplatin one dose level
Other nonhematologic toxicities[2,3] (except neurologic)*	Dose modifications for other nonhematologic adverse events at the start of subsequent courses of therapy, and at time of retreatment are the same as recommended for vomiting (above), with the following exception: **Reduce 5-FU bolus and infusion by one dose level for other Grade ≥ 3 non-hematologic events.**	

* Exceptions: alopecia, anorexia, fatigue, nausea/vomiting if can be controlled by antiemetics.

[1] Hemolytic Uremic Syndrome (HUS)/Thrombotic Thrombocytopenic Purpura (TTP): The hemolytic uremic syndrome should be suspected in individuals who experience unexplained severe hemolysis, hemoglobinemia and renal failure as demonstrated by an increase in serum creatinine. Patients suspected of experiencing HUS or demonstrating symptoms of TTP should have the following laboratory analyses conducted: creatinine, BUN, urinalysis with microscopic evaluation, CBC with differential and platelets, PT/PTT, Fibrinogen, Fibrinogen Degradation Products (FDP), Anti-thrombin III (ATIII), von Wildebrand Factor (VWF), anti-nuclear antibodies (ANA), rheumatoid factor (RhF),

C3, C4, CH50, anti-platelet antibodies, platelet associated IgG, circulating immune complexes. **Oxaliplatin should be discontinued for any suspected occurrence of HUS or TTP.**

[2] With any suspicion of veno-occlusive disease (VOD) of the liver (hyperbilirubinemia, ascites, unexplained weight gain, hepatomegaly, splenomegaly, esophageal varices or other sign of portal hypertension), chemotherapy must be held. If VOD is diagnosed clinically, chemotherapy must be discontinued.

[3] **Dose modifications should only be applied for those untoward events (including but not limited to metabolic or vascular toxicities) that might bear some relationship to study treatment.**

Rev. 7/07

5.4.1.2 Dose Modifications of Oxaliplatin for Neurologic and Pulmonary Toxicity

Neurologic Toxicity[a]		
Paresthesias/Dysesthesias	**1-7 day duration**	**> 7 day duration**[b]
Grade 1 – Paresthesias/dysesthesias that resolve and do not interfere with function	Maintain dose	Maintain dose
Grade 2 – Paresthesias/dysesthesias interfering with function, but not activities of daily living	Maintain dose[b]	Decrease ***oxaliplatin*** one dose level[b]
Grade 3 – Paresthesias/dysesthesias with pain or with functional impairment that also interfere with activities of daily living	**First episode**: Decrease only ***oxaliplatin*** one dose level[b] **Second episode**: Stop oxaliplatin only	Stop oxaliplatin only
Grade 4 – Persistent paresthesias/ dysesthesias that are disabling or life-threatening	Stop oxaliplatin only	Stop oxaliplatin only
Laryngeal Dysesthesias (Grading at physician's discretion)		
Grade 1 – Mild **Grade 2** – Moderate	Maintain dose and consider increasing duration of oxaliplatin infusion to 6 hours	Maintain dose and consider increasing duration of oxaliplatin infusion to 6 hours
Grade 3 – Severe	At physician's discretion, either stop oxaliplatin or increase duration of infusion to 6 hours	Stop oxaliplatin only
Pulmonary Toxicity		
Dyspnea grade 2 Hypoxia grade 2 Pneumonitis/pulmonary infiltrates grade 2 Pulmonary fibrosis grade 2 Cough grade 3	Hold <u>all therapy</u> until interstitial lung disease is ruled out. • If non-infectious interstitial lung disease is confirmed, oxaliplatin must be discontinued. • If non-infectious interstitial disease is ruled out and infection (if any) has resolved, patients with persistent Grade 2 dyspnea or hypoxia can resume treatment at the physician's discretion.	

a These toxicity descriptions should be used to determine dose modifications and delays. Use the CTCAE v4.0 to assess neurologic toxicity for adverse event reporting.

Rev.

b ***Hold oxaliplatin for grade 2 neurotoxicity***. When grade 1, resume treatment with dose modifications. If > grade 1 toxicity persists after 4 weeks' hold, discontinue oxaliplatin. Continue 5-FU + LV (all patients) and bevacizumab (Arm B) while oxaliplatin is held.

5.4.2 Dose Modifications for Bevacizumab (Arm B only)

NOTE: There are no reductions in the bevacizumab dose (Arm B only). If Aes occur that require holding the bevacizumab dose, the dose will remain 5 mg/kg when treatment resumes. Bevacizumab will end 12 months after administration of the first dose regardless of the number of missed doses due to toxicity or for any other reason.

NOTE: If 5-FU/LV and/or oxaliplatin are held due to chemotherapy-related Aes, bevacizumab COULD be continued if it is preferred to keep the schedule on two-

Rev. 12/08

week interval with all drugs together unless the patient's medical condition precludes this.

NOTE: Patients assigned to receive bevacizumab who discontinue oxaliplatin prior to completion of the scheduled 12 cycles of therapy may continue bevacizumab in conjunction with 5-FU/LV for the remainder of the 12-cycle course, while patients who discontinue all components of FOLFOX chemotherapy (5-FU, LV, and oxaliplatin) prior to completion of the scheduled 12 cycles may continue bevacizumab for the remainder of the treatment course.

NOTE: If bevacizumab is held or must be discontinued before completion of chemotherapy, 5-FU/LV and oxaliplatin should be continued.

Rev. 9/11

Table 5.4.2

Adverse Event	Grade CTCAE v4.0	Action to be Taken
Acute infusion reaction e.g., fever, chills, headache, nausea (see Syndrome-Cytokine reaction) **or** **Allergic reaction/hyper-sensitivity (e.g., fever, rash, urticaria, bronchospasm)**	1, 2 or 3	If infusion-related or allergic reactions occur, pre-meds should be given with the next dose, but the infusion time may not be reduced for the subsequent infusion. If the next dose is well-tolerated with pre-meds, the subsequent infusion time may be reduced by 30 ± 10 min. as long as pre-meds continue to be used. If infusion-related Aes occur with the 60-min. infusion, all subsequent doses should be given over 90 ± 15 min. (with pre-meds). If infusion-related Aes occur with the 30-min. infusion, all subsequent doses should be given over 60 ± 10 min. (with pre-meds). For patients with grade 3 reactions, the bevacizumab infusion should be stopped and not re-started on that day. At the physician's discretion, bevacizumab may be permanently discontinued or re-instituted with pre-medications and at a rate of 90 ± 15 minutes. If the reaction occurred at the 90-minute rate, initially challenge at a slower infusion rate and gradually increase to 90 minutes. When bevacizumab is re-instituted, the patient should be monitored, per physician's usual practice, for a duration comparable to duration of reaction.
	4	Permanently discontinue bevacizumab.
Hemorrhage[a]	3 or 4	Permanently discontinue bevacizumab.
Thrombosis/thrombus/ embolism-venous (including vascular access device)	2 or 3	Hold bevacizumab until resolution by clinical assessment or Doppler. • If the planned duration of full-dose anticoagulation is 2 weeks, hold bevacizumab until anticoagulation is complete. • If the planned duration of full-dose anticoag is 2 weeks, bevacizumab may be resumed during anticoag if no grade 3 or 4 hemorrhage event occurred while on therapy and: If stable dose of warfarin (or other anticoagulant), INR must be in range (usually between 2 and 3); or if unfractionated heparin, PTT must be in therapeutic range. Discontinue bevacizumab if thromboembolic events worsen or recur after resuming therapy.
	4	Permanently discontinue bevacizumab.
Visceral or peripheral arterial ischemia	2[b, c], 3 or 4	Permanently discontinue bevacizumab.
Adverse Event	**Grade**	**Action to be Taken**

	CTCAE v4.0	
Cardiac ischemia/infarction	2[b], 3 or 4	Permanently discontinue bevacizumab.
CNS ischemia	2[b], 3 or 4	Permanently discontinue bevacizumab.
GI perforation including GI leak and GI fistula	1	Permanently discontinue bevacizumab.
Intra-abdominal abscess[d]	3	Hold bevacizumab until resolved.
	4	Permanently discontinue bevacizumab.
Complication, non-infectious-wound dehiscence[e]	1	Hold bevacizumab for at least 1 month. If, in the physician's opinion, substantial healing has taken place within 1-3 months, bevacizumab may be resumed. If wound dehiscence recurs, permanently discontinue bevacizumab.
	2, 3, or 4	Permanently discontinue bevacizumab.

Rev. 9/11

Proteinuria	Grade 2 (only if > 2g/24 hrs)	Hold bevacizumab until proteinuria improves to < 2g of protein in a 24-hour urine collection. Re-check 24-hour urine protein every 2-4 weeks. If proteinuria does not improve to < 2g/24 hrs within 3 months, permanently discontinue bevacizumab. For 2+ dipstick: may administer bevacizumab; obtain 24 hour urine prior to next bevacizumab dose. For 3+ dipstick: Obtain 24 hour urine prior to bevacizumab administration. Chemotherapy (without bevacizumab) may be continued at the physician's discretion while awaiting results of the 24-hour urine collection.
	Grade 3	Hold bevacizumab. Resume when proteinuria is < 2 grams/24 hours, as determined by 24-hour collection < 2.0g Chemotherapy (without bevacizumab may be continued at the physician's discretion while awaiting results of the 24-hour urine collection.
	Grade 4	Permanently discontinue bevacizumab.
Reversible Posterior Leukoencephalopathy Syndrome (RPLS)		Bevacizumab should be held in patients with symptoms/signs suggestive of RPLS, pending work-up and management, including control of blood pressure. MRI should be performed. Bevacizumab should be discontinued upon diagnosis of RPLS. If RPLS is not diagnosed, bevacizumab may be resumed when presenting symptoms are < grade 1 and blood pressure is < 150/90.
Hypertension	3	Bevacizumab may be continued in conjunction with standard anti-hypertensive therapy at physician discretion. Bevacizumab should be held for uncontrolled or symptomatic hypertension present on the day that the bevacizumab dose is to be given. If BP is not controlled with medication within 1 month, permanently discontinue bevacizumab.
	4	Permanently discontinue bevacizumab.
Other clinically significant (Aes)[f]	3	Hold until AE has resolved to grade 1.
	4	Permanently discontinue bevacizumab.

Rev. 1/06, 7/07, 8/10

Rev. 11/06, 7/07

a If coagulation disorders develop, secondary to other medical conditions, hold bevacizumab until the PT INR and PTT return to grade 1.

b New or worsening grade 2 events. (Therapy may be continued for grade 2 conditions present at baseline that have not worsened.)

c Patients who develop brief, reversible, exercise-induced claudication (grade 2) not attributable to arterial

	thromboembolic events may continue on study.
d	Refer to grading criteria listed for the appropriate adverse event in the Infection section of the CTCAE v 4.0.
e	Refer to Dermatology/Skin section of the CTCAE v 4.0.
f	Determination of "clinically significant" is at the physician's discretion ***and applies to those adverse events that can be attributed to bevacizumab and are not related to chemotherapy.***

5.5 Supportive Care

Rev. 7/07

All supportive measures consistent with optimal patient care will be given throughout treatment.

Loperamide (Imodium): Patients will be instructed to begin taking loperamide at the earliest signs of a poorly formed or loose stool. Loperamide should be taken in the following manner: 4 mg at the first onset of diarrhea, then 2 mg every two hours around the clock until the patient is diarrhea-free for at least 12 hours. Patients may take loperamide 4 mg (2 capsules) every four hours during the night. (Refer to Appendix IX, Diarrhea Management Instructions.)

Atropine: Diarrhea or abdominal cramping that occurs can be treated with atropine (0.25 to 1 mg IV as indicated). Patients having recurrent problems with cholinergic symptoms may receive atropine prophylactically (sc or IV). Additional antidiarrheal measures may be used at the discretion of the treating physician.

Antibiotics (for patients with persistent diarrhea): Begin oral fluoroquinolone and continue for 7 days. If diarrhea persists for greater than 48 hours, parenteral hydration is recommended (including hospitalization for such). Oral fluroquinolone treatment also should be initiated for patients who develop an ANC ≤ 500 /mm³ (even in the absence of fever or diarrhea) or a fever that occurs with diarrhea (even without neutropenia). Antibiotics should continue until resolution of diarrhea. (15)

Antiemetics: Oxaliplatin is emetogenic. All patients receiving oxaliplatin (Arm A and Arm B) should be pre-medicated with an acceptable anti-emetic regimen. Patients may receive dexamethasone 10 mg IV as pre-treatment antiemetic unless there is a relative or absolute contraindication to corticosteroids. Other antiemetics may be used in addition to the suggested regimen, if clinically indicated. As the majority of patients on previous trials have not experienced significant nausea, antiemetics other than decadron are recommended only for those patients who demonstrate nausea and/or vomiting despite treatment with decadron.

Routine use of antiemetics prior to treatment with standard dose 5-FU is rarely indicated. It is recommended that patients not be given routine antiemetics for the standard arms of the study and that antiemetics be prescribed by the treating physician as clinically indicated if a patient develops nausea and/or vomiting.

Anticoagulants: Patients who are taking warfarin may participate in this study; however, it is recommended the prothrombin time be monitored carefully (at least weekly). Subcutaneous heparin is permitted.

Rev.

Hypersensitivity: Platinum hypersensitivity can cause dyspnea, bronchospasm, itching and hypoxia. Appropriate treatment includes supplemental oxygen, steroids, antihistamines, and epinephrine; bronchodilators and vasopressors may be required. Platinum hypersensitivity is an extremely rare event and should be treated promptly.

Oxaliplatin hypersensitivity occurs in approximately 0.5% of patients receiving this investigational agent. See Appendix VI for the "Comparison of the Symptoms and Treatment of Pharyngo-Laryngodysesthesias and Platinum Hypersensitivity Reactions.

Delayed hypersensitivity reactions have been noted with oxaliplatin. If a subject experiences an oxaliplatin-infusion reaction, stop the infusion, administer standard allergic hypersensitivity reaction medications including hydrocortisone 50 – 100 mg IV and diphenhydramine 25 mg IV. Observe patient for one hour. It is recommended for all subsequent doses that the patient be premedicated with an antihistamine of choice in addition to diphenhydramine 25 mg IV. All subsequent doses should be given over 4 hours.

If the patient has a Grade 3 infusion reaction, for all subsequent infusions recommended premedications include:

- Hydrocortisone 100 mg
- Diphenhydramine 25 mg IV
- H2 blocker (Pepcid, etc)
- H1 blocker: antihistamine of choice
- Prolong infusion to 6 hours

For a Grade 4 infusion reaction, permanently discontinue oxaliplatin.

Pharyngo-laryngodysesthesias: Oxaliplatin may cause discomfort in the larynx or pharynx associated with dyspnea, anxiety, swallowing difficulty and is exacerbated by cold. Appropriate therapy includes use of anxiolytics, cold avoidance and monitoring. See Appendix XI for the "Comparison of the Symptoms and Treatment of Pharyngo-Laryngodysesthesias and Platinum Hypersensitivity Reactions."

Growth Factors

Prophylactic use of G-CSF or GM-CSF is not permitted on this trial. Therapeutic G-CSF use in patients with serious neutropenic complications may be given at the investigator's discretion and should follow ASCO Guidelines for G-CSF use. (Refer to latest ASCO guidelines.)

5.6 Duration of Therapy

Patients will receive protocol therapy unless:

5.6.1 Extraordinary Medical Circumstances: If, at any time, the constraints of this therapy are detrimental to the patient's health, protocol treatment should be discontinued. In this event, submit forms according to the instructions in the E5202 Forms Packet.

5.6.2 Patient recurs while on therapy.

Rev

5.6.3 Patient experiences unacceptable toxicity.

Rev

5.6.4 Patient withdraws consent.

5.7 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early or were registered to Arm C, will be followed for recurrence and for survival

for ten years from the date of registration. All patients must also be followed through completion of all protocol therapy.

6. Measurement of Effect

6.1 Diagnosis of Colon Cancer Recurrence

The diagnosis of a first colon cancer recurrence can be made only when the clinical and laboratory findings meet the criteria of "acceptable" as defined below. Anything not listed as acceptable should be considered unacceptable for evidence of colon cancer recurrence and should not be an indication to alter protocol therapy. *Any recurrence of malignant disease should be proven by biopsy whenever possible. At the time of colon cancer recurrence, the investigator should clearly indicate the site of tumor recurrence and whether multiple sites are involved.*

Supporting documentation must be submitted following diagnosis of colon cancer recurrence or second primary cancer. Refer to the E5202 forms packet for data to be collected.

6.1.1 Abdominal and/or pelvic sites

6.1.1.1 Anastomotic

Acceptable: positive cytology or biopsy

6.1.1.2 Abdominal, pelvic and retro-peritoneal nodes

Acceptable: (i) positive cytology or biopsy, (ii) progressively enlarging node(s) as evidenced by two CT or MRI scans separated by at least a 4 week interval, (iii) ureteral obstruction in the presence of a mass as documented on CT or MRI scan, or (iv) a single CT or MRI scan showing a definite mass which is confirmed to be malignant by a positive PET scan at that site.

6.1.1.3 Peritoneum (including visceral and parietal peritoneum or omentum)

Acceptable: (i) positive cytology or biopsy or (ii) progressively enlarging intraperitoneal *solid* mass as evidenced by two CT or MRI scans separated by at least a 4 week interval, or a single scan confirmed to be malignant by a positive PET scan at that site.

6.1.1.4 Ascites

Acceptable: positive cytology

6.1.1.5 Liver

Acceptable: (i) positive cytology or biopsy or (ii) ***three*** of the following which are not associated with benign disease:

- recent or progressive hepatomegaly, abnormal liver contour;
- positive radionucleotide liver scan, or sonogram;
- positive CT scan or MRI scan;

- positive PET scan which confirms abnormal CT scan or MRI scan and is associated with a rising CEA;
- abnormal liver function studies; OR
- elevated CEA, i.e. a persistent rise in CEA titer of 10 X the upper normal value, confirmed on two determinations separated by a 4-week interval, in patients who had a normal postoperative CEA value (the determination should be performed by the same laboratory, using the same method).

NOTE: An *elevated* CEA level will, as a solitary finding, not be considered acceptable evidence of colon cancer recurrence. Non-protocol therapy will not be instituted on the basis of an abnormal CEA level. It is suggested that when CEA elevations occur without other corroborative evidence of colon cancer recurrence (hepatomegaly, elevated liver function studies, positive radionucleotide scans, etc.), the following investigation should be considered: 1) contrast and/or endoscopic exam; 2) abdominal and pelvic CT scan, sonogram, MRI scan, PET scan, or anti CEA scan; and/or 3) celiac and mesenteric arteriography.

6.1.1.6 Pelvic mass not otherwise specified (NOS)

Acceptable: (i) positive cytology or biopsy or (ii) progressively enlarging intrapelvic *solid* mass as evidenced by two CT or MRI scans separated by at least a 4-week interval or (iii) a solid mass on a single CT scan confirmed by a positive PET scan at that site.

6.1.1.7 Abdominal wall, perineum, and scar

Acceptable: positive cytology or biopsy

6.1.2 Non-abdominal and non-pelvic sites

6.1.2.1 Skeletal

Acceptable: For all suspected bone-only recurrences, a biopsy is required to demonstrate recurrence.

6.1.2.2 Lung

Acceptable: (i) positive cytology, aspirate, or biopsy or (ii) radiologic evidence of multiple pulmonary nodules that are felt to be consistent with pulmonary metastases.

NOTE: If a solitary lung lesion is found and no other lesions are present on lung tomograms, CT, PET or MRI scan, further investigations such as

biopsy, needle aspiration, or resection should be performed. Proof of neoplastic pleural effusion should be established by cytology or pleural biopsy.

6.1.2.3 Bone marrow

Acceptable: positive cytology, aspirate, biopsy, or MRI scan

6.1.2.4 Central nervous system

Acceptable: (i) positive CT or MRI scan, usually in a patient with neurologic symptoms; or (ii) biopsy or cytology (for a diagnosis of meningeal involvement).

6.2 Second primary cancer

The diagnosis of a second primary cancer must be confirmed histologically whenever possible.

6.3 Disease-Free Survival

Date of Step 2 randomization of Arms A & B to the date of recurrence or death before recurrence.

Date of Step 2 registration to the date of recurrence or death before recurrence for Arm C.

6.4 Survival

Date of Step 2 randomization of Arms A & B to date of death.

Date of Step 2 registration to date of death for Arm C.

7.

8. Study Parameters

8.1 Biological Sample Submissions

Rev.

Samples submitted after November 3, 2014 are to be submitted to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF)

The tumor risk assessment, performed by the MD Anderson Cancer Center, is mandatory for participation in this study and tissue samples must be received by the PCO NO LATER than 50 days post-surgery (see Section 10).

Rev.

Rev.

Blood samples for the Pharmacogenetic Ancillary are submitted only from patients who answer "yes" to "I agree to participate in the protein and DNA studies that are being done as part of this treatment trial.

Rev 8/09

Recurrent tumor block for banking should be submitted from patients who answer "yes" to "I agree to allow for additional specimens for research."

Rev. 8/09

	Baseline	Recurrence
Rev. 7/07 Normal Mucosa Tissue Block[1]	X	
Rev. 7/07 Resection Tumor Tissue Block[1]	X	
Rev. 12/08 Peripheral Blood, PAXgene DNA	X[2]	
Rev. 8/09 Tumor Block[3]		X

1. **MANDATORY SUBMISSION:** Tissue samples MUST be submitted within 5 working days of step 1 registration. Submission requirements are outlined in Section 10.
2. Pharmacogenetic ancillary submissions outlined in Appendix XII. Sample may be drawn any time while participating in the protocol, although baseline (prior to treatment) preferred. An ACD or EDTA tube may be submitted.

Rev 8/10

3. Recurrent tumor blocks should be submitted as outlined in Section 10 from patients consenting to banking for future research studies.

Rev. 8/09

NOTE: ECOG-ACRIN requires that all samples submitted from patients participating in E5202 be entered and tracked via the online ECOG-ACRIN Sample Tracking System for purposes of monitoring compliance and determination of reimbursement levels. See Section 10.3.

Rev 7/07

Rev. 7/07

NOTE: An informed consent MUST be signed prior to the submission of the pathology material.

8.2

8.3 Therapeutic Parameters

8.3.1 Arms A and B

Rev. 4/06

Rev. 8/10

All required prestudy chemistries and CBC, (with differential and platelet count) as outlined in Section 3, should be performed ≤ 2 weeks before Step 2 **RANDOMIZATION** for eligibility purposes. Please see the table below for criteria that must be met within 2 weeks prior to **TREATMENT** for safety reasons. Plan accordingly to avoid repeating tests/assessments.

NOTE: When recording prestudy results on the Baseline Data Form, please make sure that ALL relevant dates are provided. Do NOT indicate results under the date for Day 1 of protocol treatment unless tests were performed that day; record the actual dates.

	Test/Assessment	Within 2 Weeks Prior to Start of Treatment	Day 1 of Each Treatment Cycle	6 Weeks after Final Treatment (Chemotherapy Arm A or Chemotherapy + Bevacizumab Arm B)	Follow-Up[4]
Rev. 1/06, 7/07	History and Physical Exam[11]	X	X[8]	X	X
	Height/Body Surface	X			
	Weight	X	X	X	X
	ECOG Performance Status	X	X	X	X
	Drug Toxicity Assessment		X[1,11]	X	X
Rev. 7/07, 8/10, 9/10	CBC, differential, platelets	X[15]	X[1,12,13]	X	
Rev. 7/07, 8/10	Serum creatinine	X	X[2,12,13]		
Rev. 7/07, 8/10	SGOT (AST), Total bilirubin	X	X[2,12,13]	X	
Rev. 11/06	Alkaline phosphatase	X			
Rev. 11/06, 7/07, 12/08					
Rev. 8/10	CEA	X[14]		X	X
	Prothrombin time (PT) or INR, PTT[6]	X			
Rev. 7/07, 5/08	Colonoscopy OR Barium Enema	X[5]			X[5]
	Serum pregnancy test (premenopausal women)	X			
	Biopsy				X[3]
Rev. 7/07	Urine protein/creatinine (UPC) ratio	X	X[7, 12]		
	Blood pressure	X	X		

1. Prior to each cycle of treatment.

Rev. 8/10

2. To be obtained as clinically indicated, at the discretion of the principal investigator.
3. First recurrence should be confirmed by biopsy when possible.
4. Follow-up assessments performed every 3 months for patients within 2 years of step 2 randomization, every 6 months for patients 3--5 years from step 2 randomization and every 12 months for patients 10 years from step 2 randomization.

   NOTE: Follow-up begins after completion of chemotherapy (Arm A) or twelve (12) additional cycles of bevacizumab alone (Arm B).

Rev. 7/07,

5. Performed prior to surgery or Step 1 Registration (if colonoscopy incomplete due to presence of tumor); must be done to comply with eligibility section 3.1.3; can usually be done safely 4 weeks after surgery. Recommended at one year post-surgery and then every 5 years thereafter, provided colon is polyp –and cancer – free.
6. For patients on full-dose warfarin, the PT (INR) should be monitored throughout the study treatment period weekly or per the physician's usual practice.

Rev. 1/06, 4/06, 7/07, 12/08, 8/10,

7. UPC should be done at baseline, then day 1 of every treatment for patients on Arm B only. UPC must be < 1.0. If this criterion is not met, the patient must have a 24-hour urine collection that demonstrates < 2 gm protein over 24 hours. UPC should be performed prior to every 3rd cycle for Arm B patients receiving bevacizumab. If the 24-hour urine collection is required, the bevacizumab should be held and subsequent dosing based on the guidelines in Section 5.4.2. Chemotherapy (without Bevacizumab) may be continued at the physician's discretion while awaiting results of the 24-hour urine collection.

Rev. 4/06

8. Document aspirin use, dose and schedule. Please see forms packet for aspirin use summary form and patient submission schedule. Administer aspirin diary (see Appendix IX) to patient for data collection during each treatment cycle.

Rev. 11/06,

9. [Deleted in Addendum #8]

Rev. 7/07,

10. [Deleted in Addendum #9]

Rev. 7/07, 8/10. 9/10

11. The baseline H and P should be a complete history and physical, including past medical history performed by a physician or a mid-level provider. An H&P should be done every 2 cycles (28 days). A focused treatment-related assessment should be done by the MD or other health professional during treatment to obtain toxicity information and performance status.

Rev. 7/07, 12/08

12. Pretreatment labwork may be performed ≤ 72 hours prior to treatment.

Rev. 8/10

13. For Arm B patients receiving bevacizumab alone (cycles 13-24), to be obtained as clinically indicated at the discretion of the principal investigator.

Rev. 8/10

14. CEA may be taken within 2 weeks prior to randomization.

Rev. 9/10

15. When Arm B patients on Bevacizumab only, CBC may be done every 2 cycles (28 days).

Rev 8/10

8.3.2 Arm C

Test/Assessment	After Surgery, before registration to Step 1	Follow-Up[1]
History and Physical Exam	X	X
Weight	X	X
ECOG Performance Status	X	X
CEA		X
colonoscopy OR Barium Enema	X[3]	X[3]
Biopsy		X[2]

Rev. 7/07

1. Follow-up assessments are to be performed every 3 months for patients **within 2 years of step 2 registration**, every 6 months for patients 3--5 years from step 2 registration and every 12 months for patients 6-10 years from step 2 registration.

Rev. 8/10

2. First recurrence should be confirmed by biopsy when possible. To be obtained as clinically indicated.
3. Performed prior to surgery or step 1 registration and is recommended at one year post-surgery and then every 5 years thereafter, provided colon is polyp- and cancer-free.

Rev

9.

10. Drug Formulation and Procurement

Information for Medicare Patients

Rev. 1/06

On 1/28/05, the Centers for Medicare and Medicaid Services (CMS – formerly HCFA) made a special decision to cover Medicare patients enrolled in E5202 and 8 other Cooperative Group cancer studies. ECOG-ACRIN wants to let you know about this (Coverage Decision No. CAG-00179N), so Medicare beneficiaries considering E5202, and their families, will know that most study-related costs will be covered by Medicare.

In the event sites encounter any problem obtaining Medicare reimbursement for services to a patient enrolled in E5202, your institution's Finance personnel may wish to refer the Medicare contractor to Coverage Decision No.CAG-00179N issued January 28, 2005, which approves coverage for E5202, among other cooperative group trials. The Decision Memo from CMS, the Center for Medicare and Medicaid Services of DHHS (formerly HCFA), can be found at www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=90.

10.1 Bevacizumab

10.1.1 Generic Name

Bevacizumab.

10.1.2 Other Names

NSC 704865, RhuMAb VEGF, Recombinant Humanized Monoclonal Anti-VEGF Antibody

10.1.3 Molecular Formula

M.W. = 149 kilodaltons

10.1.4 Trade Name

Avastin™ (Genentech, Inc)

10.1.5 Classification

Antiangiogenesis agent

10.1.6 Action

Bevacizumab binds Vascular Endothelial Growth Factor (VEGF) preventing the binding of VEGF to its receptors (Flt-1 and KDR), thus inhibiting endothelial cell proliferation and new blood vessel formation.

10.1.7 Dose Form

Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration in two vial sizes:

- Each 100 mg (25 mg/mL - 4 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20 and Sterile Water for Injection, USP.
- Each 400 mg (25 mg/mL - 16 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20 and Sterile Water for Injection, USP.

10.1.8 Drug Procurement

Bevacizumab (NSC# 704865) may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval form PMB is obtained). Completed Clinical Drug Requests (NIH-986) should be submitted to the PMB by FAX (240) 276-7893 or mailed to:

Pharmaceutical Management Branch

CTEP, DCTD, NCI
EPN, Rm. 7149 MSC 7422
9000 Rockville Pike
Bethesda, MD, 20892.

See Collaborative Agreement, Appendix VI.

10.1.9 Storage and Stability

Upon receipt, bevacizumab should be refrigerated (2° to 8°C). Do not freeze. Vials should not be shaken. Protect from light. Sterile, single-use vials contain no antibacterial preservatives. Therefore, vials should be discarded 8 hours after initial opening.

10.1.10 Drug Preparation

Vials contain no preservatives and are intended for single use only. Place the calculated dose in 100 mL of 0.9% sodium chloride for injection.

Bevacizumab should NOT be administered or mixed with dextrose solutions.

10.1.11 Dose/Administration

5 mg/kg IV infusion once every 14 days.

Initial dose should be infused over 90 minutes. If no adverse reactions occur, the second dose should be administered over 60 minutes. Again, if no adverse reactions occur, the third and subsequent doses should be administered over 30 minutes. If infusion-related adverse reactions occur, subsequent infusions should be administered over the shortest period that is well-tolerated. Infusions should be run in via a volumetric infusion device. Do NOT administer as an IV push of bolus.

10.1.12 Kinetics

Estimated half-life of Bevacizumab is approximately 20 days (range 11-50 days).

The clearance of bevacizumab was higher in males and in patients with a higher tumor burden.

10.1.13 Drug Interactions

Bevacizumab may increase the concentration of SN38 (the active metabolite of irinotecan) by as much as 33%. This may potentially increase the incidence of irinotecan-induced side effects such as diarrhea and leucopenia.

10.1.14 Adverse Effects

Allergy/Immunology:	Allergic reaction/hypersensitivity. Infusion-related reactions.
Blood/Bone Marrow:	Leukopenia, neutropenia, thrombocytopenia
Cardiac:	Hypertension/hypertensive crisis, cardiac ischemia/infarction, supraventricular arrhythmia, left ventricular dysfunction (congestive heart failure), hypotension, syncope
Constitutional symptoms:	Asthenia, fever, rigors/chills, weight loss
Dermatology/skin:	Exfoliative dermatitis, complications with wound healing, rash, skin ulceration, urticaria
Gastrointestinal:	GI perforation and wound dehiscence, sometimes complicated by intra-abdominal abscesses. Large bowel leakage, GI fistula, intestinal obstruction, intestinal necrosis, mesenteric venous occlusion, colitis, mucositis/stomatitis, nausea, vomiting, anorexia, constipation, diarrhea, heartburn/dyspepsia, dry mouth, taste disturbance
Hemorrhage/Bleeding:	Life-threatening or fatal pulmonary hemorrhage (primarily in lung cancer patients), CNS bleeding, GI hemorrhage, subarachnoid hemorrhage, hemorrhagic stroke, epistaxis (nose bleeds), vaginal bleeding, gum bleeding
Infection:	Infection with normal ANC
Metabolic/Laboratory:	Increased: alkaline phosphatase, ALT (SGPT), AST (SGOT), Bilirubin, serum creatinine. Hyponatremia and hypokalemia.
Neurology:	Cerebrovascular ischemia, dizziness, abnormal gait, confusion
Ocular:	Excessive lacrimation
Pain:	Abdominal pain, chest/thoracic pain, headache, arthralgias, myalgias, generalized.
Pulmonary/	

Upper Respiratory:	Dyspnea, cough, bronchospasm/wheezing, voice changes (hoarseness)
Renal/Genitourinary:	Proteinuria, nephrotic syndrome
Vascular:	Life-threatening and potentially fatal arterial thromboembolic events: cerebral infarction, transient ischemic attacks, myocardial infarction, angina. Venous thromboembolic events: deep vein thrombosis, intra-abdominal thrombosis.

Rev. 11/06

NOTE: Reversible Posterior leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome RPLS or clinical syndromes related to vasogenic edema of the white matter have been rarely reported in association with bevacizumab therapy (< 1%). Clinical presentations are variable and may include altered mental status, seizure and cortical visual deficit. HTN is a common risk factor and was present in most (though not all) patients on bevacizumab who developed RPLS. MRI scans are key to diagnosis and typically demonstrate predominantly vasogenic edema (hyperintensity in T2 and FLAIR images and hypointensity in T1 images) predominantly in the white matter of the posterior parietal and occipital lobes; less frequently, the anterior distributions and the gray matter may also be involved. plo RPLS is potentially reversible, but timely correction of the underlying causes, including control of BP and interruption of the offending drug, is important in order to prevent progression to irreversible tissue damage.

10.1.15 Patient Care Information

1. Monitor CBC and platelets. For patients taking warfarin for thrombosis, monitor PT or INR closely (weekly until two stable therapeutic levels attained). For patients on warfarin for venous access prophylaxis, routine PT monitoring.
2. Monitor patient closely during infusion, for infusion related events and for bleeding.
3. Monitor blood pressure prior to each dose to assess for development of hypertension.
4. Instruct patient to monitor and report signs/symptoms of : bleeding (nose bleeds, blood in sputum), wound healing problems, abdominal pain, thromboembolic problems (chest or leg pain, dyspnea, vision changes, severe headache, cough, swelling)
5. Baseline urine protein must be performed and repeated with each treatment. If elevated, 24-hour urine collection must be performed, prior to every 3rd cycle.

6. Therapy should be suspended several weeks before elective surgery and should not restart until surgical incision is fully healed.

7. Treat pain, arthralgias, etc. with acetaminophen, or other pain relief strategies that do not interfere with the clotting cascade.

10.1.16 References

Bevacizumab (Avastin™) Full Prescribing Information. Genentech, Inc. December 2004.

Bevacizumab Investigators Brochure, Genentech, December 2003.

10.1.17 Date/Reviewer

Updated February, 2005/ Helen McFarland, PharmD (410)-502-1036

Rev. 7/07

10.2 Oxaliplatin

Please refer to the FDA-approved package insert for comprehensive mixing instructions and adverse drug reaction information.

10.2.1 Other Names

Eloxatin®, trans-*l*-diaminocyclohexane oxalatoplatinum, cis-[oxalato(trans-*l*-1,2-diaminocyclohexane)platinum(II)]

10.2.2 Classification

Alkylating agent

10.2.3 Mode of Action

The mechanism of action of oxaliplatin is similar to cisplatin. The main site of action is intrastrand cross-linking, therefore inhibiting DNA replication and transcription.

10.2.4 Storage and Stability

Oxaliplatin vials are stored at room temperature between 20°C and 25°C excursions are permissible between 15°C and 30°C). The reconstituted solution in sterile water or 5% dextrose may be stored for up to 24 hours at 2°C to 8°C. After further dilution in 5% dextrose, the solution is stable for 6 hours at room temperature (20°C and 25°C) or up to 24 hours under refrigeration (2°C to8°C).

10.2.5 Dose Specifics

85 mg/m² in 250 mL to 500 mL D5W.

10.2.6 Preparation

Further dilution is needed in 250 to 500 mL of 5% dextrose prior to administration.

10.2.7 Route of Administration

The diluted solution of oxaliplatin in 250 mL 5% dextrose is administered by an infusion pump over 2 hours.

10.2.8 Incompatibilities

Oxaliplatin may degrade in the presence of aluminum-containing needles or IV infusion sets or alkaline medications (such as fluorouracil). Oxaliplatin is incompatible with sodium chloride solutions.

Rev. 4/08

10.2.9 How Supplied

Rev. 12/08

Oxaliplatin is available in two distinct dosage forms:

- Oxaliplatin for injection (lyophilized sterile powder) is a preservative-free, lyophilized powder as a white to off-white cake or powder contained in clear vials, sealed with an elastomeric stopper and a flip-off cover. It is available in 50 mg and 100 mg vials containing 450 mg and 900 mg of lactose monohydrate, respectively.
- Oxaliplatin injection (sterile solution) is a preservative-free, aqueous solution containing oxaliplatin 5 mg/mL. It is available in 50 mg and 100 mg vials. The primary package is a clear glass (Type I) vial sealed with an elastomeric stopper and flip-off cover.

Oxaliplatin will be provided free-of-charge by Sanofi-Synthelabo, Inc and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), the Division of Cancer Treatment and Diagnosis (DCTD) and the National Cancer Institute (NCI).

Oxaliplatin (NSC # 266046) 50 mg or 100 mg vials may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval form PMB is obtained). Completed Clinical Drug Requests (NIH-986) should be submitted to the PMB by FAX (240) 276-7893 or mailed to:

Rev. 7/14

Pharmaceutical Management Branch
CTEP, DCTD, NCI
EPN, Rm. 7149 MSC 7422
9000 Rockville Pike
Bethesda, MD, 20892

See Collaborative Agreement, Appendix VI.

10.2.10 Drug Accountability

Rev. 4/08

The Investigator, or a responsible party designated by the investigator, must maintain careful record of the receipt, disposition and return of all drugs received from the PMB, using the NCI Investigational Agent Accountability Record Form, available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. (See the NCI Investigators Handbook for procedures on drug accountability and storage.)

Rev. 7/14

10.2.11 Side Effects

Rev. 4/08, 12/08

Refer to Comprehensive Adverse Events and Potential Risks List (CAEPR) in Section 5.3.

Rev. 4/08

10.2.12 Nursing/Patient Implications

- Do not use needles or intravenous infusion sets containing aluminum for the administration of oxaliplatin.
- Monitor for neurologic symptoms.
- Administer antiemetics as indicated by the investigator.
- Monitor complete blood cell and platelet count prior to each administration.

Rev. 4/08

10.2.13 References

Investigator's Brochure: Oxaliplatin. Sanofi Winthrop, Nov. 1996.

Eloxatin® (oxaliplatin injection) Prescribing Information. Sanofi-Aventis, May 2006.

10.3 Fluorouracil

For complete prescribing information, please refer to the approved package insert.

10.3.1 Other Names

5-Fluorouracil, 5-FU, Adrucil, Efudex.

10.3.2 Classification

Antimetabolite.

10.3.3 Mode of Action

Fluorouracil is a pyrimidine antagonist that interferes with nucleic acid biosynthesis. The deoxyribonucleotide of the drug inhibits thymidylate synthetase, thus inhibiting the formation of thymidylic acid from deoxyuridylic acid, thus interfering in the synthesis of DNA. It also interferes with RNA synthesis.

10.3.4 Storage and Stability

Stable for prolonged periods of time at room temperature if protected from light. Inspect for precipitate; if apparent, agitate vial vigorously or gently heat to not greater than 140 F in a water bath. Do not allow to freeze.

10.3.5 Dose Specifics

400 mg/m², then 2.4 g/m².

10.3.6 Administration

5-FU will be administered at 400 mg/m² IV bolus, followed by 2.4 g/m² continuous infusion over 46 hours on day 1 and day 2.

10.3.7 Incompatibilities

Incompatible with doxorubicin and other anthracyclines. When giving doxorubicin IV push or through a running IV, flush line before giving

fluorouracil. May form precipitate with fluorouracil in some concentrations.

10.3.8 Availability

Commercially available in 500 mg/10 ml ampules and vials, and 1 g/20 mL,
2.5 g/50 mL, and 5 gm/100 mL vials.

10.3.9 Side Effects

Hematologic: Leukopenia, thrombocytopenia, anemia; can be dose limiting; less common with continuous infusion.

Dermatologic: Dermatitis, nail changes, hyperpigmentation, Hand-Foot Syndrome with protracted infusions, alopecia.

Gastrointestinal: Nausea, vomiting, anorexia; diarrhea, can be dose limiting; mucositis, more common with 5-day infusion, occasionally dose limiting; severe, cholera-like diarrhea which can be fatal when given with leucovorin.

Neurologic: Cerebellar Syndrome (headache and cerebellar ataxia).

Cardiac: Angina, noted with continuous infusion.

Ophthalmic: Eye irritation, nasal discharge, watering of eyes, blurred vision.

Hepatic: Hepatitis with hepatic infusion

10.3.10 Nursing/Patient Implications

Monitor CBC, platelet counts.

Administer antiemetics as indicated.

Monitor for diarrhea. Encourage fluids and treat symptomatically - may be dose limiting.

Assess for stomatitis - oral care recommendations as indicated.

Monitor for neurologic symptoms (headache, ataxia).

Patients on continuous infusions may need instruction regarding central IV catheters and portable IV or IA infusion devices.

Inform patient of potential alopecia.

10.3.11 References

Hansen R, Quebbeman E, Ausman R, *et al*. Continuous systemic 5-fluorouracil in advanced colorectal cancer: Results in 91 patients. J Surg Oncol 1989; 40:177-181.

Freeman NJ, Costanza ME. 5-Fluorouracil-associated cardiotoxicity. Cancer 1988; 61:36-45.

10.4 Leucovorin

For complete prescribing information, please refer to the approved package insert.

10.4.1 Other Names

Leucovorin Calcium, Wellcovorin, citrovorum factor, folinic acid, 5-formyl tetrahydrofolate, LV, LCV.

10.4.2 Classification

Tetrahydrofolic acid derivative.

10.4.3 Mode of Action

Leucovorin acts as a biochemical cofactor for 1-carbon transfer reactions in the synthesis of purines and pyrimidines. Leucovorin does not require the enzyme dihydrofolate reductase (DHFR) for conversion to tetrahydrofolic acid. The effects of methotrexate and other DHFR-antagonists are inhibited by leucovorin.

Leucovorin can potentiate the cytotoxic effects of fluorinated pyrimidines (i.e., fluorouracil and floxuridine). After 5-FU is activated within the cell, it is accompanied by a folate cofactor, and inhibits the enzyme thymidylate synthetase, thus inhibiting pyrimidine synthesis. Leucovorin increases the folate pool, thereby increasing the binding of folate cofactor and active 5-FU with thymidylate synthetase.

10.4.4 Storage and Stability

All dosage forms are stored at room temperature. The reconstituted parenteral solution, 10 mg/mL, is stable for at least 7 days at room temperature. At concentrations of 0.5-0.9 mg/mL the drug is chemically stable for at least 24 hours at room temperature under normal laboratory light. The oral solution, 1 mg/mL, is stable for 14 days refrigerated and 7 days at room temperature.

10.4.5 Dose Specifics

400 mg/m^2

10.4.6 Preparation

The 50 and 100 mg vials for injection are reconstituted with 5 and 10 mL of sterile water or bacteriostatic water, respectively, resulting in a 10 mg/mL solution. The 350 mg vial is reconstituted with 17 mL of sterile water resulting in a 20 mg/mL solution.

10.4.7 Administration

Intravenous infusion over 2 hours, concurrent with oxaliplatin.

10.4.8 Compatibilities

Leucovorin (0.5-0.9 mg/mL) is chemically stable for at least 24 hours in normal saline, 5% dextrose, 10% dextrose, Ringer's injection or lactated Ringer's injection. Leucovorin (0.03, 0.24 and 0.96 mg/mL) is stable for 48 hours at room and refrigeration temperatures when admixed with floxuridine (FUDR, 1, 2 and 4 mg/mL) in normal saline. Leucovorin is compatible with fluorouracil and oxaliplatin.

10.4.9 Availability

Commercially available in parenteral formulations (50 mg, 100 mg and 350 mg vial).

10.4.10 Side Effects

Hematologic: Thrombocytosis.

Dermatologic: Skin rash.

Gastrointestinal: Nausea, upset stomach, diarrhea.

Allergic: Skin rash, hives, pruritus.

Pulmonary: Wheezing (possibly allergic in origin).

Other: Headache; may potentiate the toxic effects of fluoropyrimidine therapy, resulting in increased hematologic and gastrointestinal (diarrhea, stomatitis) adverse effects.

10.4.11 Nursing/Patient Implications

Observe for sensitization reactions.

When given with fluoropyrimidines, monitor closely for diarrhea and stomatitis.

10.4.12 References

Arbuck SG. Overview of clinical trials using 5-fluorouracil and leucovorin for the treatment of colorectal cancer. Cancer 1989; 63: 1036-1044.

Bleyer WA. New vistas for leucovorin in cancer chemotherapy. Cancer 1989; 63: 995-1007.

Grem JL. 5-Fluorouracil plus leucovorin in cancer therapy. In: Cancer: Practices and Principles of Oncology Updates. Devita VT, Hellman S, Rosenberg SA, editors. 1988; 2(7): 1-12.

11.

12. Statistical Considerations

Rev.

Based on previous molecular analysis from adjuvant studies (INT 0035 and INT 0089), it is assumed that 40% of all stage II patients will fall into the high risk patient group, defined by the combination of microsatellite stability and 18q LOH. In the months prior to closing, CALGB study C89803 accrued roughly 100 stage III patients per month. Assuming similar success with study E5202, we expect that the GI Intergroup can enroll 625 stage II patients per year, with 40% or 250 eligible patients per year to be randomized from the high risk group to either oxaliplatin + 5-FU/LV (control arm) or oxaliplatin + 5-FU/LV + bevacizumab (experimental arm) in a 1:1 ratio and the remaining 60% (low risk patients) will be followed under observation.

Given the results of the MOSAIC trial in stage II disease, it is expected that the overall (high risk and low risk) 3-year disease-free survival (DFS) in the control arm will be 87% (Andre et al., 2004, NEJM). From recent results of an extensive analysis by Sargent and colleagues on the association between 3-year DFS and 5-year overall survival (OS) presented at ASCO 2004, we expect that the combined (high risk and low risk) 5-year OS will be roughly 87%. From ECOG-ACRIN's previous experience with and analysis of MSI/18q markers, it is expected that the high risk control group will have 3-year DFS of 80% and that the low risk group undergoing observation (Arm C) may exhibit 3-year DFS of about 90%, but that rate is not exactly known.

With 250 eligible patients per year accrued for 5.5 years (1,375 eligible high risk patients randomized; 3,438 eligible patients total) and three years of follow-up, there is at least 88% power to detect a 37% difference in median disease-free survival (absolute difference of 5%, from 80% to 85%, at three years) using a stratified log-rank test, with stratification on stage (IIA versus IIB) and MSI status (MSS versus MSI-L).

Power calculations assume one-sided 0.025 level stratified log-rank tests and a truncated O'Brien-Fleming group sequential design (truncated at nominal significance level 0.0005) with 9 interim analyses of DFS starting at roughly 29% information (120 events) and continuing every six months corresponding to scheduled ECOG-ACRIN Data Monitoring Committee meetings (at roughly 7-8% increments in information). If accrual proceeds according to expectation, three interim analyses will be performed before accrual is completed. A final analysis is expected to be conducted in year 8.5 for disease-free survival. Full information for the main endpoint of disease-free survival will occur at 420 events.

The truncated O'Brien-Fleming group sequential boundary will be used to adjust for the sequential testing and the use function methodology of Lan and DeMets will be employed to adjust the boundaries if the actual interim analyses do not correspond with the projected information times given here. Simulation studies conducted by the ECOG-ACRIN Statistical Center and others (Friedlin, Korn and George, 1999) suggest that overall test size is inflated by a negligible factor from the truncation, but there may be a small gain in terms of expected stopping time.

This study will also be monitored for early stopping in favor of the null hypothesis using repeated confidence interval methodology similar to that described by Jennison and Turnbull (1989). At each interim analysis nominal one-sided (1-alpha) confidence intervals on the overall survival hazard ratio comparing the experimental arm to control will be computed, where alpha is the nominal one-sided significance level of the use function boundary at the information fraction at the particular analysis time. If the

confidence interval does not contain the target alternative of 1.37, the ECOG-ACRIN DSMC may consider stopping the trial early for overall lack of a treatment difference. Conversely, if the experimental arm is found to be statistically superior to the control arm at a particular interim analysis before accrual is completed, the ECOG-ACRIN DSMC may consider closing the trial with early reporting of results.

For the overall survival endpoint, there is approximately 84% power to detect a 37% difference in median overall survival (absolute difference of 5% at 5 years, from 80% to 85%) with the analysis conducted 5 years from the end of accrual using a one-sided 0.025 level stratified log-rank test.

There is also interest in comparing overall survival among the non-randomized populations of low risk patients (60% of 3,438 total eligible patients) to high risk patients randomized to control (oxaliplatin + 5-FU/LV) (20% of 3,438 total eligible patients). It is anticipated that the low risk group will have three-year disease-free survival in excess of 90%, but the rate is not exactly known. An unadjusted two-sided 0.05 level log-rank test comparing the two groups will have over 95% power to detect differences in disease-free survival if the low risk patients have three-year disease survival of at least 85%. Adjustment for other risk factors using proportional hazards regression will be used in the final analysis and power is expected to be reduced slightly in those analyses.

Calculations are based on the accrual and follow-up assumptions given above. The ECOG-ACRIN DSMC will closely monitor the accrual rate and the accrual patterns for both the low- and high-risk patient populations at each of its semi-annual meetings and advise the study team regarding progress of the trial. The consideration driving the accrual goal is to randomize 1,375 eligible patients. Accrual of both low- and high-risk patients will be stopped once that objective is reached and the overall accrual goal will be adjusted accordingly, based on the proportion of high-risk patients being accrued. If the proportion of high-risk patients were to be much lower than assumed, then the DSMC will evaluate the feasibility of continuing with this study. Also, the DSMC will formally evaluate accrual rates 18 months after activation. At that time, if the rate of high risk patients being randomized has not reached at least 15 patients per month (72% of the anticipated rate of 250 per year), then the DSMC will re-evaluate the feasibility of continuing accrual.

In addition to the usual continuous adverse event monitoring via ECOG-ACRIN's real time ADR mechanism, toxicity reporting through CRFs and semi-annual interim toxicity reporting that occurs on all ECOG-ACRIN studies, this trial will include a detailed toxicity review after 50 patients have accrued to each treatment arm to evaluate the rates of all toxicities and in particular those events that may be elevated due to the addition of bevacizumab (perforation, thrombosis, delays in wound healing). With 50 patients per arm, the 90% confidence interval around any given toxicity rate will be no wider than 25%. To formally evaluate treatment related mortality, we will conduct a one-sample one-sided binomial test of CTCAE v4.0 grade 5 toxicities separately in each treatment arm to evaluate the hypothesis of a null treatment related mortality rate of 1.5% versus an unacceptably high treatment related mortality rate in excess of 3.0%. With 400 patients in each treatment arm followed for 6 months, we will determine that the treatment related mortality is unacceptable if there are 10 or more patients experiencing grade 5 toxicity in any arm. Using the exact binomial this test has a type I error rate of 8.2% and power of 76.2% against an alternative true toxicity rate of 3%. If the true rate is 3.5%, the power is 89.5%. Throughout the trial we will also monitor arterial thrombotic events in patients 65 years and older in both arms and report findings to the ECOG-

Rev.

Rev. 1/06

ACRIN DSMC. Specific events to be reported include cardiac ischemia/infarction, myocardial infarction, CVA, CNS cerebrovascular ischemia and other related events that occur.

After 50 patients per arm have been accrued, the study team will also review and evaluate the timing and data flow of molecular analysis results for determination of risk categorization to ensure that risk classification is being conducted as expeditiously as possible. If more than 5% of the cases have problems in the molecular analyses (markers unable to be evaluated), in the timing of results determination (results not processed within the specified time window) or in the data flow within the system (results not being relayed to the submitting institution and ECOG-ACRIN central office expeditiously) the study team will halt recruitment to the trial to evaluate the problem(s) and determine the appropriate solution.

The statistical design assumes the Intergroup can enroll at least 625 patients per year. At the time of activation this will be the only Intergroup stage II trial and the expectation is that the entire Intergroup will participate. Focus groups with investigators and patients have indicated a high degree of enthusiasm for this trial, particularly since it will determine which patients will receive adjuvant therapy based on a suggested degree of risk (molecular profile).

The total sample size for this trial, allowing for 5% ineligibility, is expected to be 3,610 patients. Patient follow-up will be completed per protocol Section 7. All patients will be followed at least yearly for survival for a period of 10 years post registration.

Rev.

As described in Section 2.2, secondary endpoints include overall survival, toxicity and impact of tumor biological characteristics on survival. Overall survival (OS) will be analyzed as described above. No interim monitoring or sequential testing will be done on the OS secondary endpoint. In addition to the toxicity analyses described above, we will also tabulate and report adverse events by treatment arm and note those events that differ statistically between arms. No formal type I error adjustment will be done for the toxicity analyses. Analysis of tumor biological characteristics and their relationship to overall survival will be conducted between high and low risk populations as described above. In addition we will investigate the prognostic value of MSI within the high risk randomized group via the logrank test and proportional hazards regression model. We will also investigate the prognostic significance of MSI within the low risk subgroup but power is expected to be low in that population due to the expected lower event rate. Other correlative biological parameters will be analyzed with respect to relevant time-to-event endpoints once the parameters have been identified and measured from the tumor blocks that will be banked on this protocol.

12.1 Gender and Ethnicity

Based on previous data from INT 0035 and INT 0089, the anticipated accrual in subgroups defined by gender and race/ethnicity is:

Ethnic Category	Gender		
	Females	Males	Total
Hispanic or Latino	28	60	88
Not Hispanic or Latino	1610	1912	3522
Ethnic Category: Total of all subjects	1638	1972	3610

Racial Category			
American Indian or Alaskan Native	3	0	3
Asian	13	13	26
Black or African American	165	150	315
Native Hawaiian or other Pacific Islander	0	0	0
White	1457	1809	3266
Racial Category: Total of all subjects	1638	1972	3610

We are aware of no gender or racial/ethnic group by treatment interactions using the adjuvant regimens being studied in this protocol and the sample size does not provide sufficient power to target such interactions. The analysis plan will, however, involve tests for gender by treatment and racial/ethnic group by treatment interactions.

12.2 Study Monitoring

This study will be monitored by the ECOG-ACRIN Data and Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Operations Office – Boston.

Rev. 1/06

13.

14. Pathology Review

Rev.

NOTE: An informed consent MUST be signed prior to the submission of the pathology material. Samples for banking should be submitted only from patients who have given written consent for the use of their samples for these purposes.

Rev. 7/07.

14.1 Tumor and Normal Mucosa Block Submission

Rev 11/06 7/07

Tumor and normal mucosa blocks must be submitted for determination of disease recurrence risk based on 18q loss of heterozygosity (LOH) and microsatellite instability status as outlined in Section 11. **Every effort should be made to submit blocks to the CBPF immediately. Blocks CANNOT be accepted after day 50 (post-surgery) in order to allow for molecular assessment.**

Rev. 4/06

Rev. 4/06, 8/09

As of November 3, 2014, recurrent tumor blocks are to be submitted to the CBPF for banking for future research studies.

The clinical investigator and the submitting pathologist are responsible for submitting representative diagnostic material for review and classification. When a patient is registered to the study, the submitting pathologist and clinical research associate should refer to Appendix II (Pathology Submission Guidelines) which provides the following:

Rev. 7/07.

- Instruction Sheet from ECOG-ACRIN Central Biorepository and Pathology Facility providing details for the Submission of Pathology Materials
- Memorandum to the submitting pathologist from [redacted], M.D., chair, ECOG-ACRIN Laboratory Science and Pathology Committee, providing details for the Submission of Pathology Materials

Rev. 8/09

- List of required materials

Rev. 1/06

- Generic Specimen Submission Form (#2981)

14.2 Required Materials

Rev. 1/06

14.2.1 STS-generated shipping manifest

14.2.2 Copy of the surgical pathology report. Please refer to the forms schedule for instruction.

In addition to the surgical pathology report, if immunologic studies have been performed at the home institution, it is necessary that these be forwarded as well. Please submit pathology reports to the ECOG-ACRIN Operations Office – Boston, Attention DATA, as well as to the receiving laboratory. (Refer to the forms submission schedule.)

Rev.

14.2.3 Mandatory Tumor and Mucosa Block Submissions from Resection Specimens Submissions to the ECOG-ACRIN PCO at Northwestern

Rev. 7/07

Two separate formalin-fixed, paraffin embedded tissue blocks must be submitted: one block with **normal mucosa and one block with resection tumor**. (One block with both normal mucosa and tumor is acceptable if 2 blocks cannot be obtained.)

NOTE: If blocks cannot be submitted, 1 H&E stained slide and 10 unstained slides of a 4 micron section mounted on positively-charged glass slides from each type of block (mucosa and tumor) are acceptable.

Rev. 8/09

14.2.4 Tumor Block Submission from Recurrence Specimen – Submission to the ECOG-ACRIN CBPF at MD Anderson

One formalin-fixed, paraffin-embedded tumor block from resection, biopsy, or fine needle aspiration cell block of recurrence should be submitted.

NOTE: If blocks cannot be submitted, 1 H&E stained slide and 10 unstained slides with a 4 micron section from tumor block mounted on positively-charged glass slides, or a representative smear or filter slide from fine needle aspiration specimen if there is not cell block, is acceptable.

Rev 7/07

If you have any questions regarding the submission of the tumor blocks, please contact the ECOG-ACRIN CBPF at 844-744-2420.

Rev. 8/09

14.2.5 Shipping Procedures

Rev. 7/07

NOTE: ECOG-ACRIN requires that all samples submitted from patients participating in E5202 be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). See Section 10.3. An STS shipping manifest form must be generated and shipped with the sample submissions.

Rev. 8/09

14.2.5.1 Submission Schedule

The required tissue blocks must be submitted within five working days of the patient's step 1 registration.

The tumor block from recurrence should be submitted within one month of collection via standard shipping.

Rev. 8/09

Samples may be shipped at ambient temperature. Use a cool pack in warm weather.

14.2.5.2 Required samples must be shipped Federal Express OVERNIGHT EXPRESS for next morning delivery.

Rev. 8/09

14.2.5.3 As of November 3, 2014 submit materials to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

Rev. 4/06

Rev. 1/06

Include the shipping manifest generated by the Sample Tracking System If STS cannot be accessed at the time of shipment, submit samples with Generic Specimen Submission Form (#2981) and log submission after shipping.

Rev. 7/07
Rev. 1/06

14.2.5.3.1 Include the shipping manifest generated by the Sample Tracking System AND a completed ECOG-ACRIN Pathology Material Submission Form (#638 v04.2) with the samples. If STS cannot be accessed at the time of shipment, submit samples with Form #638 v04.2 and log submission after shipping.

14.2.6 Central Sample Processing and Routing

Rev. 8/09

Rev. 11/06

The appropriate materials will be distributed to Dr. [redacted] for analysis.

Blocks from recurrence will be banked for future research studies.

Rev. 4/06, 8/09

Rev. 4/06, 7/07

14.3 ECOG-ACRIN Sample Tracking System

It is **required** (barring special considerations) that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU user-name and password.

Rev. 12/08

When you are ready to log the collection and/or shipment of the any samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst.

Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demos are available by clicking this link: http://www.ecog.org/general/stsinfo.html. Please take a moment to get familiar with the software prior to using the new system.

Rev. 12/08

Direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu.

Rev 8/09

14.3.1 Study Specific Notes

Generic Specimen Submission Form (#2981) (faxed to the receiving laboratory) will be required only if STS is unavailable at the time of sample submission. Indicate the appropriate Lab on the submission form:

- ECOG-ACRIN CBPF

To obtain the overnight courier number, contact theCBPF (844-744-2420). Retroactively enter all specimen collection and shipping information when STS is available.

15.

Rev.

16. Molecular Analysis for Risk Assessment/Treatment Assignment

Rev. 7/07, 12/08

NOTE: Samples for the "Pharmacogenetic Laboratory Studies" are submitted as outlined in Appendix XII from patients who answer "yes" to "I agree to participate in the protein and DNA studies that are being done as part of this treatment trial."

Rev. 7/07

NOTE: Pathology materials required for this assessment are outlined in Section 10.

16.1 Analysis of Tumor Markers:

Rev.

Rev. 12/08

Polymolphic Dinucleotide Markers D18S69, D18S64, D18S55, D18S61, D18S1147 and D18S58 and Mononucleotide Markers BAT25, BAT26 and Transforming Growth Factors Beta Type II Receptor.

Rev.

Polymorphic dinucleotide markers on 18q (D18S69, D18S64, D18S55, D18S61, D18S1147 and D18S58 from centromere to telomere) and three mononucleotide markers (BAT25, BAT26 and transforming growth factors beta type II receptor) are to be amplified with multiplex PCR and sequenced with the ABI 3700 instrument in the Molecular Diagnostics Laboratory by the protocol-assigned technologist. Peak sizes will be quantified and the data reviewed by Drs. [redacted] and/or [redacted].

16.1.1 Tumor Marker Reporting

Microsatellite instability (MSI) status will be interpreted on the basis of shifts in allele size with the criterion of > 30% increase in tumor DNA as compared to the corresponding peak in mucosal DNA. The 5 dinucleotide and 3 mononucleotide markers will be assessed. Tumors are then classified using criteria from the National Cancer Institute-sponsored workshop on MSI in colorectal cancer (8). Results for each marker are recorded in the project database.

Classification of the tumor is based on the following criteria: microsatellite-stable cancers have shift in none of 8 markers; cancers with low levels of microsatellite instability (MSI-L) have shift in 1 or 2 of 8 alleles (< 30%); cancers with high levels of microsatellite instability (MSI-H) have shift in 3 or more of 8 markers (> 30%). In microsatellite-stable cancers, loss of an 18q allele will be determined by a > 50% reduction in the area under the curve in tumor for 1 of the 2 polymorphic bands in at least 1 marker as compared to non-neoplastic tissue. A standardized report form has been prepared and includes the list of each marker's result and the interpretation of the case as follows:

High Risk

- Microsatellite-stable with 18q allelic loss (fraction of markers and percent)
- Low levels of microsatellite instability (MSI-L) with 18q allelic loss (fraction of markers and percent)

Low Risk

- Microsatellite-stable with retention of 18q
- Low levels of microsatellite instability (MSI-L) with retention of 18q

- High levels of microsatellite instability (MSI-H) with TGFβ1RII mutation and retention of 18q alleles (fraction of markers and percent)
- High levels of microsatellite instability (MSI-H) without TGFβ1RII mutation and with retention of 18q alleles (fraction of markers and percent)
- High levels of microsatellite instability (MSI-H) with TGFβ1RII mutation and 18q allelic loss (fraction of markers and percent)
- High levels of microsatellite instability (MSI-H) without TGFβ1RII mutation and with 18q allelic loss (fraction of markers and percent)
- MSI-H with 18q status uninformative

Rev. 1/06

16.1.2 Notice to the Submitting Institution

The MD Anderson Laboratory will notify (via fax) the submitting institution and the ECOG-ACRIN Randomization Desk at the ECOG-ACRIN Operations Office – Boston of the results of the risk assessment within 4 working days of receipt of the samples from the ECOG-ACRIN CBPF.

The institution's clinical research associate (CRA) will be notified of the disease recurrence risk status via fax from the M.D. Anderson Laboratory. Do not call the M.D. Anderson laboratory for results, as testing data cannot be provided over the telephone. As soon as M.D. Anderson has notified the institution's CRA and the ECOG-ACRIN Operations Office – Boston, the CRA may initiate step 2 randomization/registration (via the ECOG webpage).

Rev. 7/07

If you have any questions pertaining to the test results, please telephone Raja Luthra at the Molecular Diagnostic Laboratory at MD Anderson Cancer Center at 713-794-4780 and ask for John Galbincea or Abdul Khitamy.

Rev. 7/07

NOTE: Due to the complexity of MSI testing, some tumor specimens submitted could require Laser Capture Microdissection (LCM). This additional procedure will delay the turnaround time for reporting results to the institution to about one week or longer. The CRA will be notified of this delay.

16.1.3 Sample Preparation Guidelines

The tumor tissue and mucosa are processed to DNA separately by the project-assigned technologist using standard methods in the Molecular Diagnostic Laboratory (MDL). An aliquot of DNA for marker analysis, an aliquot for collaborator analysis and an aliquot for backup storage are prepared.

16.1.4 [Deleted in Addendum #8]

Rev. 7/07

16.1.5 The duration of the pre-analytic, analytic and post-analytic phases of the marker analysis will be recorded in the database at the ECOG-ACRIN Operations Office – Boston and monitored in the semi-monthly conference call of the GI Committee and in the meetings of the Data

Monitoring Committee. Loss of more than 5% of eligible cases due to unsatisfactory dataflow will lead to specific corrective action of the systematic problems that are identified. If accrual problems related to molecular analysis persist uncorrected for more than 3 months, accrual will be suspended until satisfactory correction of the data generation is completed.

16.2 Institutional Reimbursements

Rev. 1/06

Pathology Reimbursements

To offset material and resource costs associated with the collection and submission of the required tissue samples, institutions will receive reimbursement in the amount of $85 per case submitted. Reimbursements will be paid from the ECOG-ACRIN Operations Office – Boston to the submitting institution and mailed to the attention of the PI/SI. Payments are made annually.

Rev. 8/09

Rev.

These pathology reimbursements are to be distributed to the pathologist responsible for collecting samples for those institutions and should not be used for any other purpose. Funds to support these pathology reimbursements are provided by a grant from Genentech.

Distribution of the pathology reimbursements require:

Rev. 8/09

- Submission of the required tissue samples - formalin-fixed, paraffin-embedded tissue blocks of normal mucosa and resection tumor.
- Receipt of samples by the CBPF
- Completion and submission of the Generic Specimen Submission Form (#2981) to the CBPF

Rev. 1/06

The ECOG-ACRIN CBPF is responsible for submitting an electronic file of samples received on a quarterly basis to the ECOG-ACRIN TST. The ECOG-ACRIN TST will instruct the CBPF of the format and data that should be included in the electronic file in order to process the reimbursements.

NOTE: Patients or their insurance companies are not to be billed for the collection or submission of these samples.

16.3 [Section 11.3 deleted in Addendum #10]

Rev. 7/07, 8/09

16.4 Sample Inventory Submission Guidelines

Inventories of all samples collected, aliquoted and used on the above-mentioned laboratory study will be submitted to the ECOG-ACRIN Operations Office – Boston on a monthly basis. Inventories will be transmitted electronically or by diskette by any laboratory holding and/or using any specimens associated with this study. Electronic submissions should be transmitted to ecog.labdata@jimmy.harvard.edu. All other correspondence should be addressed to the attention of the Translational Science Team.

Rev. 7/07

Rev. 7/07

16.5 Lab Data Transfer Guidelines

Rev. 7/07, 12/08, 8/09

The data collected on the above-mentioned correlative studies will be submitted to the ECOG-ACRIN Operations Office – Boston by the central laboratory on a quarterly basis. The quarterly cut-off dates are March 31, June 30, September 30 and December 31. Data is due at the ECOG-ACRIN Operations Office – Boston

1 week after these cut-off dates. Electronic submissions should be transmitted to ecog.labdata@jimmy.harvard.edu. All other correspondence should be addressed to the attention of the Translational Science Team.

17.

18. Records to Be Kept

Please refer to the E5202 Forms Packet for the forms submission schedule and copies of all forms. The E5202 Forms Packet may be downloaded by accessing the ECOG World Wide Web Home Page (http://www.ecog.org). Forms must be submitted to the ECOG-ACRIN Operations Office – Boston, FSTRF, 900 Commonwealth Avenue, Boston, MA 02215 (ATTN: DATA).

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP electronically.

19. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

20. References

1. Watanbe T, Wu T-T, Catalano PJ, Ueki T, Satriano R, Haller DG, Benson III AB, Hamilton SR. Molecular predictors of survival after adjuvant chemotherapy for colon cancer (E 2284/ E 2288). New Engl J of Med 344(16): 1196-206, 2001.
2. International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) Investigators. Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer. J Clin Oncol 17(5): 1356-1363, 1999.
3. Figueredo A, Germond C, Maroun J, Browman G, Walker-Dilks C, Wong S and the Gastroinestinal Cancer Disease Site Group. Adjuvant therapy for stage II colon cancer following complete resection. Cancer Prevention and Control 1(5): 379-92, 1997.
4. Haller DG, Catalano PJ, Macdonald JS, Mayer RJ. Fluorouracil (FU), leucovorin (LV) and levamisole (LEV) adjuvant therapy for colon cancer: preliminary results of INT-0089. Proc ASCO 15(486): 211, 1996.
5. Haller DG, Catalano PJ, Macdonald JS, Mayer RJ. Fluorouracil (FU), leucovorin (LV) and levamisole (LEV) adjuvant therapy for colon cancer: four-year results of INT-0089. Proc ASCO 16(940): 265a, 1997.
6. Haller DG, Catalano PJ, Macdonald JS, Mayer RJ. Fluorouracil (FU), leucovorin (LV) and levamisole (LEV) adjuvant therapy for colon cancer: five-year final report of INT-0089. Proc ASCO 17(982): 256a, 1998.
7. Kabbinavar F, Hurwitz HI, Fehrenbacher L, Meropol NJ, Novotny WF, Lieberman G, Griffing S, Bergsland E. Phase II, Randomized Trial Comparing Bevacizumab Plus Fluorour (FU)/Leucovorin (LV) with FU/LV Alone in Patients with Metastatic Colorectal Cancer. J Clin Oncol 21(1): 60-65, 2003.
8. Novotny W, Hurwitz H, Fehrenbacher L, Cartwright T, Hainsworth J, Griffing S, Holmgren E, Kabbinavar F. Bevacizumab (Avastin, a Monoclonal Antibody to Vascular Endothelial Growth Factor) Prolongs Survival in First-Line Colorectal Cancer (CRC): Results of a Phase III trial of Bevacizumab in Combination with Bolus IFL (Irinotecan, 5-Fluorouracil, Leucovorin) as First-Line Therapy in Subjects with Metastatic CRC. Proc ASCO, 2003.

9. Benson AB, Catalano PJ, Meropol NJ, O'Dwyer PJ, Giantonio BJ. Bevacizumab (anti-VEGF) plus FOLFOX4 in previously treated advanced colorectal cancer (advCRC): An interim toxicity analysis of the Eastern Cooperative Oncology Group (ECOG) study E3200. Proc ASCO, Abstract; 22(975): 243, 2003.
3. deGramont A, Boni C, Navarro M, et al. Oxaliplatin/5-FU/LV in adjuvant colon cancer; safety results of the international randomized MOSAIC trial. Poster presentation: 38th ASCO Annual Meeting; May 18-21, 2002; Orlando, Florida.
4. deGramont A, Banzi M, Navarro M, et al. Oxaliplatin/5-FU/LV in adjuvant colon cancer: results of the international randomized phase III MOSAIC trial. Oral presentation: 39th ASCO Annual Meeting; May 31-June 3, 2003; Chicago, Illinois.
5. Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW, Meltzer SJ, Rodriguez-Bigas MA, Fodde R, Ranzani GN, Srivastava S. A National Cancer Institute Workshop on microsatellite instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res 58(22): 5248-57, 1998.
6. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F. Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin for Metastatic Colorectal Cancer. New Engl J of Med 350 (23): 2335-2342, 2004.
7. André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, Topham C, Zaninelli M, Clingan P, Bridgewater J, Tabah-Fisch I, de Gramont A. Oxaliplatin, Fluoroucacil, and Leucovorin as Adjuvant Treatment for Colon Cancer. New Engl J of Med 350 (23): 2343-2351, 2004.
8. Elsaleh H, Joseph D, Grieu F, Zeps N, Spry N, Iacopetta B. Association of tumour site and sex with survival benefit from adjuvant chemotherapy in colorectal cancer. Lancet 2000; 355:1745-50.
9. Ribic CM, Sargent DJ, Moore MJ, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. N Engl J Med 2003; 349:247-57.
10. Allegra CJ, Kim G, Kirsch IR. Microsatellite instability in colon cancer. N Engl J Med 2003; 349:1774-1776.
11. Hochster H, Chachoua A, Speyer J, et al. Oxaliplatin with weekly bolus fluorouracil and low-dose leucovorin as first-line therapy for patients with colorectal cancer . J Clin Oncol 15:2703-2707, 2003.
12. Maindrault-Goebel F, Louvet C, Andre T, et al. Oxaliplatin added to the simplified bimonthly leucovorin and 5-fluorouracil regimen as second-line therapy for metastatic colorectal cancer (FOLFOX6). GERCOR. Eur J Cancer 35:1338-1342, 1999.
13. Ryan DP, Clark JW, Kulke MH, et al. A phase II study of modified deGramont 5-fluorouracil, leucovorin, and oxaliplatin in previously treated patients with metastatic colorectal cancer. Cancer Invest 21:505-511, 2003.
14. Andre T, Figer A, Cervantes A, et al. FOLFOX7 compared to FOLFOX4. Preliminary results of the randomized optimox study. Proc Am Soc Clin Oncol 22:A1016;253, 2003.
15. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. J Clin Oncol 22:229-237, 2004.

16. C.J. Allegra, G. Yothers, M.J. O'Connell, S. Sharif, L.H. colangelo, S.H. Lopa, N.J. Petrelli, R.M. Goldberg, J.N. Atkins, T.E. Seay, L. Fehrenbacher, S. O'Reilly, L. Chu, C.A. Azar, N. Wolmark. Initial safety report of NSABP C-08: A randomized phase III study of modified FOLFOX6 with or without bevacizumab for the adjuvant treatment of patients with stage II or III colon cancer. JCO 2009 Jul 10; 27(20): 3385-90.

17. N. Wolmark, G. Yothers, M.J. O'Connell, S. Sharif, J.N. Atkins, T.E. Seay, L. Feherenbacher, S. O'Reilly, C.J. Allegra. A phase III trial comparing mFOLFOX6 to mFOLFOX6 plus bevacizumab in stage II or III carcinoma of the colon. J Clin Oncol 2009 Jun 20; 27 (185): LBA4, 793s

18.

A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers

Appendix I

Informed Consent Template for Cancer Treatment Trials (English Language)
[Deleted in *Addendum #13*]

INFORMED CONSENT INTENTIONALLY REMOVED FROM PROTOCOL DOCUMENT

Appendix I was removed from the protocol document in Addendum *#13* and is posted as a separate document on the ECOG website. This was removed from the protocol to comply with NCI formatting guidelines.

A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers

Rev.

Appendix II

Pathology Submission Guidelines

The following items are included in Appendix II:

1. Guidelines for Submission of Pathology Materials
   (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. List of Required Materials for E5202
4. Generic Specimen Submission Form (#2981)

Rev. 1/06

NOTE: As of November 3, 2014 all submissions and inquiries pertaining to previous submissions are to be directed to the ECOG-ACRIN Central Biorepository and Pathology Faciltiy (CBPF) at MD Anderson, telephone 844-744-2420 or email: eacbpf@mdanderson.org

Guidelines for Submission of Pathology Materials

Rev.

The following items should always be included when submitting pathology materials to the ECOG-ACRIN Central Biorepository and Pathology Facility:

Institutional Surgical Pathology Report

Pathology materials (see attached List of Required Material)

Rev. 1/06 Generic Specimen Submission Form (#2981)

Instructions:

1. Complete blank areas of the pathologist's instructional memo, and forward it, along with the List of Required Material and the Submission Form (if used), to the appropriate pathologist.
2. The pathologist should return to you the required pathology samples and surgical pathology reports. If any other reports are required, they should be obtained from the appropriate department at this time.

Rev. 1/06

Rev. 1/06

3. Keep documentation of the submission for your records; the original should be sent to the CBPF.
4. Double-check that ALL required forms, reports, and pathology samples are included in the package to send to the Central Biorepository and Pathology Facility (see appropriate List of Required Material).

Pathology specimens submitted for a patient WILL NOT be processed by the Central Biorepository and Pathology Facility until all necessary items are received.

1. Mail pathology materials to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

If you have any questions concerning the above instructions or if you anticipate any problems meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility at Tel: 844-744-2420 or by email at eacbpf@mdanderson.org.

Rev.

List of Required Material

E5202: *A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers*

Pre-Treatment

Rev. 1/06
1. Generic Specimen Submission Form (#2981)

Rev. 11/06
2. Institutional surgical pathology report ***(must be included with EVERY pathology submission)***.

Rev. 11/06
3. Required pathology materials. **(MANDATORY)**

Rev. 11/06
Tumor and Mucosa Block Submissions from Resection Specimen

- **Tissue block of formalin-fixed, paraffin-embedded normal mucosa**
- **Tissue block of formalin-fixed, paraffin-embedded tumor**

Rev. 7/07
NOTE: Two separate blocks must be submitted: **one block with normal mucosa and one block with resection tumor.** (One block with normal and tumor tissue is acceptable if two blocks cannot be obtained.)

Rev. 11/06
NOTE: If blocks cannot be submitted, 1 H&E stained slide and 10 unstained slides of a 4 micron section mounted on positively-charged glass slides from each type of block (mucosa and tumor) are acceptable.

Rev. 8/09

Rev. 4/06

Rev. 8/09
Recurrence (Submit within one month of collection)

1. Generic Specimen Submission Form (#2981)
2. Institutional surgical pathology report **(must be included with EVERY pathology submission).**
3. Pathology materials:
   - One formalin-fixed paraffin-embedded tumor block from resection, biopsy, or fine needle aspiration cell block of recurrence should be submitted.

     NOTE: If blocks cannot be submitted, 1 H&E stained slide and 10 unstained slides with a 4 micron section from tumor block mounted on positively-charged glass slides, or a representative smear or filter slide from fine needle aspiration specimen if there is no cell block, is acceptable.

Rev.

MEMORANDUM

TO: _____
(Submitting Pathologist)

FROM: [redacted] M.D., Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

Rev.

DATE: _____

SUBJECT: Submission of Pathology Materials for E5202*: A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers*

Rev. 1/06

The patient named on the attached request has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for mandatory studies to determine treatment assignment and additional pathology for banking for future research studies.

Rev

Keep a copy for your records and return the completed Submission Form, the surgical pathology report(s), the slides and/or blocks and any other required material (see attached List of Required Material) to the Clinical Research Associate (CRA). The CRA will forward all required pathology material to the ECOG-ACRIN Central Biorepository and Pathology Facility.

Blocks and/or slides submitted for this study will be retained at the ECOG-ACRIN Central Repository for future studies. Blocks will be returned for purposes of patient management upon request.

Rev

Rev
Rev

Results of the central review of specimens submitted at trial entry will be distributed to the CRA upon completion of the review. There is no review associated with submission of the recurrence tissue.

Rev. 11/06, 8/09

NOTE: To offset materials and resource costs associated with the collection and submission at trial entry of the required blocks, pathologists will receive reimbursement in the amount of **$85 per case.** Reimbursements will be paid from the ECOG-ACRIN Operations Office – Boston to the submitting institution and mailed to the attention of the PI. Payments are made annually.

If you have any questions regarding this request, please feel free to contact the Central Biorepository and Pathology Facility at TEL: 844-744-2420 or by email at eacbpf@mdanderson.org.

The ECOG-ACRIN CRA at your institution is:

Name:

Address:

Phone:

Thank you.

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time-point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.			
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

~~9/12/14~~

A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers

Appendix III

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Rev. 1/06

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the help of people like you who participate in clinical trials, we will achieve our goal of effectively treating and ultimately curing cancer.

We believe you will receive high quality, complete care. Your physician and research staff will maintain very close contact with you. This is important so as to allow your physician to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and the ECOG-ACRIN Cancer Research Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers

Appendix IV

Staging Criteria – Colon & Rectum

Rev. 7/07, 12/08, 8/10

COLON AND RECTUM STAGING FORM

CLINICAL *Extent of disease before any treatment*	STAGE CATEGORY DEFINITIONS	PATHOLOGIC *Extent of disease through completion of definitive surgery*
❑ y clinical– staging completed after neoadjuvant therapy but before subsequent surgery	TUMOR SIZE: _____ LATERALITY: ☐ left ☐ right ☐ bilateral	❑ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
	PRIMARY TUMOR (T)	
❑ TX	Primary tumor cannot be assessed	❑ TX
❑ T0	No evidence of primary tumor	❑ T0
❑ Tis	Carcinoma *in situ:* intraepithelial or invasion of lamina propria*	❑ Tis
❑ T1	Tumor invades submucosa	❑ T1
❑ T2	Tumor invades muscularis propria	❑ T2
❑ T3	Tumor invades through the muscularis propria into pericolorectal tissues	❑ T3
❑ T4a	Tumor penetrates to the surface of the visceral peritoneum**	❑ T4a
❑ T4b	Tumor directly invades or is adherent to other organs or structures^,**	❑ T4b
	Note: Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or mucosal lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.	
	^*Note:* Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retro-peritoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (i.e., respectively, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix or vagina).	
	**Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classifications should be used to identify the presence or absence of vascular or lymphatic invasion whereas the PN site-specific factor should be used for perineural invasion.	
	REGIONAL LYMPH NODES (N)	
❑ NX	Regional lymph nodes cannot be assessed	❑ NX
❑ N0	No regional lymph node metastasis	❑ N0
❑ N1	Metastasis in 1 to 3 regional lymph nodes	❑ N1
❑ N1a	Metastasis in 1 regional lymph node	❑ N1a
❑ N1b	Metastasis in 2-3 regional lymph nodes	❑ N1b
❑ N1c	Tumor deposit(s) in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal metastasis	❑ N1c
❑ N2	Metastasis in 4 or more regional lymph nodes	❑ N2
❑ N2a	Metastasis in 4 to 6 regional lymph nodes	❑ N2a
❑ N2b	Metastasis in 7 or more regional lymph nodes	❑ N2b
	Note: A satellite peritumoral nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule may represent discontinuous spread, venous invasion with extravascular spread (V1/2) or a totally replaced lymph node (N1/2). Replaced nodes should be counted separately as positive nodes in the N category, whereas discontinuous spread or venous invasion should be classified and counted in the Site-Specific Factor category Tumor Deposits (TD).	

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

(continued on next page)

COLON AND RECTUM STAGING FORM

DISTANT METASTASIS (M)

❑ M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)	
❑ M1	Distant metastasis	❑ M1
❑ M1a	Metastasis confined to one organ or site (e.g., liver, lung, ovary, non-regional node).	❑ M1a
❑ M1b	Metastases in more than one organ/site or the peritoneum.	❑ M1b

ANATOMIC STAGE • PROGNOSTIC GROUPS

CLINICAL

GROUP	T	N	M	Dukes*	MAC*
❑ 0	Tis	N0	M0	-	-
❑ I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
❑ IIA	T3	N0	M0	B	B2
❑ IIB	T4a	N0	M0	B	B2
❑ IIC	T4b	N0	M0	B	B3
❑ IIIA	T1-T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
❑ IIIB	T3-T4a	N1/N1c	M0	C	C2
	T2-T3	N2a	M0	C	C1/C2
	T1-T2	N2b	M0	C	C1
❑ IIIC	T4a	N2a	M0	C	C2
	T3-T4a	N2b	M0	C	C2
	T4b	N1-N2	M0	C	C3
❑ IVA	Any T	Any N	M1a	-	-
❑ IVB	Any T	Any N	M1b	-	-

*Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (Any TN1 M0 and Any T N2 M0). MAC is the modified Astler-Coller classification.

❑ Stage unknown

PATHOLOGIC

GROUP	T	N	M	Dukes*	MAC*
❑ 0	Tis	N0	M0	-	-
❑ I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
❑ IIA	T3	N0	M0	B	B2
❑ IIB	T4a	N0	M0	B	B2
❑ IIC	T4b	N0	M0	B	B3
❑ IIIA	T1-T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
❑ IIIB	T3-T4a	N1/N1c	M0	C	C2
	T2-T3	N2a	M0	C	C1/C2
	T1-T2	N2b	M0	C	C1
❑ IIIC	T4a	N2a	M0	C	C2
	T3-T4a	N2b	M0	C	C2
	T4b	N1-N2	M0	C	C3
❑ IVA	Any T	Any N	M1a	-	-
❑ IVB	Any T	Any N	M1b	-	-

*Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (Any TN1 M0 and Any T N2 M0). MAC is the modified Astler-Coller classification.

❑ Stage unknown

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)

REQUIRED FOR STAGING: None

CLINICALLY SIGNIFICANT:

Pre-operative or pre-treatment carcinoembryonic antigen (CEA) ng/ml _____
Tumor Deposits (TD) _____
Circumferential Resection Margin (CRM) _____
Perineural Invasion (PN) _____
Microsatellite Instability (MSI) _____
Tumor Regression Grade (with neoadjuvant therapy) _____
KRAS gene analysis _____
18q loss of heterozygosity (LOH) assay _____

Histologic Grade (G) *(also known as overall grade)*

Grading system	*Grade*
❑ 2 grade system	❑ Grade I or 1
❑ 3 grade system	❑ Grade II or 2
❑ 4 grade system	❑ Grade III or 3
❑ No 2, 3, or 4 grade system is available	❑ Grade IV or 4

General Notes:
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

y prefix indicates those cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

(continued from previous page)

COLON AND RECTUM STAGING FORM

ADDITIONAL DESCRIPTORS

Lymphatic Vessel Invasion (L) and Venous Invasion (V) have been combined into Lymph-Vascular Invasion (LVI) for collection by cancer registrars. The College of American Pathologists' (CAP) Checklist should be used as the primary source. Other sources may be used in the absence of a Checklist. Priority is given to positive results.

- ❑ Lymph-Vascular Invasion Not Present (absent)/Not Identified
- ❑ Lymph-Vascular Invasion Present/Identified
- ❑ Not Applicable
- ❑ Unknown/Indeterminate

Residual Tumor (R)

The absence or presence of residual tumor after treatment. In some cases treated with surgery and/or with neoadjuvant therapy there will be residual tumor at the primary site after treatment because of incomplete resection or local and regional disease that extends beyond the limit of ability of resection.

- ❑ RX Presence of residual tumor cannot be assessed
- ❑ R0 No residual tumor
- ❑ R1 Microscopic residual tumor
- ❑ R2 Macroscopic residual tumor

General Notes (continued):

r prefix indicates a recurrent tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.

a prefix designates the stage determined at autopsy: aTNM.

surgical margins is data field recorded by registrars describing the surgical margins of the resected primary site specimen as determined only by the pathology report.

neoadjuvant treatment is radiation therapy or systemic therapy (consisting of chemotherapy, hormone therapy, or immunotherapy) administered prior to a definitive surgical procedure. If the surgical procedure is not performed, the administered therapy no longer meets the definition of neoadjuvant therapy.

❑ Clinical stage was used in treatment planning (describe): _____

❑ National guidelines were used in treatment planning ❑ NCCN ❑ Other (describe): _____

_____

_____

Physician signature Date/Time

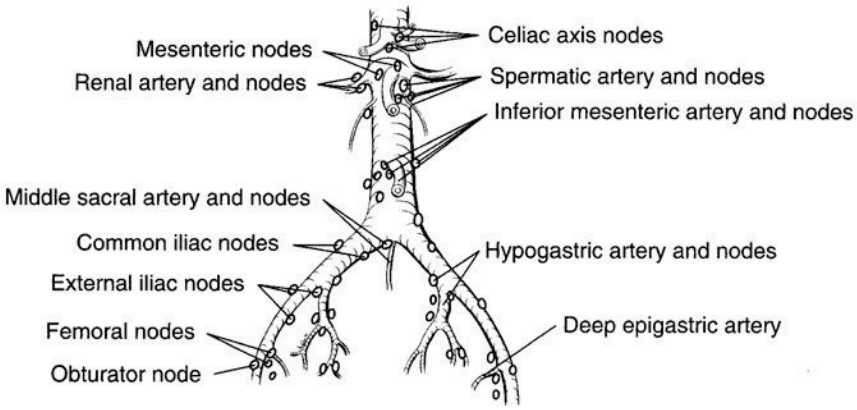
HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

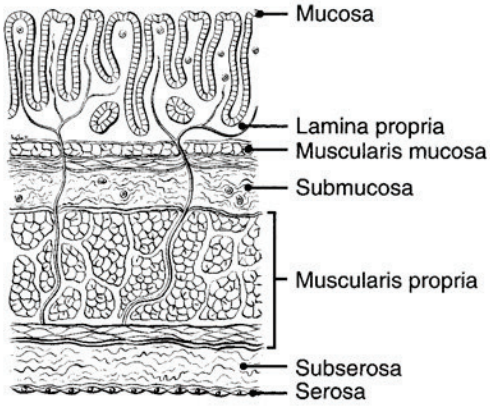
(continued on next page)

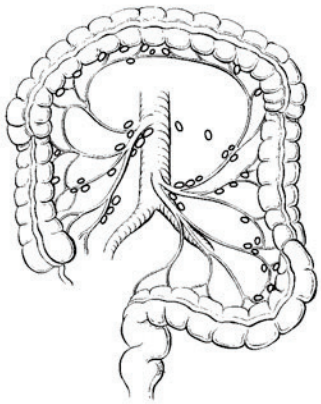
COLON AND RECTUM STAGING FORM

Illustration

Indicate on diagram primary tumor and regional nodes involved.







HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

(continued from previous page)

A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers

Appendix V

Rev. 3/07

Cancer Trials Support Unit (CTSU) Participation Procedures

REGISTRATION/RANDOMIZATION

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. 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 registered member Web site or by calling the PMB at 240-276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Rev. 7/14

Each CTSU investigator or group of investigators at a clinical 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 at http://members.ctsu.org

All forms and documents associated with this study can be downloaded from the E5202 Web page on the CTSU registered member Web site (https://members.ctsu.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

Requirements for E5202 site registration:

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

Prestudy requirements for patient enrollment on E5202:

- Patient must meet all inclusion criteria, and no exclusion criteria should apply
- Patient has signed and dated all applicable consents and authorization forms
- All baseline laboratory tests and prestudy evaluations performed within the time period specified in the protocol.

CTSU Procedures for Patient Enrollment

Step 1 Initial Registration:

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 1-301-704-2376.
2. Complete the following forms:
   - CTSU Patient Enrollment Transmittal Form

- E5202 Step 1 Eligibility Checklist

4. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 a.m. and 8:00 p.m., Mon-Fri, Eastern Time (excluding holidays). The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and follow-up with the site to resolve any discrepancies.
5. Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will contact the ECOG-ACRIN. The CTSU registrar will access the ECOG-ACRIN's on-line registration system, to obtain and assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will confirm registration by fax.
   - Mandatory tissue sample must be submitted for tumor risk assessment within 5 working days of registration to Step 1 (see Section 10). Results of the risk assessment will be reported to the submitting institution's CRA and the ECOG-ACRIN Operations Office – Boston via fax from MD Anderson Laboratory within 4 working days of receipt of the samples.

Step 2: Randomization to Arm A or B / Registration to Arm C:

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 1-301-704-2376.
2. Complete the following forms:
   - CTSU Patient Enrollment Transmittal Form (include patient id #)
   - E5202 Step 2 Eligibility Checklist
6. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 a.m. and 8:00 p.m., Mon-Fri, Eastern Time (excluding holidays). The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and follow-up with the site to resolve any discrepancies.
7. Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will contact the ECOG-ACRIN. The CTSU registrar will access the ECOG-ACRIN's on-line registration system and obtain a randomization assignment (Arm A or B) for high risk patients or to register low risk patients to Arm C observation. The CTSU registrar will confirm registration by fax.
   - High risk patients must not start protocol treatment prior to Step 2 randomization.
   - Protocol treatment on Arms A and B should begin within 5 working days from step 2 randomization.
   - Observation for Arm C patients begins at Step 2 registration.

DATA SUBMISSION AND RECONCILIATION

Rev. 7/07

1. All case report forms (CRFs) associated with this study must be downloaded from the E5202 Web page located on the CTSU registered member Web site (https://members.ctsu.org). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.

Rev. 7/07
Rev. 12/08

2. Submit all completed CRFs (with the exception of patient enrollment forms) and clinical reports directly to the ECOG-ACRIN [refer to contacts table] unless an alternate location is specified in the protocol. Do not send study data to the CTSU.

8. The ECOG-ACRIN Operations Office – Boston will mail query notices and delinquency reports directly to the site for reconciliation. Please send query responses and delinquent data to the ECOG-ACRIN Operations Office – Boston and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the ECOG-ACRIN Operations Office – Boston.

SPECIAL MATERIALS OR SUBSTUDIES

Rev. 12/08

All specimens submitted for this study must be entered and tracked using the ECOG-ACRIN Sample Tracking System. You can also access the Tracking System from the CTSU Member Web Site. Go to the E5202 protocol page and click on the link provided under the Case Report Forms header. Questions may be sent to ecog.tst@jimmy.harvard.edu.

Rev. 7/07
Rev. 12/08

1. Pathology Submission (Protocol Section 10 and 11)
   - Mandatory biological sample submission for tumor risk assessment at baseline.
   - Pathology samples requested at recurrence for banking for future research.
   - Collect, prepare, and submit specimens as outlined in the protocol.
   - Do not send specimens or supporting clinical reports to the CTSU.

Rev. 8/09

Rev. 7/07
Rev. 12/08

9. Specimen collection for ancillary study (Protocol Appendix XII)
   - Participation in the ancillary study is optional and requires patient consent.
   - Collect, prepare, and submit specimens as outlined in the protocol.
   - Do not send specimens or supporting clinical reports to the CTSU.

Rev.

Rev.

SERIOUS ADVERSE EVENT (AE) REPORTING (Section 5.2)

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.

10. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Report System (CTEP-AERS) from either the Adverse Events tab of the CTSU member homepage (https://members.ctsu.org) or by selecting Adverse Event Reporting Forms from the document center drop down list on the E5202 Web page.

11. Do not send adverse event reports to the CTSU.

12. Secondary AML/MDS/ALL reporting: Report occurrence of secondary AML, MDS, or ALL via the CTEP-AERS website (http://ctep.cancer.gov). Submit the completed form and supporting documentation as outlined in the protocol.

DRUG PROCUREMENT (Section 8.0)

Investigational IND agents: Bevacizumab (Note that the PMB will ship drug only to the shipping address specified by the CTSU investigator on their FDA form 1572.)

Commercial Agents: Oxaliplatin*, Leucovorin, 5-Fluorouracil.

***Oxaliplatin** will be provided free of charge by Sanofi-Synthelabo and distributed by the PMB.

1. Information on drug formulation, procurement, storage and accountability, administration, and potential toxicities are outlined in Section 8.0 of the protocol.
2. You may navigate to the drug forms by selecting Pharmacy Forms from the document center drop down list on the E5202 Web page.

REGULATORY COMPLIANCE AND MONITORING

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. (e.g., NSABP members may only request credit for protocols pertaining to breast or colorectal cancers). Registrations to protocols for other disease sites may still take place through CTSU without receiving credit for your NSABP activities. Per capita reimbursement will be issued directly from CTSU.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member Web site.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

Clinical Data Update System (CDUS) 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. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.

A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers

Appendix VI

Collaborative Agreement

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Pharmaceutical Company(ies) (hereinafter referred to as ACollaborator(s)@) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the AIntellectual Property Option to Collaborator@ contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data.@):
    a. NCI must provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
13. Clinical Trial Data and Results and Raw Data developed under a collaborative agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate. All data made available will comply with HIPAA regulations.
14. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for

Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

Rev.

15. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data and Safety Monitoring Committee (DSMC), if there is a DSMC for this clinical trial.

16. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

    Regulatory Affairs Branch, CTEP, DCTD, NCI
    Executive Plaza North, Suite 7111
    Bethesda, Maryland 20892
    FAX 301-402-1584
    Email: anshers@ctep.nci.hih.gov

    The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator=s confidential/ proprietary information.

A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers

Rev. 1/06, 12/14

Appendix VII

Shipment Notification Form

Rev. 7/07

NOTE: Generic Specimen Submission Form (#2981) (faxed to the receiving laboratory) will be required only if STS is unavailable at the time of sample submission. Indicate the appropriate Lab on the submission form:

- COG-ACRIN CBPF

Retroactively enter all specimen collection and shipping information when STS is available.

A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers

Appendix VIII

Rev 1/06

Procedure for Obtaining a Urine Protein/Creatinine Ratio

1) Obtain at least 4 ml of a random urine sample (does not have to be a 24 hour urine)
2) Determine urine protein concentration (mg/dL)
3) Determine urine creatinine concentration (mg/dL)
4) Divide #2 by #3 above: urine protein / creatinine ratio = protein concentration (mg /dL) / creatinine concentration (mg /dL)

The UPC directly correlates with the amount of protein excreted in the urine per 24 hrs (i.e. a UPC of 1 should be equivalent to 1g protein in a 24hr urine collection)

Protein and creatinine concentrations should be available on standard reports of urinalyses, not dipsticks. If protein and creatinine concentrations are not routinely reported at an Institution, their measurements and reports may need to be requested.

A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers

Appendix IX
Patient's Aspirin Use Diary

Rev. 1/06, 4/06

Rev. 11/06

Directions:

1. Please complete and return this diary to your doctor at the start of each cycle of treatment.
2. Please record the date, amount of aspirin and why you took aspirin (examples: pain, heart disease or stroke prevention) on this diary.
3. If no aspirin was taken since your last cycle of treatment, please check below:

_____***NO aspirin since last cycle of treatment***

Date	Dose	Reason for taking aspirin

NOTE: Baby aspirin is 81 mg

A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers

Appendix X

Rev. 7/07

Diarrhea Management Instructions

How to Manage Diarrhea

While you are receiving the chemotherapy drugs, you may experience diarrhea. In some individuals, diarrhea has been severe. Therefore, it is important that you follow the instructions noted below if you experience diarrhea while being treated.

What Is Diarrhea?

Diarrhea is when your bowel movements are loose or watery and more frequent than is usual for you. In order to help manage the diarrhea that your treatment may cause, you will need to keep track of your bowel movements. Keeping a diary may be the easiest way to do this. The diary should record how many bowel movements you have during the day, when they occur and the consistency of the stool (formed, loose or watery). Having diarrhea for a long period of time can result in problems such as dehydration. It is best to treat it early when it first begins. You should contact you doctor or nurse if you begin experiencing this side effect.

What Do I Take To Stop the Diarrhea?

The medication used to treat the diarrhea is called loperamide. The most common brand of loperamide is Imodium. Loperamide comes in the form of a 2 milligram (mg) caplet and is available without a prescription at most pharmacies and grocery stores in the health and beauty aids section.

The loperamide may cause some side effects. These side effects are drowsiness, tiredness and dizziness. It is important to avoid driving motorized vehicles or operating machinery if you experience any of these side effects.

When Should I Start Taking the Loperamide and For How Long?

At the first sign of diarrhea you will need to begin taking loperamide (Imodium) according to the directions below. (These will differ from the usual instructions found on the label.) If you do not start taking loperamide right away, severe diarrhea can occur that could require hospitalization. It is also important to stop taking any laxatives (medications to treat constipation such as milk of magnesia, Colace, Dulcolax, or Senakot).

Please follow these instructions carefully:

- Take two caplets (4 mg) at the first sign of any change in your normal bowel movement as described above.
- Continue taking one caplet (2 mg) every 2 hours until you have returned to your normal pattern of bowel movements for at least 12 hours. It is important to continue taking the loperamide even during the night. However, during the night you can take two caplets (4mg) every four hours instead of one caplet (2 mg) every two hours.
- Be sure to drink plenty of fluids each day (several glasses of water, fruit juice, soda, soup, etc). It is important to try to replace fluid that is being lost because of the diarrhea. This will help prevent dehydration and will not cause more diarrhea. You should avoid caffeinated beverages (coffee, tea, cola), alcoholic beverages and dairy products.

- Avoid high roughage foods like high-fiber cereals containing bran or whole grain, broccoli, cabbage, beans, fresh vegetables or fruit, fried food, chocolate or doughnuts.

Please call your doctor or nurse if you have any questions about taking loperamide, if your diarrhea does not improve, or if you experience new symptoms.

A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers

Appendix XI

Rev. 7/07

Comparison of Symptoms and Treatment Pharyngo-Laryngodysesthesias and Platinum Hypersensitivity Reactions

Clinical Symptoms	Pharyngo-Laryngeal Dysesthesias	Platinum Hypersensitivity
Dyspnea	Present	Present
Bronchospasm	Absent	Present
Laryngospasm	Absent	Present
Anxiety	Present	Present
O2 saturation	Normal	Decreased
Difficulty swallowing	Present (loss of sensation)	Absent
Pruritis	Absent	Present
Urticaria/rash	Absent	Present
Cold-induced Sx	Yes	No
BP	Normal or increased	Normal or decreased
Treatment	Anxiolytics, observation in a controlled clinical setting until symptoms abate or at the physician's discretion	Oxygen, steroids, epinephrine, antihistamines, bronchodilators; fluids and vascopressors, if appropriate.

A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers

Appendix XII

Rev. 12/08, 12/14

Ancillary For Pharmacogenetic and Genomic Studies: Correlation of Pharmacogenetic Studies with Response and Toxicity of Oxaliplatin

Study Co-Chairs: [redacted] Ph.D., Pharm.D.
[redacted] Ph.D., Pharm.D.

All patients participating in E5202 and E5204 are eligible to participate in this ancillary study, including patients currently receiving protocol treatment. Submit only from consenting patients who answer "yes" to "I agree to participate in the protein and DNA studies that are being done as part of this treatment trial."

XII.1 Ancillary for Pharmacogenetic and Genomic Studies

The Ancillary for Pharmacogenetic and Genomic Studies is a series of ancillary laboratory studies that seek to address questions about treatment response and toxicity that may span several studies and/or diseases. Thus, these correlatives may fall within the purview of a single disease committee, or span several. Each pharmacogenomic ancillary to be conducted in ECOG-ACRIN will be embedded into the parent protocols, with participation in the ancillary obtained via responses to questions embedded in the parent consent form. The general objectives of the pharmacogenetic ancillary are not specific to any one parent protocol: however, specific correlative objectives may be driven by the parent or related parent protocols.

Rev.

The development of novel targeted agents for the treatment of cancer has altered the process of the investigation of new treatments through the various stages of clinical research. Simultaneously, advances in biology have brought new questions regarding the mode of action, the toxicity, and the efficacy of treatments into the Phase II and III arena, historically the purview of the cooperative group. Some of the questions raised must be addressed in each tumor separately; others are independent of the tumor type and are properly asked across studies. The major questions may be summarized:

a. What tumor characteristics are responsible for some patients responding and others not?

b. What are the characteristics of normal tissues that cause some patients to have side-effects and others not?

c. When a treatment is administered at a particular dose, does it achieve the desired effect at the level of its target, in tumor and/or in normal tissue?

d. Can this variation in tumor and normal tissue make-up, and in biological responses to treatment be related to the outcome of such treatment in such a way as to refine that treatment for future patients?

The answers to these questions are in the tumors and tissues of patients treated on therapeutic trials. The analyses that accompany these studies are therefore of major importance to understanding both the successes and the failures of the trials.

The primary focus of the ancillary is in the acquisition of materials to permit pharmacogenetic and pharmacogenomic analyses to be performed. The overall purpose of these analyses is to explain and predict variability in drug responses among patients. The central **hypothesis** of the studies under this ancillary is that ***safe and effective drug use depends on an understanding of variability in both normal and tumor cells in individual patients.***

XII.2 Correlation of Pharmacogenetic Studies with Response and Toxicity study of Oxaliplatin

XII.2.1 Sample Submissions

Submit from patients who answer "yes" to "I agree to participate in the protein and DNA studies that are being done as part of this treatment trial."

Kits for sample collection and shipment are requested by contacting the Zemotak-International. Complete the KIT ORDER FORM (Appendix XII) and fax to (800)-815-4675.

It is required that all samples submitted from patients participating in E5202 be entered and tracked via the online ECOG-ACRIN Sample Tracking System (see Section 10.3).

LABELING

All samples are to be labeled with the ECOG-ACRIN protocol number E5202-PG0207, the ECOG-ACRIN patient sequence number, date and time of collection, and type of material (e.g. PAXgene DNA).

A. Tissue

Tumor tissue blocks submitted per Section 10 will be used for these studies.

Additional tumor tissue blocks, if available, are requested. Submit with appropriate pathology and surgical reports, and a completed Generic Specimen Submission Form (#2981)

B. Peripheral Blood

Rev. 8/10

Peripheral blood (Paxgene DNA, ACD, or EDTA tube) is to be drawn from each patient at any time after registration (preference: **prior to the start of treatment** or within the first 60 days after entry to the protocol). Invert tube gently 8-10 times to mix contents.

Samples may be shipped overnight at room temperature the day of collection or stored at -20˚C and shipped with a frozen kool pack within 2 weeks of collection. If several patients are accrued by the site, samples may be stored at -70˚C and batch shipped on dry ice on a quarterly basis.

Shipping Guidelines

Timeline and conditions for shipment of PAXgene tube is outlined above. Tissue submission guidelines are provided in Section 10.

A shipping manifest generated from the ECOG-ACRIN STS system must accompany the samples.

Ship overnight to:

ECOG-ACRIN Central Biorepository and Pathology Facility

MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

Blood samples are to be shipped overnight SUNDAY THROUGH THURSDAY only. Do not ship samples the day before a Holiday.

Rev. 12/08

If the STS is unavailable, an Generic Specimen Submission Form (#2981) must be submitted with the blood specimens and the laboratory must be notified of overnight shipment by emailing a completed Shipment Notification Form (Appendix XIII) to eacbpf@mdanderson.org the day of the shipment. Once STS is available, it is requested that samples be retrospectively logged into STS, using the actual collection and shipping dates.

XII.2.2 Objectives

To identify SNP profiles corresponding to response and/or toxicity (combination studies E5204 and E5202).

XII.2.3. Polymorphisms in Transporters, detoxifying enzymes, and excisions repair genes

Polymorphisms in copper influx transporter CTR1 [SLC31A1], copper influx transporters [ATP7A and ATP7B], detoxifying enzymes [GSTP1 and GSTM1], excision repair genes [ERCC1, ERCC2, and XRCC1], a renal transporter [SLC22A2] and a hepatocellular transporter [SLCO1B3].

Rev. 8/10

NOTE: Studies on DNA isolated from peripheral blood (PAXgene DNA, ACD, or EDTA vacutainer).

Rationale and Preliminary Data:

Peripheral neuropathy is the main and dose-limiting toxicity of oxaliplatin.[1-4] The acute, transient neuropathy occurs in 85% to 95% of patients and is associated with distal and perioral parathesias/dythesias. Resolution occurs within hours to days after the infusion. While, the dose-limiting form is a delayed cumulative peripheral neuropathy occurring in 10% to 20% of patients at the severity of grade 3. The delayed, cumulative toxicity persists between cycles, increases in intensity with cumulative dose, and can resolve to baseline after discontinuation of therapy usually after 4-6 months. The mechanism of delayed, cumulative neurotoxicity is unknown and prophylaxis has been attempted with little success.

Rev. 8/09

Factors more likely to correlate with drug disposition and explain much of the observed pharmacodynamic variability among individuals are being increasingly considered. Genetic polymorphisms in drug-metabolizing enzymes, drug transporter proteins, target enzymes, and DNA repair mechanisms may represent one key in elucidating the pharmacological variability.[5] CTR1 (SLC31A1) is a copper transporter that has been linked to carboplatin, cisplatin, and oxaliplatin influx transport.[6] SLC31A1 has 2 reported non-synonymous SNPs. Copper efflux transporters (ATP7A and ATP7B) have

also been associated with decreased platinum in resistant cells.[7,8] ATP7A and ATP7B have 8 and 9 reported non-synonymous SNPs, respectively. Uptake of cisplatin is mediated by SLC22A2 in renal proximal tubules which may be linked with the renal toxicity of that platinum analogue.[9] SLC22A2 has 8 reported non-synonymous SNPs. Unpublished data also demonstrates a statistically significant correlation between mRNA expression of the hepatocellular transporter SLCO1B3 and cytotoxicity (IC50 values) for platinum analogues in the NCI60 panel.[10] SLCO1B3 has 3 reported non-synonymous SNPs. There are other genes that have been assessed by other groups including excision repair genes (ERCC1, ERCC2, and XRCC1) and detoxifying enzymes (GSTM1, GSTP1 and GSTT1) and neuronal voltage-gated sodium channels (SCN1A).[11-13] ERCC1 (19007T>C;N118N) and ERCC2 (K751Q) variants have been linked to response while GSTM1 (DEL) has been linked to diarrhea and neutropenia.[11,12,14] The GSTP1 variant (I105V) is the only variant that has been linked to the onset of neurotoxicity in one study of 299 patients[13] but was negative in another study of 545 patients.[11] Most recently, a sodium-channel alpha 1-subunit (SCN1A) variant (T1067A) has been linked with improved response rates, overall survival, and frequency of severe toxicities including neuropathy.[15]

Genotyping:

Genomic DNA will be isolated from whole blood according to the manufacturer's instructions using the QIAamp DNA Blood Midi Kit (Qiagen, Valencia, CA).

The presence of ATP7A, ATP7B, ERCC2, GSTM1, GSTP1, GSTT1, SCN1A, SLC22A2, SLC31A1, SLCO1B3, and XRCC1 variants (see table) will be assessed using the polymerase chain reaction (PCR) based techniques and a DNA amplification protocol established in our laboratory at Johns Hopkins University School of Medicine. The primers for PCR will be synthesized by Invitrogen Life Technologies (Carlsbad, CA). For PCR, a 25µl PCR reaction will be carried out using HotMaster Mix (Eppendorf, Westbury NY), 0.5µl of each forward and reverse primer at a 0.2µM concentration, and 200 ng of genomic DNA which will be run for 35 cycles. The existence of the variant will be determined by direct nucleotide sequencing in the forward and reverse direction and performed using an ABI 3730XL Sequencer in the Genetics Resource Core Facility, Johns Hopkins University School of Medicine. Genotype will be called as it relates to the Refseq consensus sequence for that SNP position. Some SNP's have an available Taqman probe from ABI (Foster City CA). These will be run on a Real Time PCR instrument and the genotype will be acquired by use of allelic discrimination software and a control sample of each known genotype.

Gene	Potential Variants to Assess
ATP7A	720A > G (I189V) in exon 3 2161T > C (I669T) in exon 9 2263G > A (R703H) in exon 9 2454G > C (V767L) in exon 10 3687T > C (T1178H) in exon 18 4203G > A (E1350K) in exon 21 4356G > C (V1401L) in exon 22 4545A > G (I1464V) in exon 23

ATP7B	1373T > G (S406A) in exon 2 1523G > C (V456L) in exon 3 2186G > A (E667k) in exon 7 2450G > A (D765N) in exon 8 2490 G > T (R778L) in exon 8 2652 A > G (K832R) in exon 10 3012G > A (R952K) in exon 12 3576T > C (V1140A) in exon 16 3777A > G (H1207R) in exon 17
ERCC1	19007T > C (N118N) in exon 4
ERCC2	934 G > A (D312N)in exon 10 2251 T > G (K751Q) in exon 23
GSTM1	GSTM1*0/*0
GSTP1	313A > G (I105V) in exon 5 341C > T (A114V) in exon 6
GSTT1	GSTT1*0/*0
SCN1A	IVS5–91 G > A alternate splicing in exon 5 2623T > C (S875P) in exon 15 3166G > A (A1056T) in exon 16
SLC22A2	160C > T (P54S) in exon 1 390G > T (T(syn)) in exon 1 481T > C (F161L) in exon 2 493A > G (M165V)in exon 2 495G > A (M165I) in exon 2 669C > T (I(syn)) in exon 3 808T > G (S270A) in exon 4 890C > G (A297G) in exon 5 1198C > T (R400C) in exon 7 1203C > T (I(syn)) in exon 7 1294A > C (K432Q) in exon 8 1398C > T (G(syn)) in exon 9 1505G > A (G502E) in exon 10 1506G > A (V(syn)) in exon 10 1587C > T (A(syn)) in exon 10
SLC31A1	199C > G(P25A) in exon 2 491C > G(T122S) in exon 4
SLCO1B3	334T > G (S112A) in exon 3 699G > A (M233I) in exon 6 1557G > A (A519A) in exon 11
XRCC1	26304C > T (R194W) in exon 6 27466G > A (R280H) in exon 9 28152A > G (Q399R) in exon 10

XII.2.4. Statistical Considerations

The pharmacogenetic/pharmacodynamic studies of oxaliplatin are open to patients on the following studies with anticipated enrollment of eligible patients as follows: E5204 (2,100 patients), or E5202 (1,375 high-risk patients) for a total of 3,475 eligible patients. Throughout, it is assumed that 50% of eligible patients will participate and have adequate samples submitted, so that samples will be available for analysis for about 1,700 patients. The studies listed above

involve combination oxaliplatin and chemotherapy or other biologics in colorectal cancer.

For all studies, 85 mg/m^{2}oxaliplatin is administered intravenously over 2 hours every 2 weeks, however, cycle number of cycles vary across studies; the type of chemotherapy or other biologics differ across the combination studies.

Due to differences in disease stage, oxaliplatin schedule, and treatment regimen, the effects of genotypes on outcomes may be different across studies. Analyses will be conducted within individual studies, and by pooling across all studies as appropriate. Initial univariate analyses will not adjust for disease and treatment regimen differences. Additional analyses correlating genotypes associated with oxaliplatin activity with outcome will attempt to control for disease and treatment differences and their potential interactions with genotype on outcome using stratified analyses or adjusting for these factors in multivariate regression models.

Data Analysis Plan

To have a sufficiently high statistical power, we will include only SNPs with minor allele frequency of > 1%. However, we may include some polymorphisms for which the frequency was not previously known (taking the risk to include rare variants) but that had reasonable chances to alter the function of the gene, such as missense variants. Univariate analyses will be conducted to test associations within subgroups between each polymorphisms and outcome of interest, including toxicity and disease-free survival. The overall type I error rate of 0.05 will be controlled within each group and for each outcome by adjusting the alpha level within each set of univariate tests of polymorphisms using a resampling based approach.

The joint association of combinations of polymorphisms on outcome will be explored using logistic regression (toxicity endpoints) and Cox proportional hazards regression (survival endpoints). These multivariate analyses will also control for other important predictors of outcome and will examine interactions between polymorphisms, disease, and treatment. Recursive partitioning and other exploratory regression techniques will be used to explore SNP-SNP interactions and gene interactions in order to identify combinations of polymorphisms that can be used to predict high and low risk groups.

We base power calculations on the ability to detect differences in toxicity and disease-free survival (DFS) by individual polymorphisms both within each parent protocol and combining the studies. For the former, assuming that the overall 3-year DFS for E5202 and E5204 to be 82.5% and 68%, respectively, and that 1,050 and 650 patients are participating in E1Y03, respectively, there will be 89% [E5204] and 87% [E5202] power to detect a 50% (100%) difference in median DFS (66% vs 76% at 3 years in E5204; 80.5% vs 90% at 3 years in E5202) if the polymorphism rate is 20% and patients with polymorphism sustain a better outcome. Power for these comparisons will be higher if the polymorphism rate is higher. Polymorphisms with lower frequency will have lower power in the individual studies but differences should be detectable in these cases by combining the two parent trials in a pooled analysis. For example if the polymorphism rate is 10% and polymorphism correlates to a worse outcome, there will be 84% power to detect a combined difference of 42% in median DFS, combining the two parent studies. The above power

calculations assume a two-sided .05 level log rank test; power for detecting effects with proportional hazards regression models may be higher or lower depending upon the role of adjustment covariates in the modeling.

For toxicity, assuming a two-sided .05 level two group binomial test and an overall 80% rate of neurotoxicity due to oxaliplatin, the two parent protocols E5204 and E5202 will have 84% and 85% power to detect, respectively, absolute differences in toxicity rates of 12% and 15% between patients with and without a given polymorphism, assuming a marginal polymorphism rate of 10% and that polymorphism correlates with higher toxicity. A pooled analysis of the two studies will have greater than 90% power to detect an absolute difference in toxicity of less than 12%. In some analyses power will still be reasonable if the polymorphism rates are lower than 10%. For example, in the E5204 analysis if the true polymorphism rate is around 5% there is roughly 80% power to detect an absolute toxicity rate difference of 15%. For polymorphism with very low rates, only the pooled analyses combining studies will have adequate power, however.

For analyses of higher grade neurotoxicity that might have lower rates of occurrence (overall 15% expected of grade 3 or higher toxicity), the individual protocol (E5204, E5202) analyses will have roughly 90% and 74% power to detect an absolute difference of toxicity rates of 12% (polymorphism/no polymorphism) wherease the pooled analyses of both studies together will have greater than 90% power to detect these differences. For the toxicity analyses, power for detecting effects with logistic regression models may be higher or lower depending upon the role of adjustment covariates in the modeling.

Additional genes and exploratory analyses

Additional genes found to be important to oxaliplatin resistance or sensitivity through anti-angiogenesis or apoptosis pathways will be explored in a similar manner as above. Exploratory pathway analysis methods, including multi-dimensional scaling (Cox and Cox, 2001) will also be used.

A comprehensive analysis will be performed using the Illumina bead to identify variant genes involved in oxaliplatin toxicity and outcome. In addition to the genes mentioned, genes identified in association studies using CEPH and non-CEPH lymphoblasoid cell lines derived from large pedigrees[1617] by Drs. Eileen Dolan at the University of Chicago and Howard McLeod at the University of North Carolina may be included in the analysis.

An analysis of indirectly-measured haplotypes and their associations with phenotypes, possibly adjusting for other covariates and their interactions, will be conducted using haplo.stats software available on-line, and associations will be tested based on the family of score tests proposed by Schaid et al (2002), which assume ambiguous haplotypes due to unknown linkage phase of the genetic markers. The score test handles both continuous and categorical phenotypes.

XII.2.5. References

1. Mani S., Graham M. A., Bregman D. B., Ivy P., Chaney S. G.: Oxaliplatin: a review of evolving concepts. Cancer Invest 20:246-63, 2002

2. Extra J. M., Marty M., Brienza S., Misset J. L.: Pharmacokinetics and safety profile of oxaliplatin. Semin Oncol 25:13-22, 1998
3. Misset J. L.: Oxaliplatin in practice. Br J Cancer 77 Suppl 4:4-7, 1998
4. Cersosimo R. J.: Oxaliplatin-associated neuropathy: a review. Ann Pharmacother 39:128-35, 2005
5. McLeod H. L., Papageorgio C., Watters J. W.: Using genetic variation to optimize cancer chemotherapy. Clin Adv Hematol Oncol 1:107-11, 2003
6. Song I. S., Savaraj N., Siddik Z. H., Liu P., Wei Y., Wu C. J., Kuo M. T.: Role of human copper transporter Ctr1 in the transport of platinum-based antitumor agents in cisplatin-sensitive and cisplatin-resistant cells. Mol Cancer Ther 3:1543-9, 2004
7. Samimi G., Katano K., Holzer A. K., Safaei R., Howell S. B.: Modulation of the cellular pharmacology of cisplatin and its analogs by the copper exporters ATP7A and ATP7B. Mol Pharmacol 66:25-32, 2004
8. Samimi G., Safaei R., Katano K., Holzer A. K., Rochdi M., Tomioka M., Goodman M., Howell S. B.: Increased expression of the copper efflux transporter ATP7A mediates resistance to cisplatin, carboplatin, and oxaliplatin in ovarian cancer cells. Clin Cancer Res 10:4661-9, 2004
9. Ciarimboli G., Ludwig T., Lang D., Pavenstadt H., Koepsell H., Piechota H. J., Haier J., Jaehde U., Zisowsky J., Schlatter E.: Cisplatin nephrotoxicity is critically mediated via the human organic cation transporter 2. Am J Pathol 167:1477-84, 2005
10. Personal communication between [redacted] and, 2006
11. McLeod H. L., Sargent D. J., Marsh S., Fuchs C., Ramanathan R. K., Williamson S., Findlay B., Thibodeau S., Petersen G., Goldberg R.: Pharmacogenetic analysis of systemic toxicity and response after 5-fluorouracil (5FU)/CPT-11, 5FU/oxaliplatin (oxal), or CPT-11/oxal therapy for advanced colorectal cancer (CRC): Results from an intergroup trial. Proc ASCO 22:253 (Abtract 1013), 2003
12. Park D. J., Stoehlmacher J., Zhang W., Tsao-Wei D. D., Groshen S., Lenz H. J.: A Xeroderma pigmentosum group D gene polymorphism predicts clinical outcome to platinum-based chemotherapy in patients with advanced colorectal cancer. Cancer Res 61:8654-8, 2001
13. Grothey A., McLeod H. L., Green E. M., Sargent D. J., Fuchs C., Ramanathan R. K., Williamson S. K., Findlay B. P., Goldberg R. M.: Glutathione S-transferase P1 I105V (GSTP1 I105V) polymorphism is associated with early onset of oxaliplatin-induced neurotoxicity. Proc ASCO 23:248s (Abstract 3509), 2005
14. Stoehlmacher J., Park D. J., Zhang W., Yang D., Groshen S., Zahedy S., Lenz H. J.: A multivariate analysis of genomic polymorphisms: prediction of clinical outcome to 5-FU/oxaliplatin combination chemotherapy in refractory colorectal cancer. Br J Cancer 91:344-54, 2004
15. Nagashima F., Zhang W., Yang D., Gordon M., Schultheis A., Fazzone W., Azuma M., El-Khoueiry A., Iqbal S., Lenz H. J.: Polymorphism in sodium-channel alpha 1-subunit (SCN1A) predicts response, TTP, survival, and

toxicity in patients with metastatic colorectal cancer treated with 5-FU/oxaliplatin. Proc ASCO 24: Abstract No. 3533, 2006

16. Shukla S. J., Dolan M. E.: Use of CEPH and non-CEPH lymphoblast cell lines in pharmacogenetic studies. Pharmacogenomics 6:303-10, 2005
17. Dolan M. E., Newbold K. G., Nagasubramanian R., Wu X., Ratain M. J., Cook E. H., Jr., Badner J. A.: Heritability and linkage analysis of sensitivity to cisplatin-induced cytotoxicity. Cancer Res 64:4353-6, 2004

A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers

Appendix XIII

Rev. 12/08, 12/14

E5202 Pharmacogenetic Collection and Shipping Kit Order Form

Date: _____ **Fax:** **(800) 815-4675** _____

To obtain the proper kit, provide the following information:

E5202 patient case number: _____

PG0207 Kit Requested:

Rev. 8/10

- Pharmacogenomic (PAXgene DNA or ACD tube)

Kit is to be shipped to:

Institution Contact: _____

Phone number for contact: _____

Institution Address:

_____

_____

_____

FAX Completed form to Zemotak-International at (800) 815-4675

NOTE: Questions are to be directed to the ECOG CBPF,
Attn [redacted]
Tel: [redacted]
Pager: [redacted]

Comments:

_____

_____

_____