NSABP PROTOCOL C-08

A Phase III Clinical Trial Comparing Infusional 5-Fluorouracil (5-FU), Leucovorin, and Oxaliplatin (mFOLFOX6) Every Two Weeks with Bevacizumab to the Same Regimen without Bevacizumab for the Treatment of Patients with Resected Stages II and III Carcinoma of the Colon

NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT (NSABP)

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All institutions that are not aligned with the NSABP will enroll patients via the NCI Cancer Trials Support Unit (CTSU).

IND #7921 (Bevacizumab) sponsored by the NCI

STUDY DRUGS	NSC #	SUPPLIED BY
Oxaliplatin	266046	Sanofi-Synthelabo Inc. via the NCI
Leucovorin	3590	Commercially Available
5-Fluorouracil	19893	Commercially Available
Bevacizumab	704865	Genentech Inc. via the NCI

Version as of October 25, 2007 (REPLACES ALL OTHER VERSIONS)

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NSABP PROTOCOL C-08

A Phase III Clinical Trial Comparing Infusional 5-Fluorouracil (5-FU), Leucovorin, and Oxaliplatin (mFOLFOX6) Every Two Weeks with Bevacizumab to the Same Regimen without Bevacizumab for the Treatment of Patients with Resected Stages II and III Carcinoma of the Colon

National Surgical Adjuvant Breast and Bowel Project (NSABP)

Trial Activated: September 15, 2004

Protocol Revision Record

Original Version: August 24, 2004

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Amendment #7: October 25, 2007
Sections Changed: Cover Page, Sections 10.2.5 (Table 12), 12.4.2, 15.0 (Table 17), and Appendix H.

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TABLE OF CONTENTS

01/12/05, 02/24/05, 07/27/05, 04/21/06, 08/02/07

INFORMATION RESOURCES *01/12/05, 02/24/05, 07/27/05, 04/21/06*

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Web site: http://www.nsabp.pitt.edu

Questions concerning eligibility and clinical aspects of the trial

NSABP Operations Center
Clinical Coordinating Division
Phone: 1-800-477-7227
E-mail: ccd@nsabp.org

Questions/problems regarding IRB review & informed consent (see Appendix H)

NSABP Operations Center
Division of Regulatory Affairs
Phone: (412) 330-4600
Fax: (412) 330-4661

Patient entry information (see Section 14.0)

NSABP Biostatistical Center
Patient Entry Coordinator
Phone: (412) 383-4900

Consult the Patient Entry Guidelines section in the Members' Area of the NSABP Web site.

Submission of IRB approval

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-888-823-5923
Fax: (215) 569-0206

Submission of tumor blocks (see Section 7.1)

NSABP Biostatistical Center
Address: see above
(When sending blocks or other materials, please indicate on the package "Pathology Specimens Enclosed.")

Arrangements for blocks that are not to be stored and need to be returned as soon as possible

NSABP Division of Pathology
Phone: (412) 359-3312
Fax: (412) 359-3239

Submission of expedited adverse event reports / questions concerning expedited adverse event reporting (see Section 13.0)

NSABP Biostatistical Center
Phone: (412) 383-2552
Fax: (412) 622-2113

Questions concerning data management

NSABP Biostatistical Center
Phone: (412) 624-2666

Questions concerning drug orders, shipments, transfers, and returns (see Section 12.0)

- **Pharmaceutical Management Branch**
  Phone: (301) 496-5725
  Fax: (301) 480-4612

  For mail:
  CTEP, DCTD, NCI
  9000 Rockville Pike
  EPN, Room 7149
  Bethesda, MD 20892-7422

  For express courier:
  CTEP, DCTD, NCI
  6130 Executive Boulevard
  Room 7149
  Rockville, MD 20852

- **NSABP Biostatistical Center**
  (see above)

Submission of Blood and Serum Samples for Immunogenicity, PK, and Ovarian Function Testing, Specimen Banking, and Future Research

Submission of blood and serum samples *for banking* (See Appendix D)

Baylor College of Medicine Breast Center
NSABP Serum Bank
Room N1220
One Baylor Plaza
Houston, TX 77030
Phone: (713) 798-1647
Fax: (713) 798-1642

Submission of samples *for ovarian function tests and anti-bevacizumab antibody and PK analysis* (See Appendix C)

Covance Central Laboratory
8211 SciCor Drive
Indianapolis, IN 46214-2985
Phone: 1-800-327-7270
Fax: (317) 616-2358

Cancer Trials Support Unit (CTSU) Information Resources

This study is supported by the NCI CTSU.

Institutions not aligned with the NSABP will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix (Appendix E).

To submit site registration documents:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Phone: 1-888-823-5923
Fax: 1-215-569-0206

For patient enrollments:

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.]

Submit study data directly to the NSABP unless otherwise specified in the protocol:
Preferred method:
Fax: 412-622-2111

NSABP Biostatistical Center
One Sterling Plaza
201 North Craig Street, Suite 500
Pittsburgh, PA 15213

Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.

For patient eligibility and treatment-related questions, contact the Clinical Coordinating Division at the NSABP Operations Center at 1-800-477-7227.

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

- 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 Appendix E for specific instructions and documents to be submitted.
- Data management will be performed by the NSABP. **Case report forms** (with the exception of patient enrollment forms), **clinical reports, and other documents** must be sent to the NSABP Biostatistical Center unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by the NSABP Biostatistical Center. Please send query responses and delinquent data to the NSABP Biostatistical Center and do not copy the CTSU Data Operations. If the query is sent with a fax transmittal form, return the data to the fax number on the transmittal form, otherwise fax to 412-624-1082.
- 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 NSABP Biostatistical Center.

1.0 SUMMARY OF THE STUDY

This phase III study will evaluate the relative efficacy of infusional 5-fluorouracil (5-FU), leucovorin (LV), and oxaliplatin (mFOLFOX6) alone or the same chemotherapy regimen plus bevacizumab in patients with resected stages II and III carcinoma of the colon. The primary goal of the study is to determine whether disease-free survival (DFS) can be improved by the addition of bevacizumab to mFOLFOX6. Other goals are to compare the relative efficacy of the two regimens in prolonging survival and to evaluate adverse events related to bevacizumab.

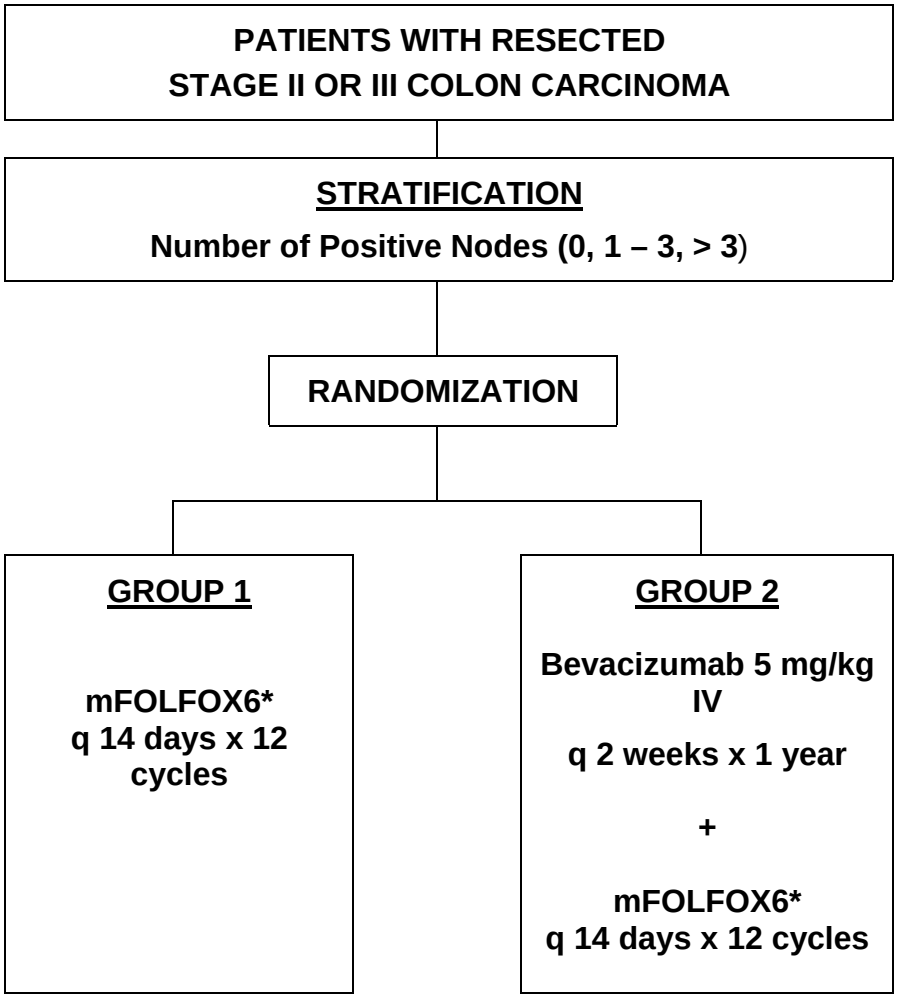
Patients in Group 1 will receive oxaliplatin 85 mg/m^2 with concurrent LV 400 mg/m^2 on Day 1 of each 2-week cycle followed by IV bolus 5-FU 400 mg/m^2 followed by a single continuous infusion of 5-FU 2400 mg/m^2 over 46 hours. This treatment regimen will be repeated every 2 weeks for a total of 12 cycles (6 months).

Patients in Group 2 will receive oxaliplatin 85 mg/m^2 with concurrent LV 400 mg/m^2 on Day 1 of each 2-week cycle followed by IV bolus 5-FU 400 mg/m^2 followed by a single continuous infusion of 5-FU 2400 mg/m^2 over 46 hours. This treatment regimen will be repeated every 2 weeks for a total of 12 cycles (6 months). Bevacizumab 5 mg/kg IV will be administered before oxaliplatin on Day 1 of each chemotherapy cycle and continue every 2 weeks during and after the completion of all chemotherapy cycles for a total duration of 1 year.

Tumor blocks and serum will be required for correlative science studies. Additionally, serum will be collected for ovarian function tests in premenopausal women, for analysis of anti-bevacizumab antibodies, and for determination of post-treatment serum levels of bevacizumab in patients assigned to receive bevacizumab. Serum will also be collected when a Group 2 patient has an allergic reaction to bevacizumab.

Figure 1.

C-08 SCHEMA



*modified FOLFOX6 regimen:

Oxaliplatin 85 mg/m^2 IV Day 1
Leucovorin 400 mg/m^2 IV Day 1
5-FU 400 mg/m^2 IV bolus Day 1
5-FU 2400 mg/m^2 by continuous IV infusion over 46 hours (Day 1 and Day 2)

2.0 BACKGROUND

2.1 Historical overview of adjuvant therapy for colon cancer

Colorectal cancer is the third most common cause of death from malignancy in both males and females in the U.S.[1] Although surgery remains the mainstay of treatment for stages II and III colon cancer, a substantial minority of patients are not cured by surgery alone. Studies from the NSABP and other cooperative groups have clearly demonstrated that adjuvant chemotherapy has altered the natural history of patients with colon cancer. Two approaches have resulted in improvement in disease free survival (DFS) and survival (S).

The first treatment approach that resulted in improved survival rates is the combination of 5-FU and levamisole (LEV). Intergroup Protocol 0035 confirmed an earlier study conducted by the NCCTG[2] and demonstrated a prolongation in DFS and S in patients with stage III carcinoma of the colon treated with the combination of 5-FU and LEV versus LEV alone or no postoperative therapy.[3] There was no clear benefit from adjuvant therapy among patients with stage II disease.

The second approach relates to the biochemical modulation of 5-FU by LV. The superiority of the LV modulation over 5-FU alone has been convincingly demonstrated in a reported meta analysis involving nine randomized clinical trials and a total of 1,381 patients with metastatic colon cancer.[4] The addition of folinic acid stabilizes the 5-FU/thymidylate synthase complex, maximizing and prolonging the inhibition. This therapeutic efficacy of LV-modulated 5-FU in the metastatic setting heightened interest in 5-FU + LV-based therapies in the adjuvant setting for colon cancer patients.[5] Subsequently, the results of three studies that randomized approximately 1,500 patients with stage III colon cancer to either surgery alone or to postoperative treatment with regimens of 5-FU + LV were published. The IMPACT study pooled the analysis of these three studies (FFCD, NCI-Canada, and GIVIO) in which 6 cycles (6 months) of bolus 5-FU + LV were compared with follow-up alone. Of a total of 1,526 patients randomized, 45% (685 patients) had stage III disease. The group of patients that received 5-FU + LV showed a DFS of 62% compared to 44% in the non-treatment group after 37 months of follow-up.[6] The treatment arm achieved a significant advantage over observation alone in reducing 5-year recurrence rates (34% vs. 59%) and longer overall 5-year survival (69% vs. 43%).[7] Using the combination of 5-FU 500 mg/m^2 and "high-dose" LV (500 mg/m^2) in the adjuvant setting for 1 year, the NSABP reported a significant prolongation in DFS and S over that reported with the use of the methyl CCNU, vincristine sulfate, and 5-FU (MOF) regimen (73% vs. 64%, and 84% vs. 77%, respectively) in patients with stages II and III colon cancer.[8]

The Intergroup 0035 study using 5-FU and LEV for 1 year, the Intergroup study using 6 months of 5-FU and LV, and the IMPACT study using 5-FU and LV for 6 months demonstrated similar improvements in DFS and S rates. These encouraging results led to direct comparison of these regimens as summarized below. Intergroup study (INT-0089) was initiated in 1989. Twenty percent of the 3759 patients were diagnosed with high-risk Dukes' stage B2 disease. Patients were randomly assigned to receive standard 5-FU + LEV for 12 months, 5-FU + high-dose LV, 5-FU + low-dose LV, or 5-FU + low-dose LV + LEV. The latter three regimens were administered for approximately 6 months. The results affirmed that 6 months of therapy with 5-FU + LV should represent standard adjuvant treatment for patients with resected high-risk colon cancer.[9]

The results of NSABP C-04, in which 2152 patients (41% Dukes' B) were randomized, were similar. The 5-year DFS was 74% for 5-FU + LV, and 70% for 5-FU + LEV and 73% for 5-FU + LV + LEV; therefore, LEV did not appear to add to the survival advantage associated with 5-FU + LV. Duration of therapy was approximately 1 year for all groups. No significant differences in toxicity were noticed.[10]

A large NCCTG and NCIC adjuvant study compared 1 year with 6 months of treatment and addressed whether LV was a useful addition to the original LEV-based regimen. Therapy consisted of 5-FU + LEV or 5-FU + LV + LEV. Two conclusions can be drawn from this study: first, 12 months of adjuvant chemotherapy offers no advantage over 6 months; and second, triple therapy for 6 months showed significantly superior survival compared to the combination of 5-FU + LEV for the same time period (75% vs. 63%).[11]

Based on data from these trials, adjuvant chemotherapy using 6 months of 5-FU + LV, has become a current standard of care in the United States.

2.2 **Oxaliplatin**

Oxaliplatin (trans-*l*-diaminocyclohexane oxalatoplatinum) is a novel platinum derivative with an oxalato-leaving group and a 1,2-diaminocyclohexane (DACH) carrier.

2.2.1 ***Mechanism of action of oxaliplatin***

Studies conducted to date indicate that the mechanism of action of oxaliplatin is similar to that of cisplatin in terms of types and percentages of DNA-Pt adducts formed.[12-14] However, the following preclinical data suggest several unique attributes related to the cytotoxic/antitumoral activity of oxaliplatin compared to cisplatin.

- DACH-Pt adducts are bulkier and more hydrophobic than cis-diamine-Pt adducts and may be more effective in DNA synthesis inhibition.[12,15,16]
- DNA mismatch repair complexes do not recognize DACH-Pt adducts.[17,18]
- Experimental data on naked and intracellular DNA suggest a higher cytotoxic efficacy of oxaliplatin DNA-Pt adducts compared to cisplatin DNA-Pt adducts.[12]

Oxaliplatin demonstrates a broad spectrum of *in vitro* cytotoxic activity and *in vivo* antitumor activity that differs from that of either cisplatin or carboplatin. In addition, oxaliplatin is active against several cisplatin-resistant cell lines, colon carcinoma, and other solid tumors that are not responsive to cisplatin. Oxaliplatin in combination with 5-FU leads to synergistic antiproliferative activity *in vitro* as well as to *in vivo* synergism in several tumor models.

2.2.2 ***Clinical experience with oxaliplatin in combination with 5-FU + LV***

The efficacy of oxaliplatin 85 mg/m^2 administered in combination with 5-FU + LV every 2 weeks (q 2w) was investigated in multiple studies.[19-25] This dose level provided the same dose intensity as the 130 mg/m^2-every-3 week (q 3w) regimen and allowed oxaliplatin to be administered in combination with bimonthly 5-FU + LV regimens.

A supra-additive effect of the oxaliplatin/5-FU + LV combination has been noted with all 5-FU schedules and delivery modalities employed in the developmental clinical trials.[23-25] In previously untreated patients, objective response rates as high as 50-60% have been observed, and response rates in previously treated patients range from 10-30%.

A recent report by Rothenberg and coworkers[23] demonstrated a 9.9% response rate in 150 patients with irinotecan, 5-FU, LV (IFL) refractory colorectal cancer treated with a regimen containing bolus 5-FU (400 mg/m^2), infusional 5-FU (600 mg/m^2 over 22 hours) and LV (200 mg/m^2) given on Days 1 and 2 with oxaliplatin (85 mg/m^2 given on Day 1 of each 2-week cycle (FOLFOX4). The median time to tumor progression was 4.6 months. This randomized phase III trial demonstrated the superiority of FOLFOX4 over either oxaliplatin as a single agent or infusional 5-FU + LV. In August 2002, the FDA approved oxaliplatin for the treatment of patients with refractory advanced colorectal cancer on the basis of this trial.

Results of a randomized, first-line colorectal cancer trial were published by deGramont and coworkers.[20] Four-hundred-twenty patients were enrolled in this phase III study in which 5-FU + LV ± oxaliplatin 85 mg/m^2 was administered every 2 weeks. Median progression-free survival (PFS) was 26.4 weeks in the control arm and 37.9 weeks in the investigational (oxaliplatin) arm. The overall response rate (ORR) was statistically significantly higher in patients treated with the combination oxaliplatin + 5-FU + LV arm, in comparison with those treated with 5-FU + LV alone (50.7% vs. 22.3%). Although survival was slightly longer for the oxaliplatin-treated group (16.2 vs. 14.7 months), this difference did not reach statistical significance.

Intergroup N9741 was recently published in the *Journal of Clinical Oncology*.[21] In this study, 795 patients with previously untreated metastatic colorectal cancer were randomized to one of three treatment arms including standard IFL, FOLFOX, or the non-5-FU containing regimen of CPT-11 plus oxaliplatin. Results for the first two arms demonstrated a statistically superior ORR (45 vs. 31%; p=0.03), TTP (8.7 vs. 6.9 months; p<0.001), 1-year survival (70 vs. 57%; p=0.002) and median survival (19.5 vs. 15 months; p=0.002) for the FOLFOX arm compared with IFL. These results strongly support the superiority of the FOLFOX regimen over standard IFL for the treatment of patients with advanced colorectal cancer.

Various modifications of the combination of oxaliplatin with 5-FU + LV regimens (FOLFOX1-FOLFOX7) have been evaluated.[26-29] 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.[27] 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%.[28] 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.[29] 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.[30] 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.

The 3-year results of the MOSAIC trial were reported at ASCO 2003.[22] This randomized trial compared the efficacy of FOLFOX4 to a standard deGramont regimen of infusional 5-FU + LV for the treatment of 2246 patients with stage II (40%) and III (60%) colon cancer. The 3-year DFS was significantly improved with the addition of oxaliplatin to 5-FU + LV (77.8% vs. 72.9%, respectively) when compared with the same 5-FU + LV regimen without oxaliplatin (Hazard Ratio [HR]= 0.77 $p < 0.01$). Grade 3/4 toxicities associated with the FOLFOX regimen are listed in Table 1. Of note, 12% of patients treated with oxaliplatin were observed to develop grade 3/4 neurotoxicity. Six months following completion of therapy, fewer than 10% of these patients had persistent grade 3 neurotoxicity. This trial, in conjunction with data from patients with advanced colorectal cancer treated with FOLFOX, strongly support the value of FOLFOX as a superior regimen when compared with 5-FU + LV alone therapy in both the adjuvant and advanced disease settings.

Table 1 lists the more commonly encountered grade 3/4 toxicities associated with the various oxaliplatin containing regimens in combination with either 5-FU + LV or capecitabine. Toxicities associated with the IFL regimen and the weekly 5-FU + LV Roswell Park regimen are shown for comparison.

TABLE 1. Percentage of patients experiencing grade 3-4 toxicities associated with the use of oxaliplatin or irinotecan in combination with 5-FU + LV or capecitabine

	No. Patients	Nausea/ Vomiting	Diarrhea	Dehydration	Neutropenia	Neutropenia with fever	Neurotoxicity
FLOX C-07	1201	15	35	17	7	2	8
FOLFOX N9741	267	6	12	4	48	4	18
FOLFOX MOSAIC	1108	6	11	N/A	41	1	12
IFL N9741	264	16	34	8	40	15	2
FU/LV C-07	1202	11	29	11	3	1	1
Capecitabine/ Oxaliplatin (CAPOX) Sastre/ Van Cutsem[31]	96	13	16	N/A	7	N/A	17

2.2.3 ***Safety profile of oxaliplatin***

The major toxicities and their occurrence rates are presented in Table 1. The unique toxicity associated with the use of oxaliplatin is a predictable cumulative dose-dependent peripheral sensory neuropathy.

- *Neurologic toxicity:* Neurologic toxicity is dose-limiting for oxaliplatin and characterized primarily by a peripheral sensory neuropathy, with dysesthesias and/or distal paresthesias often triggered or exacerbated by cold. This toxicity generally regresses between courses of treatment but tends to last longer with subsequent courses. In patients treated with 12 cycles of FOLFOX4 therapy in the adjuvant setting, 12% developed grade 3 neuropathy.[22] One year following the end of adjuvant therapy, fewer than 1% of the patients who developed grade 3 neuropathy had persistent grade 3 neuropathy. Thus, the neuropathy associated with the use of oxaliplatin is largely reversible.

  E3200 compared FOLFOX4 alone to FOLFOX4 + bevacizumab (10 mg/kg) and to bevacizumab (10 mg/kg) alone in patients with advanced or metastatic colon cancer.32 A total of 757 patients registered on the study were evaluable for toxicity. Among the 262 patients evaluable for toxicity who were assigned to receive FOLFOX4 + bevacizumab, 11% had ≥ grade 3 sensory neuropathy and 6% had ≥ grade 3 neuropathy/other. In contrast, among patients assigned to receive either FOLFOX4 alone (N = 265) or bevacizumab alone (N = 230), the incidence of ≥ grade 3 sensory neuropathy and ≥ grade 3 neuropathy/other were reported to be 5% and 3% and < 1% and 1%, respectively. However, these differences may be the result of

differences in cumulative oxaliplatin doses received by patients on two of the three arms of this study.

01/12/05

- *Other toxicities:* Severe allergic reactions, which usually included facial flushing, rash, urticaria, and less frequently, Quincke's edema, bronchospasm, or anaphylactic-like reactions, were reported in less than 0.5% of patients. Bronchospasm should be differentiated from the more common pharyngo-laryngeal dysesthesia associated with the administration of oxaliplatin. This latter toxicity may be alleviated by prolonging the infusion time of oxaliplatin. As expected, cutaneous toxicity was observed in combination with 5-FU (hand-foot syndrome). Additionally, use of oxaliplatin has been associated with morphologic changes that are characteristic of veno-occlusive disease (VOD) of the liver. The majority of these cases demonstrate no clinical evidence of VOD.

01/12/05

2.3 Bevacizumab

Bevacizumab (rhuMAb VEGF), developed by Genentech, Inc., is a recombinant humanized monoclonal antibody against human VEGF.

2.3.1 *Mechanism of action of bevacizumab*

Vascular endothelial growth factor (VEGF) is a critical regulator of both normal and pathologic angiogenesis.[33] It is a highly conserved homodimeric glycoprotein whose dominant isoform has a molecular weight of 45kD. The biologic activity of VEGF is mediated by binding to two receptors on the surface of endothelial cells namely, Flt-1 and KDR. Increased levels have been demonstrated in colon cancer and presumably represent an important factor needed to support the cancer through the growth to tumor vasculature.[34] Folkman and coworkers provide convincing evidence linking tumor growth and metastases with angiogenesis and several investigators have demonstrated a correlation between vascular density in colorectal cancer and metastases, recurrence and survival.[35-42] Inhibition of VEGF, either alone or in combination with chemotherapy, results in growth inhibitions of a number of human tumor xenografts in the nude mouse model, including colorectal cancer cell lines, LS174T, HM7, and LSLiM6.[33,43]

2.3.2 *Phase I clinical experience with bevacizumab*

The dose and toxicities associated with bevacizumab were investigated in two phase I trials.[44,45] Study AVF0737g was an open-label dose-escalation study of single agent bevacizumab in patients with advanced cancers. Three patients in this trial experienced tumor-related hemorrhagic events (two cases were considered serious). Linear pharmacokinetics were observed for doses of drug in excess of 1 mg/kg. The drug's half-life was found to be approximately 15 days. Study AVF0761g evaluated bevacizumab in combination with three cytotoxic regimens including 5-FU + LV, carboplatin + paclitaxel, and doxorubicin in patients with advanced cancers. No patients in this study experienced serious hemorrhagic events and the co-administration of bevacizumab with chemotherapy did not alter the pharmacokinetics of the cytotoxic agents. Neither study detected antibodies to bevacizumab.

2.3.3 ***Phase II and III clinical experience with bevacizumab***

- *Phase II studies in patients with advanced colorectal cancer*

Two phase II trials have been conducted in patients with advanced colorectal cancer. Trial AVF0780g was a randomized, multicenter phase II trial designed to evaluate the safety, efficacy and pharmacokinetics of bevacizumab in combination with 5-FU + LV using the weekly Roswell Park regimen.[46] Patients were randomized to either 5-FU + LV alone or with either 5 or 10 mg/kg bevacizumab given IV every 2 weeks. A total of 104 patients were randomized into the three treatment arms. Patients in the control arm were permitted to crossover to receive single agent bevacizumab if they developed progressive disease. Of the 21 patients who crossed over, 2 patients achieved a partial response with single agent therapy. The response, time to progression, and survival associated with each of these arms are summarized below in Table 2.

TABLE 2. Phase II trial of bevacizumab in untreated metastatic colorectal cancer [46]

	5-FU + LV weekly 6/8 (n = 36)	**5-FU + LV + bevacizumab 5 mg/kg** (n = 35)	**5-FU + LV + bevacizumab 10 mg/kg** (n = 33)
Response Rate (%)	17	40 (p = 0.03)	24
Time to Progression (months)	5.2	9 (p = 0.009)	7.2
Median Survival (months)	13.8	21.5 (p = 0.135)	16.1

The Eastern Cooperative Oncology Group (ECOG) performed study E2200 and Giantonio and coworkers reported on the results of this phase II trial at ASCO 2002 and 2003.[47,48] Ninety-two previously untreated patients with advanced colorectal cancer were treated with the IFL regimen (CPT-11 100-125 mg/m^2, 5-FU 500 mg/m^2, LV 20 mg/m^2 weekly x 4 every 6 weeks) plus bevacizumab 10 mg/kg every 2 weeks. The ORR was 45.7%. The toxicity data suggests: "the addition of bevacizumab to IFL does not appear to increase the rates of known toxicities for that regimen. No significant bleeding events have been reported to date." In the ASCO 2003 update, the authors reported grade 1 bleeding in 43 patients of which 23 events were epistaxis. There was one grade 4 epistaxis and one grade 3 melena. They reported eight grade 3/4 thrombotic episodes and "infrequent" hypertension and proteinuria.

- *Phase III studies in patients with advanced colorectal cancer*

  At the time of development of NSABP C-08, two phase III trials are presently ongoing in patients with advanced colorectal cancer and each is designed to test the relative merits of combining bevacizumab with standard cytotoxic combinations with known efficacy.

  Study E3200 is being conducted by ECOG and patients with previously treated metastatic colorectal cancer are randomized to FOLFOX (oxaliplatin 85 mg/m^2 Day 1 plus LV 200 mg/m^2 Days 1 and 2, plus 5-FU 400 mg/m^2 bolus followed by 600 mg/m^2 over 22 hours Days 1 and 2 every 2 weeks); FOLFOX plus bevacizumab 10 mg/kg; or bevacizumab 10 mg/kg alone.[32] Enrollment was initiated for this trial in November 2001. Benson and co-workers reported preliminary analysis of toxicity in 123 patients treated on this trial. Overall, grade 3/4 events were similar between the patients treated with FOLFOX vs. those treated with FOLFOX plus bevacizumab. The exception was a higher incidence of hypertension (1 vs. 9%) observed in the bevacizumab-treated group.

  In study AVF2107g, 815 patients with advanced and untreated colorectal cancer were randomly assigned to receive either the standard IFL regimen or IFL plus bevacizumab 5 mg/kg every 2 weeks. Hurwitz and coworkers presented the results of this trial at ASCO 2003.[49] The addition of bevacizumab to IFL resulted in a significant increase in response rate (44.9 vs. 34.7%), response duration (10.4 vs. 7.1 months), PFS (10.6 vs. 6.2 months) and OS (20.3 vs. 15.6 months). In addition, grade 3/4 neutropenia (31 vs. 37%), diarrhea (25 vs. 33%), and vomiting (10.6 vs. 7.7%) were observed between the arms without and with bevacizumab, respectively. Toxicities potentially related to the use of bevacizumab, including grade 3/4 bleeding (2.5 vs. 3.1%), proteinuria (0.8 vs. 0.8%) and <u>any</u> thromboembolic event (16.1 vs. 19.3%), did not significantly differ between the patients treated without or with bevacizumab, respectively. However, the incidence of grade 3/4 hypertension was significantly increased in the group receiving bevacizumab compared with those treated with IFL alone (10.9 vs. 2.3%).

  This study in patients with advanced colorectal cancer was the first to demonstrate clear and tangible clinical benefit associated with the addition of an antiangiogenesis agent to standard chemotherapy. The results of this trial led the FDA to approve the use of bevacizumab in combination with a 5-FU-based regimen for the first line treatment of patients with advanced colorectal cancer in February 2004. Given this compelling evidence for clinical benefit in the management of patients with advanced colorectal cancer, the present trial seeks to support its utility in patients with colon cancer treated in the adjuvant setting, with a goal of improving disease-free and overall survival.

2.3.4 ***Safety profile of bevacizumab***

The safety profile of bevacizumab in the setting of metastatic cancer has been established in a variety of clinical trials, including large, randomized, placebo-controlled trials in metastatic colorectal cancer.[50] However, several observed or potential issues related to bevacizumab therapy, including gastrointestinal

perforation and wound dehiscence, proteinuria, hypertension, vascular events, fertility/pregnancy, and immunogenicity are of special interest in the adjuvant therapy setting.

- *Gastrointestinal perforation and wound dehiscence*

  Gastrointestinal perforation and wound dehiscence, complicated by intra-abdominal abscesses, occurred at an increased incidence in patients receiving bevacizumab as compared to controls in study AVF2107g. Bevacizumab has also been shown to impair wound healing in pre-clinical animal models.

  In study AVF2107g, 1 of 396 (0.3%) patients receiving IFL + placebo, 6 of 392 (2%) patients receiving IFL + bevacizumab, and 4 of 109 (4%) patients receiving 5-FU + LV + bevacizumab developed gastrointestinal perforation. These episodes occurred at various time points during treatment. In addition, 2 of 396 (0.5%) patients receiving IFL + placebo, 4 of 392 (1%) patients receiving IFL + bevacizumab, and 1 of 109 (1%) patients receiving 5-FU + LV + bevacizumab developed a wound dehiscence during study treatment.

  Although the appropriate *interval between surgery and subsequent initiation of bevacizumab* required to avoid the risks of impaired wound healing has not been determined, in study AVF2107g the clinical protocol did not permit initiation of bevacizumab for at least 28 days following surgery. There was 1 patient (among 501 patients receiving bevacizumab on study AVF2107g) in whom an anastomotic dehiscence occurred when bevacizumab was initiated per protocol. This data suggests that initiation of bevacizumab 29-50 days following surgery as required in NSABP C-08 should be associated with a very low incidence of anastomotic dehiscence.

01/12/05

  There is limited data concerning the rate of complications in patients *undergoing major surgical procedures while receiving bevacizumab.* Of 40 patients on the IFL/bevacizumab arm of AVF2107g who underwent major surgery while on study, 4 had significant post-operative bleeding or wound-healing complications (10%). This rate is in contrast to none of 25 patients in the control arm who had major surgery while on study. While no major surgery is planned during bevacizumab therapy in NSABP C-08, patients requiring surgery will require careful monitoring by their physician.

- *Proteinuria:* Bevacizumab therapy is associated with an increased incidence of proteinuria, although most proteinuria events are asymptomatic and do not result in any change to bevacizumab therapy or chemotherapy. In the AVF2107g study, risk factors for the development of proteinuria included a history of hypertension, an adverse event of hypertension, and a history of diabetes. In three patients, proteinuria decreased in severity several months after discontinuation of bevacizumab. Although there is substantial information available regarding bevacizumab-associated proteinuria, there remain a number of important unanswered questions, including whether bevacizumab-associated proteinuria is reversible upon discontinuation of bevacizumab therapy; what clinical sequelae, if any, result from bevacizumab-associated proteinuria; and what patient characteristics predict the development of bevacizumab-associated proteinuria.

- *Hypertension:* In the collective experience of 1,032 patients being treated with bevacizumab on Genentech-sponsored trials, the incidence of hypertension was 15%. However, there is little data available regarding whether hypertension persists in patients in whom bevacizumab therapy is discontinued.

- *Vascular events:* In the randomized clinical trial in patients with colorectal cancer, AVF2107g, the overall rate of vascular events (venous and arterial) were similar between the two primary treatment arms. However, no substantial information regarding the risk of delayed vascular events was obtained.

05/17/05

- *Arterial thromboembolic events:* In the AVF2107g study, there was a 1% incidence of arterial thromboembolic events (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 arterial thromboembolic events from five randomized studies showed that treatment with bevacizumab increased the risk of these events 2- to 3-fold (up to 5%). Furthermore, certain baseline characteristics conferred additional risk; specifically, age ≥ 65 years and prior arterial thromboembolic event. Problems due to blood clots in the arteries were seen in about 2.9% of patients 65 or older receiving chemotherapy alone, and about 8.5% of patients 65 or older receiving bevacizumab with chemotherapy. Patients who were both 65 or older and reported a history of past problems with blood clots in their arteries appeared to be at even higher risk, although further study is required before an estimate of the risk can be provided.

- *Fertility/pregnancy:* As an antiangiogenic agent, bevacizumab therapy may alter corpus luteum development and endometrial proliferation, thereby having a negative effect on fertility. Additionally, bevacizumab therapy is associated with teratogenicity in animal models. However, data from clinical trials regarding the immediate or persistent effect of bevacizumab therapy on ovarian function, fertility, and pregnancy is lacking.

- *Immunogenicity:* Genentech has not detected the presence of anti-bevacizumab antibodies in any subject during the clinical development of bevacizumab. The lack of positive results from this assay in any of the 494 subjects with pre- and post-baseline measurements strongly suggests that bevacizumab is not immunogenic. However, the question arises whether increasing the sensitivity of the assay would improve our ability to detect low titer antibodies.

2.4 Rationale for the selection of the control group

As detailed in Section 2.2.2, the MOSAIC trial demonstrated a superior outcome (3-year DFS) with the addition of oxaliplatin to 5-FU + LV. This data, coupled with the data in patients with advanced disease demonstrating that the addition of oxaliplatin to 5-FU + LV is superior to not only 5-FU + LV but also to combination therapy such as IFL, strongly support the use of FOLFOX as the control arm for the NSABP C-08 study.[21] FOLFOX4 has been the most commonly studied version of the FOLFOX

regimens and little data is available that allows for direct comparisons between the various other versions of FOLFOX and FOLFOX4. Based on indirect comparisons among sequential phase II investigations reported by de Gramont et al and a randomized comparison between FOLFOX4 and FOLFOX7, it appears reasonable to conclude that the more convenient versions of the FOLFOX regimen, i.e., those that drop the Day 2 5-FU + LV bolus, have similar clinical value when compared with FOLFOX4.[29] For the present trial, we have elected to use a modification of the FOLFOX6 regimen that maintains the same dose of oxaliplatin as FOLFOX4 (85 mg/m^2 q 2w) and the identical 5-FU + LV schedule as the more convenient FOLFOX6 regimen. Use of the higher dose of oxaliplatin as is used in FOLFOX6 (100 mg/m^2) would almost certainly result in greater grade 3 neurotoxicity than that seen in the MOSAIC trial using 85 mg/m^2 (12%). Thus the rationale for the use of 85 mg/m^2 of oxaliplatin is to maintain an acceptable level of neurotoxicity.

In summary, we have elected to employ mFOLFOX6 as the control arm of this trial because of its similarity to the FOLFOX4 regimen, its demonstrated activity in advanced colorectal cancer, its use of oxaliplatin at a moderate dose of 85 mg/m^2 to limit neuropathy in this patient population, its improved toxicity profile compared to bolus regimens of these same drugs in combination (such as FLOX as used in NSABP C-07)[51], and convenience of administration. It should be noted that the GI Intergroup has also elected to employ this identical regimen as the control arm in its current generation colon cancer adjuvant trial (N0147), indicating consensus among cooperative group investigators in the United States.

2.5 Justification for inclusion of patients with Dukes' B (stage II) colon cancer

Although the benefit from adjuvant chemotherapy has been established for Dukes' C (stage III) colon cancer patients, many still question the worth of such therapy in patients with Dukes' B disease. In 1990, an NIH consensus panel recommended that patients with Dukes' C colon cancer who are unable to enter a clinical trial should be offered adjuvant therapy with 5-FU and LEV. The same panel did not recommend any specific adjuvant therapy for Dukes' B colon cancer patients outside clinical trials.

These recommendations were mainly derived from results of Intergroup trial 0035, which demonstrated a significant reduction in the risk of recurrence and death in patients with Dukes' C colon cancer treated with postoperative 5-FU + LEV when compared to those treated with surgery alone. The same trial failed to indicate a significant reduction in the rates of recurrence or death with the combination of 5-FU + LEV in patients with Dukes' B colon cancer when compared to the group treated with surgery alone, although there was a trend toward prolonged DFS and OS in patients in this subgroup. Many have attributed the lack of statistically significant benefit to the relatively small number of Dukes' B patients included and to the lower event rate for treatment failure and death in these patients.

The NSABP has included Dukes' B and C colon cancer patients in four adjuvant chemotherapy trials where outcome results are available.[52] Overall, 41% of patients accrued in these four trials were Dukes' B patients. Protocol C-01 compared adjuvant MOF to surgery alone, Protocol C-02 compared perioperative portal vein infusion (PVI) of 5-FU to surgery alone, Protocol C-03 compared adjuvant 5-FU + LV to MOF, and Protocol C-04 compared 5-FU + LV to 5-FU + LEV.

Table 3 provides the 5-year DFS and S results. In C-01, patients on MOF had higher DFS and S than those assigned to surgery alone; in C-02, DFS and S were higher for perioperative portal vein infusion (PVI) than for surgery alone; in C-03, DFS and S were higher for 5-FU + LV than for MOF; and in C-04, DFS and S were higher for 5-FU + LV than for 5-FU + LEV.

TABLE 3. Five-year DFS and S in NSABP C-01, C-02, C-03, and C-04

	C-01		**C-02**		**C-03**		**C-04**	
	MOF (353 pts)	SURGERY (379 pts)	PVI (340 pts)	SURGERY (342 pts)	FU-LV (519 pts)	MOF (522 pts)	FU-LV (693 pts)	FU-LEV (691 pts)
% 5-YR S	67	60	76	68	76	65	74	69
% 5-YR DFS	58	52	67	58	66	54	64	60

We recently examined the relative efficacy of treatment in these four trials according to Dukes' stage. Table 4 lists the cumulative odds for mortality with their respective 95% confidence intervals.

TABLE 4. Cumulative odds for death in NSABP C-01, C-02, C-03, and C-04

	C-01 MOF vs. SURGERY	**C-02 PVI vs. SURGERY**	**C-03 FU-LV vs. MOF**	**C-04 FU-LV vs. FU-LEV**
All Patients	0.79 (0.61 - 1.01)	0.74 (0.55 - 0.99)	0.67 (0.53 - 0.84)	0.79 (0.64 - 0.98)
Dukes' B	0.93 (0.60 - 1.43)	0.50 (0.30 - 0.82)	0.51 (0.26 - 1.01)	0.75 (0.49 - 1.14)
Dukes' C	0.73 (0.54 - 0.98)	0.92 (0.64 - 1.32)	0.72 (0.56 - 0.93)	0.80 (0.62 - 1.02)
These values represent the odds ratio with a 95% confidence interval.				

Quantitative interaction was observed in C-02, where a greater benefit from adjuvant chemotherapy was seen in patients with Dukes' B disease when compared to those with Dukes' C disease. The results in Table 4 indicate that, for Protocols C-02, C-03, and C-04 in patients with Dukes' B disease, the relative reduction in mortality was at least comparable to that observed in patients with Dukes' C disease. Thus, it is reasonable to include patients with Dukes' B disease in adjuvant protocols which employ an active treatment control arm.

2.6 **Study rationale**

The hypothesis of this trial is that the addition of the anti-VEGF antibody (bevacizumab) to infusional 5-FU + LV and oxaliplatin (mFOLFOX6) will be more beneficial than mFOLFOX6 alone in prolonging DFS and S in patients with resected stages II and III carcinoma of the colon. Therefore, this trial is designed to evaluate the efficacy of

adding bevacizumab administered every 2 weeks for a total duration of 1 year to postoperative mFOLFOX6 administered for twelve 2-week cycles (for a total duration of 6 months) in patients with resected stages II and III carcinoma of the colon.

In addition, there is speculation that bevacizumab activity may be dependent upon the expression of circulatory VEGF and VEGF receptors in tumor tissue and that these same parameters may be of both predictive and prognostic significance. We intend to quantify the expression of these parameters among patients assigned to receive bevacizumab and patients not assigned to receive bevacizumab and to correlate them with benefit and prognosis.

The primary goal of this clinical trial is to determine in the most direct and definitive manner possible whether bevacizumab has a beneficial role in the colon cancer surgical adjuvant setting. This goal is the primary motivating factor for a straightforward two-arm study design asking a single question: Does the addition of bevacizumab to the currently most promising combination chemotherapy improve long-term patient outcome?

Choosing the appropriate duration of bevacizumab therapy was based on the following considerations. First, VEGF has direct mitogenic and survival effects on endothelial cells in preclinical model systems. In addition, binding and clearing VEGF with bevacizumab has demonstrated a reversal of the increase in interstitial pressure in xenograft models with improved local delivery of systemic chemotherapy and enhanced anti-tumor effects when bevacizumab and chemotherapy are administered concurrently. Importantly, significant improvements in patient survival were seen in patients with advanced colorectal cancer who were treated with bevacizumab in combination with chemotherapy as compared to chemotherapy alone.[49]

Second, despite potent biologic effects, bevacizumab is rarely curative in xenograft models. Cessation of bevacizumab therapy is associated with eventual tumor re-growth, suggesting a mixed cytotoxic and cytostatic effect in vivo. This latter observation supports the hypothesis of "tumor dormancy" as one potential goal of anti-angiogenic therapy with the associated implication for chronic therapy. Bevacizumab has been shown to have single agent activity in human adenocarcinomas of the breast and kidney. In both of these settings, the effect on time-to-tumor progression was much more significant when compared to the modest objective response rates that were observed, implying the importance of a cytostatic mechanism of action.

In clinical trials when bevacizumab was combined with chemotherapy in the first-line treatment of metastatic colorectal cancer, similar observations were made.[46,49] Although response rates were modestly improved, the treatment effect on time-to-tumor progression and overall survival appeared to be much more robust, again implying the clinical value of a cytostatic effect. Although these trials were designed to treat patients concurrently with chemotherapy and bevacizumab until disease progression, a proportion of patients discontinued chemotherapy because of either associated toxicity or maximal clinical benefit, but continued on bevacizumab as a single agent with prolonged disease stabilization.

The original hypothesis of the "angiogenic switch" suggested that tumor growth beyond 1 mm^3 would be dependent on the production of autocrine and/or paracrine angiogenic growth factors. This would imply that the cytostatic role of bevacizumab, blocking neovascularization of micrometastatic disease, may be most critical in the minimal

residual disease environment and that longer rather than shorter durations of therapy may be more efficacious.

Taking all of this information into account, we wish to be as certain as possible to avoid administration of bevacizumab in a suboptimal manner, since a negative study would undoubtedly delay or derail its further development as an adjuvant treatment for colon cancer. Therefore, we have elected to administer bevacizumab for a full year in this protocol: 6 months in combination with chemotherapy, followed by 6 months as a single agent. If a significant improvement in patient outcome is seen, then subsequent studies to explore shorter (or longer) durations of treatment will be appropriate.

3.0 SPECIFIC AIMS

In patients who have undergone a potentially curative resection of a stage II or III carcinoma of the colon, the aims are described in the following sections.

3.1 Primary aim

The primary aim of this study is to compare the relative efficacy of mFOLFOX6 + bevacizumab with that of mFOLFOX6 alone in prolonging disease-free survival (DFS).

3.2 Secondary aim

The secondary aim of this study is to compare the relative efficacy of mFOLFOX6 + bevacizumab with that of mFOLFOX6 alone in prolonging survival (S).

3.3 Tertiary aims

The tertiary aims of the study are to evaluate if incidence and duration of certain adverse events are possibly related to treatment with bevacizumab. The specific tertiary aims are as follows:

i. to assess the persistence of proteinuria following the discontinuation of bevacizumab;
ii. to correlate the development of proteinuria with clinical sequelae;
iii. to evaluate the risk factors for development of proteinuria;
iv. to determine the effect of discontinuation of bevacizumab on hypertension;
v. to estimate the incidence of delayed vascular events such as myocardial infarction, CNS ischemia, and thrombosis in patients receiving chemotherapy + bevacizumab;
vi. to assess the effect of bevacizumab on ovarian function in premenopausal women; and
vii. to assess the incidence rate of immunogenicity and examine post-treatment serum levels of bevacizumab in patients receiving bevacizumab.

4.0 ENDPOINTS

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4.1 Primary endpoint

The primary endpoint to be used for statistical analysis is duration of DFS. Events for DFS include first documented evidence of colon cancer recurrence, second primary cancer (other than basal cell and squamous cell carcinoma of the skin, Bowen's disease, carcinoma in situ of the cervix, and carcinoma in situ of the colon), or death from any cause.

4.2 Secondary endpoint

The secondary endpoint to be used for statistical analysis is duration of S. Events for S include death from any cause.

4.3 Tertiary endpoints

The tertiary endpoints to be used for statistical analysis are as follows:

- For tertiary aims 3.3 (i), 3.3 (ii), and 3.3 (iii), "proteinuria" is defined as ≥ 1.0 g of protein excretion per 24 hours.

- The tertiary endpoints to evaluate the effect of discontinuation of bevacizumab on hypertension (3.3 [iv]) will include evaluation of periodic assessment of systolic and diastolic blood pressure and the use (type and dose) of antihypertensive medication.

- To estimate the incidence of delayed vascular events (3.3 [v]), vascular adverse events per CTCAE v3.0 will be collected (specifically, myocardial infarction, CNS ischemia, venous and arterial thromboses).

- To assess ovarian function (3.3 [vi]), ovarian failure will be defined as: negative pregnancy test, ≥ 3 months of amenorrhea, and serum FSH ≥ 30 mIU/ml.

5.0 PATIENT ELIGIBILITY AND INELIGIBILITY

Male and female patients who satisfy the conditions stated below are the only patients who will be eligible for the study.

5.1 Conditions for patient eligibility

5.1.1 Patients must consent to be in the study and must have signed and dated an IRB-approved consent form conforming to federal and institutional guidelines.

5.1.2 Patients must be ≥ 18 years old.

5.1.3 Randomization must occur during the three-week interval beginning on postoperative Day 29 and ending on postoperative Day 50.

5.1.4 The distal extent of the tumor must be ≥ 12 cm from the anal verge on endoscopy. If the patient is not a candidate for endoscopy, then the distal extent of the tumor must be ≥ 12 cm from the anal verge as determined by surgical examination.

5.1.5 The patient must have had an en bloc complete gross resection of tumor (curative resection) by open laparotomy or laparoscopically-assisted colectomy. Patients who have had a two-stage surgical procedure, to first provide a decompressive colostomy and then in a later procedure to have the definitive surgical resection, are eligible.

5.1.6 Patients must have histologically confirmed adenocarcinoma of the colon that meets one of the criteria below:

- Stage II carcinoma ($T_{3,4}$ N_0 M_0) The tumor invades through the muscularis propria into the subserosa or into non-peritonealized pericolic or perirectal tissues (T_3); or directly invades other organs or structures, and/or perforates visceral peritoneum (T_4).
- Stage III carcinoma (any T $N_{1,2}$ M_0) The tumor has invaded to any depth, with involvement of regional lymph nodes.

Appendix A provides TNM nomenclature and staging for colon cancer.

5.1.7 Patients with T_4 tumors that have involved an adjacent structure (e.g., bladder, small intestine, ovary, etc.) by direct extension from the primary tumor are eligible if <u>all</u> of the following conditions are met:

- all or a portion of the adjacent structure was removed <u>en bloc</u> with the primary tumor;
- in the opinion of the surgeon, all grossly visible tumor was completely resected ("curative resection");
- histologic evaluation by the pathologist confirms the margins of the resected specimen are not involved by malignant cells; and
- local radiation therapy will not be utilized.

5.1.8 Patients with more than one synchronous primary *colon* tumor are eligible. (Staging classification will be based on the more advanced primary tumor.)

5.1.9 In the opinion of the investigator, patients must have a life expectancy of at least 5 years, excluding their diagnosis of cancer.

5.1.10 Patients must have an ECOG performance status of 0 or 1. (See Appendix B.)

5.1.11 At the time of randomization, postoperative absolute granulocyte count (AGC) must be $\geq 1500/mm^3$ (or $< 1500/mm^3$, if in the opinion of the investigator, this represents an ethnic or racial variation of normal).

5.1.12 At the time of randomization, the postoperative platelet count must be $\geq 100{,}000/mm^3$.

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5.1.13 There must be postoperative evidence of adequate hepatic function.

- Bilirubin must be ≤ ULN for the lab unless the patient has a chronic grade 1 bilirubin elevation due to Gilbert's disease or similar syndrome due to slow conjugation of bilirubin.
- Alkaline phosphatase must be < 2.5 x ULN for the lab.
- AST must be < 1.5 x ULN for the lab.

If AST is > ULN, serologic testing for Hepatitis B and C must be performed and results must be negative.

04/21/06

5.1.14 There must be postoperative evidence of adequate renal function.

- Serum creatinine ≤ 1.5 x ULN for the lab.
- 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 the 24-hour urine collection in order to participate in the study (see Appendix G).

5.1.15 Patients with prior malignancies, including colorectal cancers, are eligible if they have been disease-free for ≥ 5 years and are deemed by their physician to be at low risk for recurrence. Patients with squamous or basal cell carcinoma of the skin, melanoma in situ, carcinoma in situ of the cervix, or carcinoma in situ of the colon or rectum that have been effectively treated are eligible, even if these conditions were diagnosed within 5 years prior to randomization.

5.2 Conditions for patient ineligibility

The existence of one or more of the following conditions will render the patient ineligible for this study:

5.2.1 Patients < 18 years old.

5.2.2 Colon tumor other than adenocarcinoma, i.e., sarcoma, lymphoma, carcinoid, etc.

5.2.3 Rectal tumors, i.e. a tumor located < 12 cm from the anal verge on endoscopy, or by surgical exam if the patient is not a candidate for endoscopy.

5.2.4 Isolated, distant, or non-contiguous intra-abdominal metastases, *even if resected*.

5.2.5 Any systemic or radiation therapy initiated for this malignancy.

5.2.6 Any significant bleeding that is not related to the primary colon tumor within 6 months before study entry.

5.2.7 Serious or non-healing wound, skin ulcers, or bone fracture.

5.2.8 Gastroduodenal ulcer(s) determined by endoscopy to be active.

5.2.9 Invasive procedures defined as follows:

- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to randomization.
- Anticipation of need for major surgical procedures during the course of the study.
- Core biopsy or other minor procedure, excluding placement of a vascular access device, within 7 days prior to randomization.

5.2.10 Uncontrolled blood pressure defined as > 150/90 mmHg.

05/17/05 5.2.11 History of TIA or CVA.

05/17/05 5.2.12 History of arterial thrombotic event within 12 months before study entry.

05/17/05 5.2.13 Symptomatic peripheral vascular disease.

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05/17/05 5.2.14 PT/INR > 1.5, unless the patient is on therapeutic doses of warfarin. 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.
- The subject must not have active bleeding or a pathological condition that is associated with a high-risk of bleeding.

5.2.15 Concomitant halogenated antiviral agents.

5.2.16 Clinically significant peripheral neuropathy at the time of randomization (defined in the NCI Common Terminology Criteria for Adverse Events Version 3.0 [CTCAE v3.0] as grade 2 or greater neurosensory or neuromotor toxicity).

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5.2.17 Non-malignant systemic disease (cardiovascular, renal, hepatic, etc.) that would preclude any of the study therapy drugs. Specifically excluded are the following cardiac conditions:

- New York Heart Association Class III or IV cardiac disease;
- History of myocardial infarction within 12 months before study entry;
- Unstable angina within 12 months before study entry; and
- Symptomatic arrhythmia.

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5.2.18 History of chronic or persistent viral hepatitis or other chronic liver disease.

5.2.19 Pregnancy or lactation at the time of proposed randomization. Eligible patients of reproductive potential (both sexes) must agree to use adequate contraceptive methods during study therapy and for at least 3 months after the completion of bevacizumab.

5.2.20 Psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements.

6.0 REQUIRED ENTRY AND FOLLOW UP STUDIES

Table 5 lists the studies required prior to study entry and during year 1.

TABLE 5. Studies required before entry and during year 1 *01/12/05, 02/24/05, 05/17/05, 04/21/06*

Required studies[a]	**Prior to study entry**	**Year 1**					
		After entry; before therapy begins	**During mFOLFOX6 ± bevacizumab (Groups 1 and 2)**	**During bevacizumab alone (Group 2)**	**Post-randomization**		
			Every 2 weeks before chemotherapy	Every 6 weeks before bevacizumab	6 months	9 months	12 months
History & physical examination[b]	X		X[c]	X[c]	X[c]	X[c]	X[c]
BP & anti-HTN meds assessment	X		X[d]	X[d]	X[d]	X[d]	X[d]
Weight	X		X	X	X	X	X
Height	X						
Adverse event assessment			X	X	X	X	X
CBC	X[e]		X		X		X
Differential	X[e]		X		X		
Platelet count	X[e]		X	X	X		
PTT	X[e]						
PT INR	X[e]		X[f]	X[f]			
Serum creatinine	X[e]		X[g]				
Bilirubin	X[e]		X[g,h]				
Alkaline phosphatase	X[e]		X[g,h]				
AST	X[e]		X[g,h]				
Urine protein/creatinine (UPC) ratio	X[e,i]		X[j]	X[j]			
Chest x-ray (PA & Lat.) or chest CT	X[k]						
Liver scan, sonogram, abdominal CT or MRI	X[l]						X[l]
Barium or gastrografin enema or colonoscopy	X[k,m]						X
For female patients:							
Menopausal status (Appendix B)	X						
Pregnancy test (serum β-HCG)	X[n]						
Menstrual status					X[o]		X[o]
Serum for ovarian function tests		X[o,p]			X[o,p]		X[o,p]
Serum for anti-bevacizumab antibodies and PK analysis[q]		X	X[r]	X[r]			
Serum collection for banking[s]		X					
Tumor block submission[t]							

a H&P, vital signs, bloodwork, x-rays, scans and other testing may be performed more frequently or in the presence of signs of metastatic disease.

b Complete H&P, including vital signs, performance status and collection of personal and family history of specific medical conditions, at baseline.

c Focused treatment-related exams may be done by the MD or other healthcare professional during therapy and follow-up.

d BP and changes in anti-HTN meds should be assessed as indicated and will be reported on Form HT (refer to Table 17). Depending on the grade, there may also be adverse event reporting requirements.

e Postoperative testing.

f For patients on full dose warfarin, the PT INR should be frequently monitored per MD's usual practice. (PT INR is not required for patients not receiving therapeutic doses of warfarin.)

g Every 6 weeks (or more often at the physician's discretion).

h If ≥ grade 3 elevation in bilirubin, alkaline phosphatase, or AST, ***ALT must be obtained***. See Table 10 for monitoring requirements.

i If UPC ratio is ≥ 1.0, a 24-hour urine collection is required. See Section 5.1.14.

j Groups 1 and 2: at the end of every 3 cycles during chemotherapy ± bevacizumab; then for Group 2 only, continue every 6 weeks for an additional 6 months. If the UPC ratio is ≥ 1.0 at the end of treatment (after chemotherapy ends for Group 1 or after bevacizumab ends for Group 2), continue testing every 12 weeks. At any time point, if this ratio is ≥ 1.0, a 24-hour urine collection is required. See Appendix G.

k To be completed within 3 months prior to study entry.

l Only required in the presence of hepatomegaly and/or elevation of liver function tests.

m Complete exam of the colon must be done *before* study entry, but may be done either preoperatively or postoperatively.

n For women of childbearing potential.

o Only women who were premenopausal at baseline.

p For women (who were premenopausal at baseline) who have consented to this testing. See Appendix C.

q Only for Group 2 patients. See Appendix C.

r Submit serum for anti-bevacizumab antibodies within 2 weeks following any grade 3 or 4 *bevacizumab-related* allergic reaction. See Table 12 and Appendix C.

s For patients who have consented to specimen banking. Also at time of first colon cancer recurrence. See Appendix D.

t For patients who have consented to sample banking, index tumor blocks are required; submit within 3 months from randomization (Section 7.0).

Table 6 lists the studies required during follow-up.

TABLE 6. Studies required after year 1 *05/17/05, 04/21/06*

Required studies[a]	Year 2			Years 3-5		After Year 5
	Every 3 months	Every 6 months	At 12 months	Every 6 months	Every 12 months	Every 12 months
Exams and assessments						
History & physical examination[b]	X			X		X
BP & anti-HTN meds assessment	X[c]					
Adverse event assessment	X					
Hematologic studies						
CBC		X		X		
Platelet count		X		X		
Chemistries						
Serum creatinine		X		X		
Bilirubin		X				
Alkaline phosphatase		X		X		
AST		X		X		
Urine protein/creatinine (UPC) ratio	X[d]					
X-rays, scans, other exams						
Liver scan, sonogram, abdominal CT or MRI[e]						
Barium or gastrograffin enema or colonoscopy			X[f]		X[f]	X[f]
*Only women who were **premenopausal at entry***						
Menstrual history		X				
Serum for ovarian function tests		X[g]				
Serum for anti-bevacizumab antibodies and PK analysis	X[h]					
Serum collection for banking[i]						

a H&P, vital signs, bloodwork, x-rays, scans and other testing may be performed more frequently or in the presence of signs of metastatic disease.

b Complete H&P or focused treatment-related exams may be done by the MD or other healthcare professional during follow-up.

c For one year post-treatment.

d For patients who had a UPC ratio ≥ 1.0 at the last assessment during treatment: repeat every 3 months for 12 months following end of treatment (after chemotherapy ends for Group 1 or after bevacizumab ends for Group 2). At any time point, a 24-hour urine collection is required if the ratio is ≥ 1.0. See Appendix G.

e Only required in the presence of hepatomegaly and/or persistent elevation of liver function tests > the grade at baseline.

f Complete exam of the colon must be done. If in the previous procedure the patient was not polyp-free, repeat the procedure yearly. Once a polyp-free procedure is achieved, repeat the procedure at least every 3 years.

g For women (who were premenopausal at baseline) who have consented to this testing.

h For Group 2 patients: *only at 3 and 6 months after the completion of bevacizumab*. See Appendix C.

i At time of first colon cancer recurrence if the patient has consented to specimen banking. See Appendix D.

7.0 REQUIRED PATHOLOGY STUDIES, ASSESSMENT OF BIOMARKERS, AND SERUM COLLECTION

NSABP C-08 requires the collection and submission of tumor and serum samples by all participating institutions. However, individual patients may refuse the collection, storage, and the use of their tissues and serum by answering "No" to the appropriate questions in the C-08 consent form. These patients may still participate in the trial; however, tumor and/or serum samples should **not** be submitted for patients who have answered "no" to Questions #1, #2, and #4 as presented in the NSABP Sample Consent Form [Appendix H]). If the patient answered "Yes" to Questions #1, #2, **or** #4, samples should be submitted. Non-submission of index tumor or serum samples will be a protocol violation unless a patient has not consented to collection, use, and storage of his/her tumor and serum.

NOTE: With the exception of the serum collected for antibody testing and pharmacokinetic analysis of the post-treatment serum levels of bevacizumab as described in Section 7.2.2 and the serum collected for the evaluation of ovarian function as described in Section 7.2.3, the tissue and serum samples that will be collected in this study and sent to the NSABP may be used for studies as described in Section 7.1.1, as well as for other unspecified future research. (Note: The samples collected for anti-bevacizumab antibody testing, pharmacokinetic analysis of the post-treatment serum levels of bevacizumab, and testing related to ovarian function will be used solely by Genentech, Inc. for those purposes.) ***The specimens procured for any evaluations in C-08 will not be used for hereditary genetic studies involving genes conferring susceptibility to cancer or other diseases unless additional consent is obtained from the patient or an anonymization process is used.*** Analysis of a patient's tumor pathology or results of the serum tested for ovarian function, antibodies, or bevacizumab levels, will not be reported to the patients or their physicians and will not have any bearing on the patient's treatment.

7.1 Pathology and correlative science studies

7.1.1 *Overview*

The collected tissue blocks may be used to develop or test markers that are predictive of response to bevacizumab as well as general prognosticators in colon cancer. Although at the time of protocol development there were no compelling candidate markers available to be included in this protocol, it is almost certain that such markers will be available to be tested by the time the accrual is complete. A variety of techniques will be utilized including real time RT-PCR, array comparative genomic hybridization, fluorescence in-situ hybridization, and immunohistochemistry, to develop/test candidate markers using collected paraffin blocks. Tissue microarrays will be generated and made available to the scientific community for projects of significant value. Collected sera will be used for proteomics studies in order to examine protein markers (or entire serum proteins) that may be prognostic and/or predictive of response to regimens used in the study. Since the field of proteomics is rapidly evolving, the NSABP has not yet committed to any one methodology. At the end of the trial, the best methodologies will be identified and employed.

7.1.2 *Tissue-block submission requirements*

The following blocks must be submitted for all patients who consent to the use of these samples. This use is not related to their care.

- a block of primary tumor with minimal necrosis,
- a block of positive lymph node (for patients with Stage III disease), and
- a block of uninvolved margin of resection.

As an alternative, 2-mm core samplings of the blocks plus 20 unstained sections are acceptable. A 2-mm core kit can be obtained from the NSABP Division of Pathology.

08/02/07

7.1.3 *Submission instructions*

- *Instructions for pathology materials submission:* Submit all NSABP pathology material to the NSABP Biostatistical Center at the address listed under "Information Resources" (see page iv).

- Submitted slides and blocks are initially logged into the database at the NSABP Biostatistical Center. These samples are then stripped of patient identifiers except NSABP study numbers and forwarded to the NSABP Division of Pathology (refer to Information Resources, page iv) where they are assigned a code number for further processing and study.

7.1.4 *Processing of submitted tumor blocks*

The NSABP Division of Pathology uses a state-of-the-art microtome with a Histo Collimator that allows very accurate orientation of the block to the correct knife angle of the microtome. The use of this device allows sections to be cut without much depletion of the tissue block. For the proposed study, a minimum of three 0.6 or 1-mm cores will be sampled from the blocks using an Automated Tissue Arrayer (Beecher Instrument) after the pathologist examines one H&E-stained section (usually the first section cut without any loss of tissue), and these cores will be seeded to three recipient tissue microarray blocks. When an institution requests the return of the block, after the pathologist obtains three 1-mm cores, up to 30 four-micron thick sections will be cut before the block is returned.

08/02/07

7.2 Serum collection

7.2.1 *Serum collections for the NSABP Serum Bank*

- *Timing of serum collections for the NSABP Serum Bank*

  Serum will be collected at the following time points for all patients who consent to the collection of these samples not related to their care:

  – baseline (after randomization but before study therapy begins), and
  – at the time of first recurrence.

- *Instructions for serum collection for the NSABP Serum Bank*

  - Investigators must follow the procedures outlined in Appendix D, *Procedures for Collecting, Processing, and Shipping Serum Specimens.*
  - CTSU INVESTIGATORS: CTSU investigators should refer to additional information regarding supplies for serum collection outlined in Appendix E, Section 4.0, *Serum Collection by CTSU Investigators*.

- *Processing of serum samples by the NSABP Serum Bank*

  Serum samples are submitted to the NSABP Serum Bank at Baylor where they are logged into the database and assigned a serum bank number. Serum samples are stripped of patient identifiers except NSABP study numbers, processed, and stored.

- *Future use of serum specimens*

  Decisions about the tests to be performed on these specimens will be made by the members of the NSABP Colorectal Committee and consulting researchers with expertise in this area.

7.2.2 ***Serum collections for antibody and pharmacokinetic testing for Group 2 patients***

- *Timing of collections for antibody and pharmacokinetic testing*

  Serum will be collected at the following time points for all Group 2 patients:

  - Baseline (after randomization but before study therapy begins)
  - At the time of ≥ grade 3 bevacizumab infusion-related reactions (See Table 12)
  - 3 and 6 months after the completion of bevacizumab

- *Instructions for serum collection*

  Investigators must follow the procedures outlined in the Covance Central Laboratory Services, Inc. Manual. Refer to Appendix C.

- *Future use of serum specimens*

  Serum samples will be used for the specified testing to determine the incidence of antibodies to bevacizumab and examine post-treatment serum levels of bevacizumab. No samples will be stored for future use.

7.2.3 ***Serum collections for evaluation of ovarian function***

- *Timing of collections for evaluation of ovarian function*

  Serum will be collected at the following time points for premenopausal patients who consent to the collection of these additional samples not related to their care:

  – Baseline (after randomization but before study therapy begins)
  – At 6, 12, 18, and 24 months after registration to the trial

- *Instructions for serum collection*

  Investigators must follow the procedures outlined in the Covance Central Laboratory Services, Inc. Manual. Refer to Appendix C.

- *Future use of serum specimens*

  Serum samples will be used for the specified testing of evaluation of ovarian function in premenopausal patients. No samples will be stored for future use.

8.0 TREATMENT REGIMEN

04/21/06

8.1 Group 1: mFOLFOX6

- Central venous access is strongly recommended.
- Chemotherapy should begin within 1 week following randomization.
- Drugs are to be administered ***in the order listed*** and according to the instructions in Table 7.

TABLE 7. Chemotherapy regimen for Group 1

Drug	Dose	Administration	Dosing Interval	Planned Duration
Oxaliplatin	85 mg/m^2	Administered IV concurrently with separate infusion bags of 250 mL D5W and separate lines connected by Y-line tubing over 2 hours**a**	Day 1 q 14 days	12 Cycles**b**
Leucovorin	400 mg/m^2			
5-FU	400 mg/m^2	IV bolus over 2-4 minutes		
5-FU	2400 mg/m^2 over 46 hours	IV continuous infusion over 46 hours	Days 1 and 2 q 14 days	

a Note that oxaliplatin is not compatible with normal saline solution or with 5-FU. The infusion line must be thoroughly flushed with D5W before and after the administration of 5-FU.

b The mFOLFOX6 cycle is 2 weeks.

04/21/06 8.2 **Group 2: mFOLFOX6 + bevacizumab**

- Chemotherapy and bevacizumab should begin within 1 week following randomization.
- The surgical incision must be completely healed before beginning therapy.
- Central venous access is strongly recommended. A delay in initiation of chemotherapy and bevacizumab is not required.
- Drugs are to be administered ***in the order listed*** and according to the instructions in Table 8.

TABLE 8. Chemotherapy and bevacizumab regimen for Group 2

Drug	Dose	Administration	Dosing Interval	Planned Duration
Bevacizumab	5 mg/kg	IV diluted in 100 mL of 0.9% NaCl solution given over a period of: 90 minutes – 1st dose 60 minutes – 2nd dose**a** 30 minutes – all subsequent doses**a** Flush infusion line**b**	Day 1 q 14 days	12 Months**c**
Oxaliplatin	85 mg/m2	IV given concurrently with separate infusion bags of 250 mL D5W and separate lines connected by Y-line tubing over 2 hours**d**	Day 1 q 14 days	12 Cycles**e** (6 months)
Leucovorin	400 mg/m2			
5-FU	400 mg/m2	IV bolus over 2-4 minutes		
5-FU	2400 mg/m2 over 46 hours	IV continuous infusion over 46 hours	Days 1 and 2 q 14 days	

a If no infusion-related reactions occur when given over 90 minutes, the 2nd dose may be given over 60 minutes. Again, if no infusion-related reactions occur, the 3rd and all subsequent doses may be given over 30 minutes. If infusion-related reactions do occur, pre-medications may be given and subsequent infusions should be administered over the shortest period that is well tolerated. (See Table 12.)

b Add an additional 50 mL of 0.9% NaCl for injection to the bevacizumab infusion bag (or use a new 50 mL bag of 0.9% NaCl) and infuse a volume equal to the volume contained in the tubing.

c Bevacizumab must end 12 months after the first dose regardless of any missed doses or treatment delays.

d Note that oxaliplatin is not compatible with normal saline solution or with 5-FU. The infusion line must be thoroughly flushed with D5W before and after the administration of oxaliplatin.

e The mFOLFOX6 cycle is 2 weeks.

8.3 **Concomitant therapy**

8.3.1 Treatment with any other investigational drug is not permitted.

8.3.2 **WARNING:** Halogenated antiviral agents such as sorivudine are prohibited in patients receiving 5-FU. Severe myelosuppression and CNS toxicity can result.

8.4 Supportive therapy

Patients may receive supportive care for treatment-related symptoms.

8.4.1 *Antiemetics*

The gastrointestinal toxicity of oxaliplatin requires pre-medication with an antiemetic regimen. It is strongly recommended that a 5-HT3 receptor antagonist be included in the regimen. Management of nausea and/or vomiting during chemotherapy cycles is at the physician's discretion.

04/21/06

8.4.2 *Growth factors*

- Use of growth factors *as primary prophylaxis for neutropenia is not permitted.* Growth factors (G-CSF) may be used at the physician's discretion in the following circumstances, ***but they should not be used as a substitute for dose reductions:***

  - as part of the clinical management of neutropenia with infection and/or fever,
  - to prevent delay in subsequent cycles following grade 2 ANC that required a treatment delay - refer to Table 10, and
  - if necessary for patient safety.

- Erythropoetin or darbepoetin may be used at the physician's discretion for patients who have hemoglobin ≤ 12 gm on Day 1. (Refer to the prescribing information for these drugs.)

8.4.3 *Management of pharyngolaryngeal dysesthesias*

Oxaliplatin may cause discomfort in the larynx or pharynx associated with the sensation of dyspnea, anxiety, and swallowing difficulty. Exposure to cold can exacerbate these symptoms.

- Refer to Table 11 for dose modification instructions.
- Do NOT use ice chips or other forms of oral cryotherapy to decrease stomatitis in conjunction with oxaliplatin.
- Anxiolytics may be used at the physician's discretion.

8.5 Non-protocol therapy

8.5.1 Treatment with any other antineoplastic agent, including biological response modifiers, is not permitted before time of recurrence or diagnosis of a second primary cancer.

8.5.2 Radiation therapy as part of the adjuvant therapy for this colon cancer is not permitted.

9.0 DOSE DETERMINATION

9.1 Re-calculation of dose

Based on the patient's weight and BSA, recommended *chemotherapy and bevacizumab doses* will be provided by NSABP at study entry. Re-calculation of the BSA and chemotherapy and/or bevacizumab doses is required if the patient has a ≥ 10 lb. weight change from baseline. The BSA and drug doses may also be re-calculated prior to each treatment cycle at the physician's discretion. Also at physician discretion, the doses of oxaliplatin, leucovorin, and 5-FU may be adjusted based on ideal body weight in the setting of morbid obesity.

9.2 Rounding drug doses

Rounding the 5-FU, leucovorin, bevacizumab, and oxaliplatin doses is optional. If the treating physician decides to round the dose(s), follow these rules which also apply to dose modifications:

- **Bolus 5-FU (400 mg/m^2)**
  Bolus 5-FU should be rounded to the ***nearest*** 25 mg.
  Example: 612 mg = 600 mg
  613 mg = 625 mg

- **Continuous infusion 5-FU (2400 mg/m^2)**
  Continuous infusion 5-FU should be rounded to the ***nearest*** 50 mg.
  Example: 4724 mg = 4700 mg
  4725 mg = 4750 mg

- **Leucovorin (400 mg/m^2)**
  Leucovorin should be rounded to the ***nearest*** 25 mg.
  Example: 612 mg = 600 mg
  613 mg = 625 mg

- **Oxaliplatin (85 mg/m^2)**
  Oxaliplatin should be rounded to the ***nearest*** 5 mg.
  Example: 142 mg = 140 mg
  143 mg = 145 mg

- **Bevacizumab (5 mg/kg)**
  Bevacizumab should be rounded to the ***nearest*** 5 mg.
  Example: 367 mg = 365 mg
  368 mg = 370 mg

10.0 DOSE MODIFICATIONS AND DELAYS

Dose modification instructions for chemotherapy are outlined in Section 10.1.

There are no dose modifications for bevacizumab. Refer to Section 10.2 for instructions regarding temporary suspension or permanent discontinuation of bevacizumab.

10.1 mFOLFOX6 dose modifications and delays

10.1.1 *General instructions*

Chemotherapy dose modifications for all C-08 patients are detailed in Tables 9, 10, and 11. Additionally, the following ***mFOLFOX6 dose modification instructions*** must be followed:

- The Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) must be used to grade the severity of adverse events.
- All dose modifications should be based on the adverse event requiring the greatest dose modification.
- Chemotherapy should be held for at least 1 week until any adverse event requiring delay returns to ≤ grade 1. The exception is neutropenia (see Table 10). If recovery to ≤ grade 1 has not occurred after 4 weeks of delay, mFOLFOX6 must be discontinued.
- If ≥ grade 2 toxicity occurs ***during the 46 hour infusion of 5-FU***, discontinue the infusion and refer to Table 10 for dose modifications for the next cycle of mFOLFOX6.
- Doses that have been reduced may not be escalated.
- The leucovorin dose remains 400 mg/m2 regardless of changes in the 5-FU and oxaliplatin doses. If 5-FU is held, leucovorin should also be held.

10.1.2 *mFOLFOX6 dose levels*

- mFOLFOX6 dose modification instructions are based on the dose level changes outlined in Table 9.
- Note that only two dose level reductions are permitted for each drug.

TABLE 9. mFOLFOX6 dose levels

	Dose Level 0 ***Starting Dose*** **(mg/m^2)**	**Dose Level -1 (mg/m^2)**	**Dose Level -2 (mg/m^2)**	**Dose Level -3**
Oxaliplatin	85	65	50	Discontinue
Leucovorin	400	400	400	Discontinue
5-FU bolus	400	320	260	Discontinue
5-FU infusion	2400	1900	1500	Discontinue

10.1.3 *mFOLFOX6 dose modifications*

TABLE 10. Dose modifications for mFOLFOX6 (See Table 11 for oxaliplatin-specific toxicities.) *01/12/05*

NCI CTCAE v3.0 Category/Grade	**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.**	
	Modifications for AEs that occurred during a cycle but DID NOT REQUIRE DELAY IN TREATMENT[a]	Modifications for AEs that required TREATMENT DELAY[b]
Blood/Bone Marrow		
Neutrophils/Granulocytes[c]		
Grade 2 (ANC 1000 - < 1500/mm^3)	Maintain dose	Consider G-CSF to avoid delay with subsequent cycles.
Grade 3 (ANC 500-999/mm^3)	Maintain dose	↓ one dose level.
Grade 4 (ANC < 500/mm^3)	↓ one dose level	↓ one dose level.
Platelets[d]		
Grade 2 (PLT 50,000-74,999/mm^3)	Maintain dose	↓ one dose level
Grade 3 (PLT 25,000-49,999/mm^3)	↓ one dose level	↓ one dose level
Grade 4 (PLT < 25,000/mm^3)	↓ two dose levels	↓ two dose levels
Gastrointestinal[e]		
Diarrhea		
Grade 2	Maintain dose[f]	↓ only 5-FU one dose level
Grade 3	↓ only 5-FU one dose level	↓ only 5-FU two dose levels
Grade 4	↓ 5-FU 2 dose levels; ↓ oxal 1 dose level	↓ 5-FU 2 dose levels; ↓ oxal 1 dose level
Stomatitis		
Grade 2	Maintain dose	↓ only 5-FU one dose level
Grade 3	↓ 5-FU one dose level	↓ only 5-FU two dose levels
Grade 4	↓ 5-FU 2 dose levels; ↓ oxal 1 dose level	↓ 5-FU 2 dose levels; ↓ oxal 1 dose level
Vomiting *(despite antiemetics)*		
Grade 2	Maintain dose	↓ one dose level
Grade 3	↓ one dose level	↓ two dose levels
Grade 4	↓ two dose levels	↓ two dose levels
Hepatic function		Hold until bilirubin returns to baseline grade and AST & alk phos are ≤ grade 1
Total bilirubin, alk phos, or AST		
Grade 2	↓ oxaliplatin one dose level	↓ oxaliplatin one dose level
Grade 3[g]	↓ both drugs one dose level	↓ both drugs two dose levels
Grade 4[g]	D/C	D/C
Infection		
Febrile neutropenia		
Grade 3	↓ one dose level[h]	↓ one dose level[h]
Grade 4	↓ two dose levels[h]	↓ two dose levels[h]
Infection with Grade 3 or 4 ANC		
Grade 3	↓ one dose level[h]	↓ one dose level[h]
Grade 4	↓ two dose levels[h]	↓ two dose levels[h]
Infection with normal ANC		
Grade 3	Maintain dose	Maintain dose
Grade 4	↓ one dose level	↓ one dose level
Other clinically significant AEs[i]		
Grade 2	Maintain dose	↓ one dose level
Grade 3	↓ one dose level	↓ two dose levels
Grade 4	↓ two dose levels	↓ two dose levels

a Treatment may not proceed until toxicity is ≤ grade 1. (Exception: refer to the table for neutrophils.)
b Hold and check weekly. With exception of ANC, resume treatment when toxicity is ≤ grade 1. If toxicity has not resolved to ≤ grade 1 after 4 weeks of delay, D/C mFOLFOX6.
c Proceed with treatment when ANC is ≥ 1200/mm^3.
d If ≥ grade 2 thrombocytopenia, consider hemolytic uremic syndrome/thrombotic thrombocytopenia purpura. If confirmed, D/C oxaliplatin.
e Dose level should be modified ***only if the toxicity is attributable to chemotherapy***.
f If multiple episodes of grade 2 diarrhea occur during the cycle but do not delay the subsequent cycle, 5-FU may be decreased one dose level at the physician's discretion.
g LFT elevation to ≥ grade 3 will require all LFTs (***including ALT***) to be monitored wkly. If all elevations do not resolve to ≤ grade 1 after 4 wks, stop study therapy. LFTs must then be monitored q 2 wks for 2 mos, then q 4 wks until 1 yr from entry or until all elevations resolve to ≤ grade 1. (See Table 17.) With any suspicion of veno-occlusive disease (VOD) of the liver (hyperbilirubinemia, ascites, weight gain due to fluid retention, hepatomegaly, splenomegaly, or other signs of portal hypertension), hold all study therapy. If VOD is diagnosed, D/C all study therapy.
h Administer G-CSF during subsequent cycles.
i Determination of "clinically significant" adverse events is at the discretion of the investigator.

TABLE 11. Dose modifications for oxaliplatin-specific toxicities *04/21/06*

Neurologic Toxicity[a]		
Paresthesias/Dysesthesias	**1-7 day duration**	**> 7 day duration[b]**
Grade 1 – Paresthesias/dysesthesias that 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 investigator'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 investigator 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 discretion of the investigator.	

a The toxicity descriptions in Table 11 should be used to determine dose modifications and delays. Use the CTCAE v3.0 to assess neurologic toxicity for adverse event reporting.

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

10.2 **Bevacizumab treatment delays**

10.2.1 There are no reductions in the bevacizumab dose. If adverse events occur that require holding bevacizumab, 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.

10.2.2 If 5-FU/LV and/or oxaliplatin are held due to chemotherapy-related adverse events, continue bevacizumab unless the patient's medical condition precludes this.

10.2.3 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, leucovorin, and oxaliplatin) prior to completion of the scheduled 12 cycles may continue bevacizumab for the remainder of the treatment course.

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

10.2.5 Adverse events requiring delays or permanent discontinuation of bevacizumab are listed with instructions on Table 12.

TABLE 12. Bevacizumab treatment delays and instructions *04/21/06, 10/25/07*

Adverse Event	Grade CTCAE v3.0	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 ↓ for the subsequent infusion. If the next dose is well-tolerated with pre-meds, the subsequent infusion time may be ↓ 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. - *If a grade 3 or 4 allergic reaction occurs that is thought to be due to bevacizumab,* collect serum for anti-bevacizumab antibodies within 2 weeks. (See Appendix C.)
	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 - 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.
Cardiac ischemia/infarction	2**[b]**, 3 or 4	Permanently discontinue bevacizumab.
CNS ischemia	2**[b]**, 3 or 4	Permanently discontinue bevacizumab.
Signs/symptoms of RPLS (see Section 12.4.3)	≥ 1	For clinical features suggestive of RPLS, hold bevacizumab and obtain MRI. If RPLS is diagnosed ***or*** if ANY symptoms were grade 4, permanently D/C bevacizumab. If RPLS is not diagnosed, bevacizumab may be resumed when presenting symptoms are ≤ grade 1 ***and*** blood pressure < 150/90.
GI perforation including GI leak and GI fistula	≥1	Permanently discontinue bevacizumab.
Non-GI perforation including non-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.
Proteinuria	2 (only if > 2 g /24 hrs) 3	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.
	4	Permanently discontinue bevacizumab.
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.

a If coagulation disorders develop secondary to other medical conditions, hold bevacizumab until the PT INR and PTT return to ≤ grade 1.
b New grade 2 events. (Therapy may be continued for grade 2 conditions present at baseline.)
c Pts. 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 3.0.
e Refer to Dermatology/Skin Section of the CTCAE v 3.0.
f Determination of "clinically significant" is at the physician's discretion and applies to those ***adverse events that are not clearly associated with chemotherapy and could be related to bevacizumab.***

11.0 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. The following section is offered as a guide. 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 with Form F following diagnosis of colon cancer recurrence or second primary cancer. The documentation will be reviewed at the NSABP Biostatistical Center to determine the method(s) used to document the recurrence, the anatomic location(s) of the recurrence, and the type of second primary cancer.

11.1 Abdominal and/or pelvic sites

11.1.1 *Anastomotic*

Acceptable: positive cytology or biopsy

11.1.2 *Abdominal, pelvic, and retroperitoneal 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.

11.1.3 *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.

11.1.4 *Ascites*

Acceptable: positive cytology

01/12/05 11.1.5 *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 times 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. Nonprotocol 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 CEA scan; and/or 3) celiac and mesenteric arteriography.

DOCUMENTATION OF THE ABOVE BY BIOPSY IS STRONGLY RECOMMENDED.

11.1.6 ***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.

11.1.7 ***Abdominal wall, perineum, and scar***

Acceptable: positive cytology or biopsy

11.2 **Nonabdominal and nonpelvic sites**

11.2.1 ***Skeletal***

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

11.2.2 ***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.

11.2.3 ***Bone marrow***

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

11.2.4 ***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).

11.3 Second primary cancer

The diagnosis of a second primary cancer must be confirmed histologically whenever possible. Representative slides are not required unless requested by the NSABP Biostatistical Center for review.

11.4 Postmortem examination

Autopsy reports should be secured whenever possible and submitted to the NSABP Biostatistical Center. A copy of the death certificate, if it is readily available or if it contains important cause of death information not documented elsewhere, should be forwarded to the Biostatistical Center.

12.0 DRUG INFORMATION

12.1 5-Fluorouracil (5-FU) [NSC# 19893]

5-FU should be obtained from commercial sources. Please refer to the current FDA-approved package insert provided with the medication or the *Physician's Desk Reference* for information regarding possible side effects and instructions regarding preparation, handling, dosing, and storage of the drug.

12.2 Leucovorin calcium (LV) [NSC# 3590]

In this study, parenteral leucovorin calcium will be used. Leucovorin should be obtained from commercial sources. Please refer to the current FDA-approved package insert provided with the medication or the *Physician's Desk Reference* for information regarding possible side effects and instructions regarding preparation, handling, dosing, and storage of the drug.

12.3 Oxaliplatin [NSC# 266046]

Oxaliplatin will be provided free-of-charge by Sanofi-Synthelabo, Inc. and distributed by the NCI. Refer to the current FDA-approved package insert provided with the medication or the *Physician's Desk Reference* for information regarding possible side effects and instructions regarding preparation, handling, dosing, and storage of the drug.

12.3.1 *Procurement*

Oxaliplatin (Eloxatin®) will be supplied free-of-charge by Sanofi-Synthelabo, Inc. and will be 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 must be requested by the principal investigator (or their authorized designee) at each participating institution. PMB policy requires that oxaliplatin 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 from PMB is obtained). The CTEP-assigned protocol number (i.e., NSABP C-08) must be used for ordering all PMB-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through the annual submission of an FDA Form 1572 (Statement of Investigator), a Curriculum Vitae, a Supplemental Investigator Data Form (IDF), and a Financial Disclosure Form (FDF). If there are several participating investigators at one institution, PMB-supplied investigational agent for this study should be ordered under the name of one lead investigator at that institution.

Oxaliplatin may be requested by completing a Clinical Drug Request (NIH-986) and faxing it to (301) 480-4612 or by mailing it to:

Pharmaceutical Management Branch
CTEP, DCTD, NCI
9000 Rockville Pike, EPN, Room 7149
Bethesda, MD 20892-7422

05/17/05

If you have questions, call (301) 496-5725, Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern Time.

12.3.2 ***Transfer of oxaliplatin***

PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). Oxaliplatin may not be used outside the scope of this protocol, nor can oxaliplatin be transferred or licensed to any party not participating in this clinical trial.

01/12/05

12.3.3 ***Return of unused oxaliplatin***

All unused (unopened) vials of oxaliplatin must be returned to the PMB. Because oxaliplatin is classified as a dangerous good/infectious agent for shipping purposes, special procedures must be followed to return this agent to the NCI. If your institution does not have dangerous good/infectious agent capability, please call PMB at (301) 496-5725 and ask to speak to the "Local Destructions Coordinator".

12.3.4 ***Drug accountability***

The investigator, or a responsible party designated by the investigator, must maintain a 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 (301) 496-5725. (Refer to the NCI Investigator's Handbook for procedures for Drug accountability and Storage.)

12.4 **Bevacizumab [IND 7921; NSC# 704865]**

01/12/05

12.4.1 ***Chemical information***

- *Classification:* Recombinant humanized monoclonal antibody
- *Molecular weight*: Approximate molecular weight is 149,000 daltons
- *Mode of action:* Bevacizumab blocks the binding of vascular endothelial growth factor (VEGF) to its receptors resulting in inhibition of angiogenesis.
- *Description:* Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody, consisting of 93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and murine antigen-binding complementarity-determining regions.

- *How supplied:* 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.

- *Preparation:* Withdraw the necessary amount of bevacizumab for a dose of 5 mg/kg and dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP. Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. No incompatibilities between bevacizumab and polyvinylchloride or polyolefin bags have been observed. Bevacizumab should not be administered or mixed with dextrose solutions.

- *Storage and stability*

  – Storage
    Upon receipt, bevacizumab should be refrigerated (2º to 8º C).
    Do not freeze. Do not shake. Protect from light.
  – Stability
    Shelf-life studies of rhuMAb VEGF are ongoing. The sterile single use vials contain no antibacterial preservatives. Therefore, vials should be discarded 8 hours after initial entry.

    Once diluted in 0.9% sodium chloride, solutions of bevacizumab must be administered within 8 hours.

- *Route of administration:* Intravenous – Do not administer as an IV push or bolus

- *Dose specifics:* 5 mg/kg IV as per Section 8.2.

01/12/05
04/21/06
08/02/07
10/25/07

12.4.2 ***Adverse events***

Refer to the Investigator's Brochure for bevacizumab. The Package Insert was prepared for commercial Avastin but not the investigational bevacizumab being used in this protocol. The Package Insert should therefore only be used as a reference in combination with the Investigator's Brochure.

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single, complete list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. As the holder of the IND, the National Cancer Institute (NCI) has required the NSABP to include the entire CAEPR list within the protocol document. These adverse events should ***not*** be used for adverse event reporting purposes. See Section 13.0 for information regarding Adverse Event reporting.

TABLE 13. Cancer Therapy Evaluation Program (CTEP) Comprehensive Adverse Events and Potential Risks List (CAEPR) for bevacizumab (NSC # 704865)

Version 1.2 June 19, 2007

Category (Body System)	Adverse Events with Possible Relationship to Bevacizumab (CTCAE v3.0 Term)
ALLERGY/IMMUNOLOGY	
	Allergic reaction/hypersensitivity (including drug fever)
	Allergic rhinitis (including sneezing, nasal stuffiness, and postnasal drip
BLOOD/BONE MARROW	
	Hemoglobin
	Leukocytes (total WBC)
	Neutrophils/granulocytes (ANC/AGC)
CARDIAC ARRHYTHMIA	
	Supraventricular arrhythmia NOS
	Ventricular fibrillation
CARDIAC GENERAL	
	Cardiac ischemia/infarction
	Cardiac troponin I (cTnI)
	Hypertension
	Hypotension
	Left ventricular diastolic dysfunction
	Left ventricular systolic dysfunction
CONSTITUTIONAL SYMPTOMS	
	Fatigue (asthenia, lethargy, malaise)
	Fever (in the absence of neutropenia, where neutropenia is defined as ANC $<1.0 \times 10^9$/L)
	Rigors/chills
	Weight loss
DERMATOLOGY/SKIN	
	Pruritis/itching
	Rash/desquamation
	Ulceration
	Urticaria (hives, welts, wheals)
	Wound complication, non-infectious

TABLE 13. CAEPR list for bevacizumab version 1.2 (continued)

GASTROINTESTINAL	
	Anorexia
	Colitis
	Constipation
	Diarrhea
	Fistula, GI - Select
	Heartburn/dyspepsia
	Ileus (functional obstruction of bowel, i.e., neuroconstipation)
	Leak (including anastomotic), GI: large bowel
	Mucositis/stomatitis (functional/symptomatic) - Select
	Nausea
	Perforation, GI - Select
	Ulcer, GI - Select
	Vomiting
HEMORRHAGE/BLEEDING	
	Hemorrhage GI - Select
	Hemorrhage, CNS
	Hemorrhage, GU: vagina
	Hemorrhage, pulmonary/upper respiratory: lung
	Hemorrhage, pulmonary/upper respiratory: nose
INFECTION	
	Infection with normal ANC or Grade 1 or 2 neutrophils - Select
	Infection with normal ANC or Grade 1 or 2 neutrophils - Select (pelvis, peritoneal cavity, rectum, scrotum, skin, wound)
METABOLIC/LABORATORY	
	Alkaline phosphatase
	ALT, SGPT (serum glutamic pyruvic transaminase)
	AST, SGOT (serum glutamic oxaloacetic transaminase)
	Bilirubin (hyperbilirubinemia)
	Creatinine
	Proteinuria
NEUROLOGY	
	CNS cerebrovascular ischemia
	Dizziness
	Neurology - Other; (Leukoencephalopathy syndrome including reversible posterior leukoencephalopathy syndrome [RPLS])
PAIN	
	Pain - abdomen NOS
	Pain - chest/thorax NOS
	Pain - head/headache
	Pain - joint
	Pain - muscle
	Pain NOS

TABLE 13. CAEPR list for bevacizumab version 1.2 (continued)

PULMONARY/UPPER RESPIRATORY	
	Bronchospasm, wheezing
	Cough
	Dyspnea (shortness of breath)
	Fistula, pulmonary/upper respiratory - Select
	Nasal cavity/paranasal sinus reactions
	Pulmonary/upper respiratory - Other (nasal-septal perforation)
	Voice changes/dysarthria/e.g., hoarseness, loss or alteration in voice, laryngitis)
RENAL/GENITOURINARY	
	Fistula, GU - Select
	Renal failure
SYNDROMES	
	Cytokine release syndrome/acute infusion reaction
VASCULAR	
	Thrombosis/thrombus/embolism
	Visceral arterial ischemia (non-myocardial)

- Additional adverse events:

  The following (also from the CAEPR List, version 1.2) are adverse events which have been reported on bevacizumab trials; however, the relationship to bevacizumab is currently undetermined.

  Note: Bevacizumab 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.

  - Blood/Bone Marrow – Idiopathic thrombocytopenia purpura; platelets
  - Cardiac general – Cardiac arrest; pericardial effusion; pulmonary hypertension
  - Coagulation – DIC
  - Death – Sudden death (cause unknown)
  - Dermatology/Skin – Hypopigmentation
  - Gastrointestinal – Rectal abscess/necrosis; small bowel obstruction; taste alteration
  - Metabolic/Laboratory – Hyperglycemia; hypoglycemia; hypomagnesemia; hyponatremia
  - Musculoskeletal/Soft Tissue – Aseptic necrotic bone; gait/walking; myasthenia gravis
  - Neurology – Aseptic meningitis; confusion; peripheral neuropathy; seizure; syncope
  - Ocular/Visual – Cataract; watery eye
  - Pulmonary/Upper Respiratory – ARDS; pneumonitis/pulmonary infiltrates; pneumothorax
  - Renal/Genitourinary – Urinary frequency

- Additional adverse events from the FDA approved September 2005 Package Insert for Avastin® (bevacizumab):

  Metabolic/Laboratory – Hypokalemia

- Other reported adverse events:

  Renal/Genitourinary: Perforation, GU - Select

04/21/06

12.4.3 ***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 headache, altered mental status, seizure, and cortical visual deficit. Hypertension 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 in the differential diagnosis in patients presenting with unexplained mental status change, visual disturbance, seizure, or other CNS findings. RPLS is potentially reversible with early recognition of symptoms and timely correction of the underlying causes, including control of blood pressure and interruption of the offending drug, which are important in order to prevent progression to irreversible tissue damage.

12.4.4 ***Administration***

Method of Administration

The 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. If no adverse reactions occur after the second dose, all subsequent doses should be administered over a minimum of 30 minutes. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

To insure complete delivery of bevacizumab, the IV infusion line must be flushed with 0.9% sodium chloride. The following are two recommended methods for flushing the bevacizumab IV infusion line:

Method 1: When the bevacimuzab infusion is complete, add an additional 50 mL of 0.9% sodium chloride for injection to the bevacizumab infusion bag. Continue the infusion until a volume equal to that of the volume contained in the tubing has been administered.

Method 2: Replace the empty bevacizumab infusion bag with a 50 mL bag of 0.9% sodium chloride for injection and infuse a volume equal to the volume contained in the tubing.

Note: the flush is not included in the total recommended infusion times.

01/12/05 12.4.5 ***Procurement***

Bevacizumab will be supplied free-of-charge by Genentech, Inc. and will be 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).

The bevacizumab to be supplied for this protocol is intended for clinical trial use only and is not the commercially available Avastin. Investigational bevacizumab and commercially available Avastin may be produced at separate facilities and some difference may exist between the two products, although both are required to meet similar product testing criteria and are expected to be very similar in safety and activity. For further details and molecule characterization, see the updated bevacizumab Investigator Brochure.

Bevacizumab (NSC# 704865) 100 mg (25 mg/ mL – 4 mL fill) and 400 mg (25 mg/mL – 16 mL fill) vials must be requested by the principal investigator (or their authorized designee) at each participating institution. PMB policy requires that bevacizumab 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 from PMB is obtained). The CTEP-assigned protocol number (i.e., NSABP C-08) must be used for ordering all PMB-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through the annual submission of an FDA Form 1572 (Statement of Investigator), a Curriculum Vitae, a Supplemental Investigator Data Form (IDF), and a Financial Disclosure Form (FDF). If there are several participating investigators at one institution, PMB-supplied investigational agent for this study should be ordered under the name of one lead investigator at that institution.

Bevacizumab may be requested by completing a Clinical Drug Request (NIH-986) and faxing it to (301) 480-4612 or by mailing it to:

Pharmaceutical Management Branch
CTEP, DCTD, NCI
9000 Rockville Pike, EPN, Room 7149
Bethesda, MD 20892-7422

If you have questions, call (301) 496-5725, Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern Time.

12.4.6 ***Transfer of bevacizumab***

PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). Bevacizumab may not be used outside the scope of this protocol, nor can bevacizumab be transferred or licensed to any party not participating in this clinical trial.

12.4.7 ***Return of unused bevacizumab***

All unused (unopened) vials of bevacizumab must be returned to the PMB.

12.4.8 ***Drug accountability***

The investigator, or a responsible party designated by the investigator, must maintain a 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 (301) 496-5725. (Refer to the NCI Investigator's Handbook for procedures for Drug Accountability and Storage.)

08/02/07 13.0 **ADVERSE EVENT REPORTING REQUIREMENTS**

Please refer to Appendix F, "Information Basics for Adverse Event Reporting" for general information required for adverse event reporting.

13.1 **Definitions for adverse event reporting**

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.

13.1.1 ***Investigational agent***

In C-08 the investigational agent is bevacizumab. For patients who receive bevacizumab, prior experience (expectedness) of adverse events is based on the current NCI Agent-Specific Adverse Event List. NCI's Agent-Specific Adverse Events List is available in the Assessment Results screen of the AdEERS web-based application located at http://ctep.cancer.gov.

13.1.2 ***Commercial agent***

In C-08 the commercial agents are oxaliplatin, 5-FU, and leucovorin. For patients who receive oxaliplatin, 5-FU or leucovorin, prior experience (expectedness) of adverse events is based on the current drug package insert for each agent.

13.1.3 ***Investigational combination therapy***

When bevacizumab (investigational agent) is administered concurrently with oxaliplatin, 5-FU, or leucovorin (commercial agents) and an adverse event occurs that is expected for oxaliplatin, 5-FU, or leucovorin, but is not listed for bevacizumab, the adverse event should be considered expected for the combination. However, ***if based on clinical judgment, the investigator believes the adverse event is possibly, probably, or definitely related to bevacizumab rather than oxaliplatin, 5-FU, or leucovorin***, the adverse event should then be considered unexpected for the combination.

07/27/05 13.2 **Adverse event assessment**

NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 must be used to identify the type and to grade the severity of the adverse events in C-08.

Reporting oxaliplatin-specific neurologic toxicities: report neurologic adverse events of paresthesias/dysesthesias as "neuropathy sensory" (CTCAE v3.0 Short Name).

01/12/05
07/27/05

13.3 Expedited reporting of adverse events

The NSABP follows procedures for centralized reporting of adverse events. Centralized reporting requires that adverse events be reported to the NSABP Biostatistical Center. The NSABP forwards reports and documentation to the appropriate regulatory agencies and the pharmaceutical companies involved in the trial. C-08 utilizes the National Cancer Institute's (NCI) Adverse Event Expedited Reporting System (AdEERS) for all expedited reporting of adverse events. The NCI's guidelines for creating an AdEERS report can be found at http://ctep.cancer.gov.

The NSABP Biostatistical Center is identified in AdEERS as the NSABP Lead Group for NSABP protocols which require AdEERS reporting. An AdEERS report must be submitted to the NSABP Lead Group using the electronic web-based application located at http://ctep.cancer.gov. If web access is not available, the NCI Adverse Event Expedited Report-Multiple Agents template (located at http://ctep.cancer.gov) must be completed and faxed to the NSABP Biostatistical Center at **(412) 622-2113**.

01/12/05
07/27/05

13.3.1 *Expedited reporting methods*

- **AdEERS 24-Hour Notification** – requires that an AdEERS 24-hour notification is electronically submitted to the NSABP Lead Group within 24 hours of learning of the adverse event. Each AdEERS 24-hour notification must be followed by either an AdEERS 3 Calendar Day Report (see Table 14) or an AdEERS 5 Calendar Day Report (see Table 15).
- **AdEERS 3 Calendar Day Report** – requires that a complete AdEERS report is electronically submitted to the NSABP Lead Group within 3 calendar days of the initial 24-hour report.
- **AdEERS 5 Calendar Day Report** – requires that a complete AdEERS report is electronically submitted to the NSABP Lead Group within 5 calendar days of the investigator learning of the event.
- Fax supporting documentation for all expedited reports to the NSABP Biostatistical Center at **(412) 622-2113**.

07/27/05

13.3.2 *Expedited reporting requirements*

- When reporting neurologic adverse events of paresthesias/dysesthesias in AdEERS, select the CTCAE v3.0 Short Name "neuropathy sensory" as the adverse event in the Adverse Event (CTCAE) section of the AdEERS report. Also, enter the terms "paresthesias/dysesthesias" as a "Comment".
- There may be protocol-specific requirements or exceptions for expedited reporting. Refer to Tables 14 and 15 for instructions.
- Adverse events reported via AdEERS must also be reported on Form AE according to the instructions for form submission described in Section 13.4 "Routine reporting of adverse events" and according to instructions on Form AE.

13.3.3 *Expedited reporting for veno-occlusive disease of the liver*

Veno-occlusive disease (VOD) of the liver is a rare and potentially serious adverse event associated with oxaliplatin-based chemotherapy. For a list of the signs associated with VOD, please refer to footnote "g" on Table 10. If ≥ grade 1 VOD is diagnosed, it must be reported in an expedited manner via AdEERS using the "Other (Specify)" AE term in the Hepatobiliary/Pancreas category of the CTCAE v3.0.

For reporting purposes, grading of VOD is as follows:

- **Grade 1** – (mild) Asymptomatic finding on pathologic evaluation of liver tissue; criteria for higher grades not met.

- **Grade 2** – Hepatomegaly with (moderate) total bilirubin elevation (1.5 – 3.0 x ULN) and weight gain < 5% of baseline but *no ascites on clinical exam.*

- **Grade 3** – Hepatomegaly with either (severe) total bilirubin elevation (> 3.0 – 10 x ULN) *or* weight gain 5-10% of baseline but *no ascites on clinical exam*.

- **Grade 4** – Hepatomegaly with either (life-threatening) total bilirubin elevation (> 10 x ULN) *or* weight gain > 10% of baseline *or* ascites on clinical exam *or* findings of portal hypertension.

- **Grade 5** – Death

13.3.4 *Other recipients of adverse event reports*

The NSABP will forward reports and documentation to the appropriate regulatory agencies and the pharmaceutical companies involved in this trial.

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

01/12/05
07/27/05

13.3.5 ***Expedited adverse event reporting requirements for patients receiving the <u>investigational</u> agent (bevacizumab) are listed in Table 14***

TABLE 14. Phase 2 and 3 trials utilizing an agent under a CTEP IND: AdEERS expedited reporting requirements for adverse events that occur within 30 days[1] of the last dose of the investigational agent (bevacizumab) *01/12/05, 07/27/05, 04/21/06*

	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 Hospitali-zation	without Hospitali-zation	with Hospitali-zation	without Hospitali-zation	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	5 Calendar Days	Not Required	5 Calendar Days	Not Required	5 Calendar Days	5 Calendar Days
Possible Probable Definite	Not Required	5 Calendar Days	Not Required	5 Calendar Days	5 Calendar Days	5 Calendar Days	Not Required	24-Hour; 3 Calendar Days	5 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:

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

- Grade 4 and Grade 5 unexpected events

AdEERS 5 calendar day report:

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

2 Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

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 defined:
  - "24 hours; 3 calendar days" – The investigator must initially report the AE via AdEERS within <u>24 hours</u> of learning of the event followed by a complete AdEERS report within <u>3 calendar days</u> of the initial 24-hour report.
  - "5 calendar days" – A complete AdEERS report on the AE must be submitted within <u>5 calendar days</u> 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 AdEERS 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.

Please note that Table 14 is continued on the next page.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP-IND:

a) Reports submitted via AdEERS 24-hour notification are available for review by both the NCI and the NSABP after submission. All other AdEERS reports are first sent to the NSABP Lead Group and then are forwarded to the NCI. The timelines in the table above have been set so that the information can be forwarded to the NCI in a timely manner per the NCI/CTEP's guidelines.

b) On all reports, use the NCI protocol number, AdEERS ticket number, and the protocol-specific ID provided during the trial registration. **Fax supporting documentation to the NSABP Biostatistical Center**.

c) Hospitalization associated with an adverse event is defined as any hospitalization lasting ≥ 24 hours (or a prolongation of an existing hospitalization).

d) Refer to Section 13.1.3 for instructions regarding assignment of attribution and expectedness for ***Investigational Combination Therapy***.

e) AdEERS reporting is required for grade 2 unexpected adverse events and grade 3 unexpected adverse events without hospitalization **only** if the adverse event is possibly, probably or definitely related to the **investigational agent**.

f) **Protocol-specific expedited reporting requirements**: For this study, the adverse events listed below, regardless of attribution, require expedited reporting via AdEERS within 5 calendar days of learning of the event:

- 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
- 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 (see Section 13.3.3 for grading criteria)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) ≥ grade 1 reported as Neurology – other (leukoencephalopathy syndrome) (see Section 12.4.3)

g) **Protocol-specific expedited reporting exceptions:** For this study, 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 AdEERS: Beginning 30 days following the last dose of chemotherapy and when a patient is receiving bevacizumab alone, these events should be reported according to instructions in the table above.

- Blood/Bone Marrow: grades 3 & 4 leukocytes (total WBC), neutrophils/granulocytes
- Constitutional: grades 3 & 4 fatigue
- Dermatology/Skin: grade 3 hand-foot reaction
- Gastrointestinal: grades 3 & 4 dehydration, diarrhea (including associated electrolyte imbalances), dysphagia, esophagitis, mucositis (clinical exam or functional/symptomatic), nausea, vomiting
- Infection: grades 3 & 4 febrile neutropenia
- Pain: grades 3 & 4
- Secondary Malignancy: grades 3 & 4

13.3.6 ***Expedited adverse event reporting requirements for patients receiving only <u>commercial</u> agents are outlined in Table 15.***

07/27/05

TABLE 15. AdEERS expedited reporting requirements for adverse events that occur within 30 days of the last dose of study therapy with a commercial agent (oxaliplatin, 5-FU, and leucovorin)

01/12/05, 02/24/05, 07/27/05, 04/21/06

Attribution	**Grade 2**	**Grade 3**		**Grade 4[b]**		**Grade 5[a,b]**		**Protocol-Specific Requirements/ Exceptions**
	Unexpected	*Unexpected*	*Expected*	*Unexpected*	*Expected*	*Unexpected*	*Expected*	-See footnote **(c)** for other requirements -See footnote **(d)** for special ***requirements*** -See footnote **(e)** for special ***exceptions***
Unrelated or Unlikely				AdEERS		AdEERS	AdEERS	
Possible, Probable, Definite		AdEERS if hospitalized		AdEERS-24 and AdEERS		AdEERS-24 and AdEERS		

AdEERS-24: Indicates an AdEERS 24-hour notification must be electronically submitted to the NCI and to the NSABP Lead Group *within 24 hours* of learning of the event.

AdEERS: Indicates a complete expedited report must be electronically submitted to the NSABP Lead Group *within 5 calendar days* of learning of the event.

Hospitalization: Hospitalization associated with an adverse event is defined as any hospitalization lasting ≥ 24 hours (or a prolongation of an existing hospitalization).

All Reports: On all reports, use the NCI protocol number, AdEERS ticket number, and the protocol-specific patient ID provided during trial registration. ***Fax supporting documentation to the NSABP Biostatistical Center.***

a All deaths within 30 days of the last dose of study therapy require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided. **Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a complete AdEERS report is required as outlined in the table.**

b Adverse events that occur <u>greater</u> than 30 days after the last dose of study therapy with attribution of possible, probable or definite to study therapy require reporting as follows:

- AdEERS 24-hour notification followed by a complete AdEERS report within 5 calendar days of learning of the event for:
  - grade 4 unexpected events
  - grade 5 unexpected events
- AdEERS 5-calendar day report for:
  - grade 5 expected events

c Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment.

d Protocol-specific expedited reporting requirements: For this study, the adverse events listed below, regardless of attribution, require expedited reporting via AdEERS to the NSABP Lead Group within 5 calendar days of learning of the event:

- 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
- Cardiac ischemia ≥ grade 4
- CNS ischemia ≥ grade 4
- Peripheral arterial ischemia ≥ grade 4
- Visceral arterial ischemia ≥ grade 4
- Fistula, GI ≥ grade 3
- Leak, GI ≥ grade 3
- Veno-occlusive disease of the liver ≥ grade 1 (see Section 13.3.3 for grading criteria)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) ≥ grade 1 reported as Neurology – other (leukoencephalopathy syndrome) (see Section 12.4.3)

e Protocol-specific expedited reporting exceptions:

- Secondary Malignancy: grades 3 and 4

07/27/05

13.3.7 *Reporting secondary AML/MDS/ALL*

All cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) and acute lymphocytic leukemia (ALL) that occur in patients on NCI-sponsored trials following their chemotherapy for cancer must be reported to the Investigational Drug Branch (IDB) of the NCI Cancer Therapy Evaluation Program (CTEP). Submit the following information to the NSABP Biostatistical Center within 30 days of an AML/MDS/ALL diagnosis:

- completed NCI/CTEP Secondary AML/MDS Report Form;
- copy of the pathology report confirming the AML/MDS/ALL; and
- copy of the cytogenetics report (if available).

The NSABP will submit the form and any accompanying reports to the IDB of the NCI.

Note: If a patient has been enrolled in more than one NCI-sponsored study, the NCI/CTEP Secondary AML/MDS Report Form must be submitted for the most recent trial. The NSABP must also be provided with a copy of the report even if the NSABP study was not the patient's most recent trial.

07/27/05

13.3.8 *Pregnancy occurring while patient is on protocol therapy*

If a female patient (or the sexual partner of a male patient) becomes pregnant while receiving protocol therapy, notify the NSABP Clinical Coordinating Division immediately.

01/12/05
07/27/05

13.4 Routine reporting of adverse events

Routine reporting includes adverse events for which expedited reporting was required, as well as those events that do not require expedited reporting. All adverse events reported via AdEERS must also be reported on Form AE (Adverse Event Form). Report adverse events on Form AE as described below and according to instructions on the Form AE.

13.4.1 *Reporting on Form AE*

- Report all grade 3, 4, and 5 adverse events, including those adverse events previously reported via AdEERS.

- Report grade 2 adverse events that are listed only under the category "Neurology" of the CTCAE Version 3.0.

- When reporting neurologic adverse events of paresthesias/dysesthesias on Form AE, select the CTCAE v3.0 Short Name "neuropathy sensory" as the adverse event. Also, include the terms "paresthesias/dysesthesias" in the "Comment" section of the Form AE. Do not report neurologic paresthesias/dysesthesias in the "Other" section of the Form AE.

- Do not report the following on Form AE:

  - Grade 1 adverse events.
  - Grade 2 adverse events which are not listed under the category "Neurology" of the CTCAE Version 3.0.
  - Adverse events which occur after colon cancer recurrence or development of a second primary cancer.

13.4.2 *Submission of Form AE*

For C-08, one cycle of therapy, which includes treatment and recovery, is approximately 2 weeks. Submit Form AE according to the following schedule:

- **All patients receiving chemotherapy (oxaliplatin, 5-FU and leucovorin) without bevacizumab**

  - *During chemotherapy:* Submit Form AE at the end of every 3 cycles, i.e., at the end of cycles 3, 6, 9 and 12.
  - *After the final dose of chemotherapy:* Submit Form AE every 3 months for 12 months following the final dose of chemotherapy.

- **All patients receiving bevacizumab**

  - *During chemotherapy and bevacizumab:* Submit Form AE at the end of every 3 cycles, i.e., at the end of cycles 3, 6, 9 and 12.
  - *During bevacizumab only:* Submit Form AE every 6 weeks.
  - *After the final dose of bevacizumab:* Submit Form AE every 3 months for 12 months following the final dose of bevacizumab.

- Provide supporting documentation for all grade 3, 4 and 5 adverse events if documentation has not previously been submitted for that adverse event. Remove patient identifiers as described in Appendix F and submit to the NSABP Biostatistical Center (see Information Resources on page iv).

TABLE 16. Routine adverse event reporting requirements for all C-08 patients

Attribution	**Grades 1**		**Grade 2**		**Grades 3, 4 & 5**		**Special Reporting Requirements**
	Unexpected	*Expected*	*Unexpected*	*Expected*	*Unexpected*	*Expected*	
Unrelated, Unlikely			Form AE (Neuro AEs only)	Form AE (Neuro AEs only)	Form AE	Form AE	
Possible, Probable, or Definite			Form AE (Neuro AEs only)	Form AE (Neuro AEs only)	Form AE	Form AE	

Form AE: Submit Form AE to the NSABP Biostatistical Center at the end of every 3 cycles of chemotherapy (with or without bevacizumab), every 6 weeks during bevacizumab, and every 3 months for 12 months following the final dose of protocol therapy. Provide supporting documentation for all grade 3, 4, and 5 adverse events if documentation has not previously been submitted for those adverse events.

Hospitalization: Submit supporting documentation for any hospitalization ≥ 24 hours.

07/27/05

13.5 Reporting cancer recurrence and second primary cancer

Report colon cancer recurrence and all second primary malignancies (including AML/MDS/ALL) on the NSABP follow-up form (Form F). Attach supporting documentation that confirms the colon cancer recurrence or second primary cancer diagnosis.

14.0 PATIENT ENTRY PROCEDURES

14.1 Patient consent form

Before the patient is entered, the consent form (see Appendix H) including any addenda, must be signed and dated by the patient and the person who explains the study to that patient.

14.2 Entry

14.2.1 *NSABP investigators*

Note: NSABP investigators who are also registered with the CTSU must enter C-08 patients through the NSABP; they are <u>NOT</u> permitted to enter C-08 patients through the CTSU.

Patient entry instructions can be found in the "Patient Entry Guidelines" section of the Members' Area of the NSABP Web site, http://nsabp.pitt.edu.

14.2.2 *CTSU investigators*

CTSU investigators must follow procedures outlined in Appendix E, Section 1, *Patient Entry for CTSU Investigators*.

14.3 Patient study number

After all of the eligibility criteria have been met, the institution will receive 1) the patient's nine-digit study number; 2) the treatment assignment and schedule; and 3) the initial BSA and drug dose. See Section 9.0 for instructions regarding recalculation of doses for subsequent cycles.

14.4 Patient-initiated discontinuation of study therapy

Even after a patient agrees to take part in this study, the patient may stop study therapy or withdraw from the study at any time. If the patient stops study therapy but still allows the study doctor to follow his/her care, the patient should continue to be followed according to the study schedule.

Alternatively, the patient may choose to have no further interaction regarding the study. In this case, the investigator must provide the NSABP Biostatistical Center with written documentation of the patient's decision to fully withdraw from the study.

14.5 Investigator-initiated discontinuation of study therapy

In addition to the conditions outlined in the protocol, the investigator may require a patient to discontinue study therapy if one of the following occurs:

- the patient develops a serious side effect that he/she cannot tolerate or that cannot be controlled with other medications,
- the patient's health gets worse,
- the patient is unable to meet the study requirements, or
- new information about the drug or other treatments for colon cancer becomes available.

If study therapy is stopped but the patient still allows the study doctor to follow his/her care, the patient should continue to be followed according to the study schedule.

01/12/05

14.6 Criteria for permanent discontinuation of bevacizumab

Patients will discontinue bevacizumab if:

- There is evidence of disease recurrence.
- There is excessive or prolonged bevacizumab-related toxicity that requires discontinuation per criteria outlined on Table 12.
- Veno-occlusive disease of the liver is diagnosed.
- The patient requests discontinuation or withdraws consent for the study (See Section 14.4).
- The patient becomes pregnant.
- A second primary cancer is diagnosed.

Therapy may be discontinued at the discretion of the physician for reasons outlined in Section 14.5.

15.0 **RECORDS TO BE KEPT**

TABLE 17. Required forms and materials *01/12/05, 02/24/05, 10/25/07*

Form/material	Description	Submission
PRE-ENTRY		
Consent form	Signed /dated informed consent	Complete prior to registration. For submission, consult Patient Entry Guidelines Section of the Members' Area of the NSABP Web site, http://nsabp.pitt.edu
Form A	Registration Form	
ENTRY		
Form ON	On-study form	Within 30 days of registration
Dictated operative report	Typed operative report	
Dictated pathology report	Typed pathology report	
Form HT-B	Form for patient baseline hypertension history, status, and treatment	
Pathology materials with Form BLK	Pathology blocks	Within 3 months of registration
Baseline serum specimen for banking with Form BNK	Serum specimen collected after randomization (prior to beginning study treatment)	See Protocol Appendix D (Do <u>not</u> submit to the NSABP Biostatistical Center)
Baseline serum specimen for antibody and PK testing with the requisition from the appropriate Covance serum kit	Serum specimen collected from Group 2 patients only after randomization (prior to beginning study treatment)	See Protocol Appendix C (Do <u>not</u> submit to the NSABP Biostatistical Center)
Baseline serum specimen for ovarian function testing with the requisition from the appropriate Covance serum kit	Serum collected from premenopausal women only (who consent to collection) after randomization (prior to beginning study treatment)	
TREATMENT		
Form AE	Routine reporting form for grade 2 neurologic and all grade 3, 4, and 5 adverse events	Every 3 cycles during mFOLFOX6, every 6 weeks during bevacizumab alone
Form HT	Form for patient hypertension history, status, and treatment	
Form P	Proteinuria report form	
Form MS	Form for menstrual status and related hormone tests	Every 6 months for women identified as pre-menopausal at baseline
Form FF	mFOLFOX6 treatment form	When mFOLFOX6 therapy is permanently discontinued or if mFOLFOX6 therapy never begins
Form CAMG	Form for reporting number of cycles where calcium/magnesium infusions were given with oxaliplatin	Submit when patient fails to start oxaliplatin or when oxaliplatin treatment has ended.
Form BEV	Bevacizumab treatment form	When bevacizumab therapy is permanently discontinued or if a Group 2 patient never begins bevacizumab therapy
Form LFT	Reporting form for grade 3 or 4 elevation in bilirubin, AST, or alkaline phosphatase	Submit within 2 weeks of ≥ grade 3 elevation.
Form LFT-F	Follow-up form for grade 3 or 4 elevation in bilirubin, AST, or alkaline phosphatase	Submit *once* after resolution of LFT to ≤ grade 1 (or at 1 year after study entry, if no resolution).
Form F	Follow-up form (For positive or suspicious tests, provide documentation.)	Every 3 months until 2 years post-registration, every 6 months for years 3-5, and annually thereafter
Serum specimen for anti-bevacizumab antibody collection with the requisition from the appropriate Covance serum kit	Serum specimens for anti-bevacizumab antibody testing following ≥ grade 3 allergic reaction attributable to treatment with bevacizumab	Group 2 patients only, submit following all ≥ grade 3 allergic reactions attributable to treatment with bevacizumab. See Protocol Appendix C. (Do <u>not</u> submit to the NSABP Biostatistical Center)
Serum specimen for ovarian function testing with the requisition from the appropriate Covance serum kit	Serum specimen for ovarian function testing for women identified as premenopausal at baseline	Submit every 6 months for women identified as premenopausal at baseline who consent to this collection. See Protocol Appendix C. (Do <u>not</u> submit to the NSABP Biostatistical Center)

TABLE 17. (cont.) Required forms and materials *01/12/05*

FOLLOW-UP		
Form F	Follow-up form (For positive or suspicious tests, provide documentation.)	Every 3 months until 2 years post-registration, every 6 months for years 3-5, and annually thereafter
Form AE	Routine reporting form for all adverse events	Every 3 months for one year following treatment
Form HT	Form for patient hypertension history, status, and treatment	
Form MS	Menstruation status form	Every 6 months until 2 years post-registration for women identified as premenopausal at baseline
Serum specimen for ovarian function testing with the requisition from the appropriate Covance serum kit	Serum specimen for ovarian function testing from women identified as premenopausal at baseline	Submit every 6 months until 2 years post-randomization for women identified as premenopausal at baseline who consent to this collection. See Protocol Appendix C. (Do <u>not</u> submit to the NSABP Biostatistical Center)
Form P	Proteinuria report form	Every 3 months for 1 year following treatment for all patients whose protein/creatinine ratio was $\geq$ 1.0 at the end of treatment
Serum specimen for anti-bevacizumab antibody collection and determination of post-treatment serum levels of bevacizumab with the requisition from the appropriate Covance serum kit	Serum specimens collected for anti-bevacizumab antibody and PK testing	Group 2 patients only, submit at 3 and 6 months following discontinuation/ completion of bevacizumab. See Protocol Appendix C for instructions. (Do <u>not</u> submit to the NSABP Biostatistical Center.)
RECURRENCE		
Serum specimen with Form BNK collected at time of recurrence	Serum specimen collected at time of first recurrence with transmittal form	Submit to the NSABP Serum Bank at Baylor. See Protocol Appendix D for instructions. (Do <u>not</u> submit to the NSABP Biostatistical Center.)

ALL NSABP REPORT FORMS MUST BE SENT TO:
NSABP Biostatistical Center
One Sterling Plaza
201 North Craig Street, Suite 500
Pittsburgh, PA 15213
Phone: (412) 624-2666
Fax: (412) 624-1082

16.0 STATISTICAL CONSIDERATIONS

16.1 Design, monitoring, and analysis

16.1.1 *Accrual*

The accrual rate for Protocol C-07 averaged 73 patients per month over the life of the protocol and 89 patients per month for the first 9 months of 2002. For the power computations, we are assuming that we will initially accrue patients at a rate of approximately 63 patients per month with accrual increasing in a roughly linear fashion over the first 2 years to a rate of approximately 105 patients per month. Our design calls for accruing 2,632 patients. The accrual phase of our trial will take approximately 2.5 years.

Based on prior experience with Protocol C-07, we expect that 70% of these patients, roughly 1,840 of them, will have stage III disease. In order to support certain regulatory analyses, we require at least 1,840 stage III patients. Thus, accrual will continue until we exceed both 1,840 stage III patients and 2,632 total patients.

16.1.2 *Treatment allocation and stratification factors*

Patients will be assigned treatment using the NSABP biased-coin minimization algorithm.[53] Patients will be stratified by institution and by number of positive lymph nodes (0, 1-3, and > 3). Treatment assignments will be balanced 1:1 between the two treatment arms.

16.1.3 *Background for power considerations*

We have reviewed data from 3,048 patients with a known Dukes' class of B or C who received 5-FU and leucovorin on Protocols C-03, C-04, C-05 or C-06. This review indicates that the disease-free survival (DFS) rate at 3 years post-randomization is approximately 0.71 (we are using 0.70623 in our computations), assuming 30% of the patients are Dukes' B and 70% of the patients are Dukes' C. This ratio of Dukes' B/C was observed on Protocol C-07, which has similar eligibility criteria to C-08. Assuming an exponential model, the 3-year DFS rate of 0.70623 translates into an estimated hazard rate of $\lambda = 0.11594$ events per year (first recurrence, second primary, or death). It has been our experience in previous trials that when a treatment improves DFS, most of the improvement is observed in the first 3 years. This is due in part to the fact that in adjuvant colon trials, the event rate (for DFS) drops considerably after 3 years. On the 5-FU plus LV regimens, the rate drops to approximately $\lambda = 0.04261$ events per year and slightly less than half of these ($\lambda = 0.01676$) are recurrences (the other half are second primaries and deaths from other causes, which are not likely to be reduced by additional chemotherapeutic agents).

In order to estimate the hazard rate for the control arm of C-08, we have to account for the effect of adding oxaliplatin to the regimen described in the previous paragraph. We assume that the addition of oxaliplatin will result in a 23% reduction in DFS event rate during the first 3 years. Subsequent to 3 years, we assume the same reduction in event rate, but we assume the effect is limited

to recurrence events and there is no effect on second primaries and death due to other causes. These are the same assumptions which were made for the purpose of power calculations in protocol C-07 for the FLOX regimen. We assume that the mFOLFOX6 regimen which will serve as the control arm for C-08 will result in rates of DFS events similar to what were assumed for the FLOX arm of C-07. We estimate the hazard rate to be $\lambda_{control} = (0.11594 \times (1 - 0.23)) = 0.08927$ during the first 3 years and $\lambda_{control3+} = (0.04261 - 0.01676 \times 0.23) = 0.03875$ during subsequent years. The hazard rate due to recurrence after the third year is estimated as $\lambda = (0.01676 \times (1 - 0.23)) = 0.01291$. Under these assumptions we anticipate a 3-year DFS rate of approximately 0.765 on the control arm of C-08.

16.1.4 ***Power for primary endpoint DFS***

During the first 3 years after randomization, we assume that the addition of bevacizumab will result in a 25% decrease in event rate as compared to control (i.e., the hazard ratio $\lambda_{Bev} / \lambda_{control} = 0.75$). Thus we assume $\lambda_{Bev} = 0.06695$ and the 3-year DFS rate on the bevacizumab arm will be approximately 0.818.

Subsequent to 3 years, we assume the same treatment effects as above, but we assume the benefit is restricted to reducing the rate of recurrence only and that the rates of second primaries and death due to other causes will be unaffected. In the previous section, we estimated the hazard rate on the control arm for all DFS events subsequent to 3 years to be $\lambda_{control3+} = 0.03875$ and restricted to recurrence events $\lambda_{control3+} = 0.01291$. The hazard rate for the bevacizumab arm is $\lambda_{Bev3+} = (0.03875 - 0.01291(1 - 0.75)) = 0.03552$.

Under the assumptions above, our plan is to analyze the data when 592 events have been observed. If we accrue 2,632 patients in 2.5 years, we should reach this number of events approximately 5 years after the initiation of the study. The exact length of time until 592 events are observed will depend on the actual hazard rates associated with each treatment arm. If we have not observed 592 events 4 years after the last patient is entered, we will still analyze the data at that time, using whatever events we have observed. Using the log-rank statistic stratified for number of positive lymph nodes (0, 1-3, and >3), the operating characteristics of the interim monitoring plan detailed in the following section are such that we have a power of approximately 0.90 to detect the alternative hypothesis specified in the previous two paragraphs.

The primary analysis will be based on the intent to treat principal. Exploratory analyses will be done using the cohort of patients who received their randomized treatment. Any material difference in the results of these analyses will be discussed in any subsequent manuscripts.

16.1.5 ***Interim analyses***

The first interim analysis will be performed for the first scheduled meeting of the Data Monitoring Committee (DMC) following the 148th event for the primary endpoint of DFS. All subsequent interim analyses will be performed for the regular scheduled meetings of the DMC (approximately every 6 months.) The definitive analysis for DFS will be performed when a fixed number of events

have occurred as specified in the previous section. The number of interim analyses is not pre-specified, and may vary depending upon the time required to accumulate sufficient DFS events for the definitive analysis. We intend to use asymmetric boundaries indexed by one-sided p-values. This will allow us to stop early for futility if there is little or no evidence that bevacizumab is beneficial. We could also stop early to declare control + bevacizumab superior to control if there is strong evidence to support this conclusion.

Crossing the upper boundary will result in a conclusion that mFOLFOX6 + bevacizumab is superior to mFOLFOX6 alone. The first 3 interim analyses will use one-sided upper significance levels of 0.00025, 0.0005, and 0.001, respectively. Subsequent interim analyses (should they be necessary) will continue to use a significance level of 0.001. Alpha spending will be used to determine the significance level of the definitive final analysis.[54] We anticipate the significance level of the final analysis will be approximately 0.0246, one-sided. Crossing the lower boundary will result in a conclusion that mFOLFOX6 + bevacizumab is not superior to mFOLFOX6 alone (i.e., roughly equivalent or detrimental). The first 3 interim analyses will use one-sided lower significance levels of 0.05, 0.25, and 0.5, respectively. Subsequent interim analyses will continue to use a significance level of 0.5. A possible schedule of interim analyses is given in Table 18.

The probability of falsely concluding mFOLFOX6 + bevacizumab is superior to mFOLFOX6 alone when in fact there is no difference in DFS between these groups is 0.025 and the power to conclude bevacizumab is superior at any one of these analyses is 0.9055 (based on hazard rate assumptions of Sections 16.1.3 and 16.1.4). If the difference in DFS between bevacizumab and no bevacizumab arms is significant at these alpha levels, the DMC will consider a recommendation of early reporting of the results.

TABLE 18. Possible schedule of interim analyses (assuming accrual per Section 16.1.1 and hazard rates per Sections 16.1.3 and 16.1.4)

Interim analysis	**Approximate time (years)**	**Lower boundary significance level**	**Upper boundary significance level**	**Approximate number of events**	**Approximate number accrued**
1	2.0	0.05	0.00025	148 fixed	2,006
2	2.5	0.25	0.0005	220	2,632
3	3.0	0.5	0.001	312	2,632
4	3.5	0.5	0.001	398	2,632
5	4.0	0.5	0.001	473	2,632
6	4.5	0.5	0.001	538	2,632
Definitive analysis	5.0	N/A	~0.0246	592 fixed	2,632

16.1.6 ***Survival***

Although, we do plan to report our DFS results as specified in Section 16.1.4, we will also perform a planned survival analysis to compare the bevacizumab group to the group not receiving bevacizumab. We anticipate a death rate of 0.0487 per

year over the first 5 years and 0.0286 per year in subsequent years for the control arm. This translates into a 5-year survival rate of approximately 78%.

Seven years after the trial opens, we expect to have observed approximately 542 deaths, which will allow us to have a power of 82% to detect a 5% absolute improvement in the 5-year survival rate to 83%. This would be equivalent to a reduction in the annual death rate of 25%. This power statement applies when the analysis is a two-sided log-rank test stratified for number of positive lymph nodes (0, 1-3, > 3) performed at a Type I error rate of 0.05.

16.1.7 ***Tertiary aims***

The tertiary aims of the study are to evaluate if the incidence and duration of certain adverse events are possibly related to treatment with bevacizumab. The specific aims are as follows:

a. To assess the persistence of proteinuria following the discontinuation of bevacizumab;

b. To correlate the rates of proteinuria with clinical sequelae;

c. To evaluate the risk factors for development of proteinuria;

d. To determine the effect of discontinuation of bevacizumab on hypertension;

e. To estimate the incidence of delayed vascular events such as myocardial infarction, CNS ischemia, and thrombosis in patients receiving chemotherapy + bevacizumab;

f. To assess the effect of bevacizumab on ovarian function in premenopausal women; and

g. To assess the incidence rate of immunogenicity and the pharmacokinetic analysis of post-treatment serum levels of bevacizumab in patients receiving bevacizumab.

Time to the resolution of proteinuria will be used to study persistence. Kaplan Meier curves will be used to describe time to resolution for the two treatment arms. Should sufficient proteinuria events be observed, time to the development of proteinuria will be used in Cox models to determine the effect of clinical sequelae and baseline risk factors.

Counts and proportions will be used to describe the development and resolution of hypertension in each arm. Resolution of hypertension after treatment will be compared between treatment arms using logistic regression models.

The development of delayed vascular events and ovarian failure will each be compared between treatment arms using logistic regression models. Counts and proportions will be used to describe the development of these conditions in each arm of the study. Should sufficient events be observed for any of these endpoints, time-to- event analyses will also be performed.

16.1.8 *Toxicity monitoring*

The protocol officer will review the rates of adverse events on the two arms of this study on a monthly basis. In addition, the independent NSABP Data Monitoring Committee (DMC) will routinely review safety data every 6 months and may convene for a special session when necessary.

In addition to the standard safety monitoring described in the previous paragraph, we have developed a formal monitoring plan for treatment-related mortality. A group sequential monitoring plan will be implemented to monitor the rate of treatment-related mortality (CTCAE v. 3.0 grade 5 toxicity) separately in each treatment arm. We consider a treatment-related mortality rate of up to $p_0 = 1.5\%$ to be acceptable, but larger rates are considered unacceptable. We wish to achieve high power to rule out a treatment-related mortality rate of $p_A = 3\%$. Note that treatment-related mortality was approximately 1.2% for both arms of NSABP Protocol C-07, a trial with similar eligibility criteria which employed 5-FU + LV on the control arm and 5-FU + LV + oxaliplatin on the experimental arm.

Monitoring plan

Two formal statistical comparisons will be made when the following milestones are reached:

1) 300 patients per treatment arm have been followed for at least 6 months.

2) 500 patients per treatment arm have been followed for at least 6 months.

Toxicity will be considered unacceptable if ≥ 9 of 300 or ≥ 12 of 500 patients experience grade 5 toxicity. If unacceptable toxicity is observed on any treatment arm, the DMC will consider suspending accrual pending a determination of the need to enact a protocol amendment or to discontinue the trial; otherwise, accrual continues. Based on 1 million simulations, the type I error rate of this procedure is approximately 0.089 and the power is approximately 0.829 for each treatment that the procedure is applied to.

16.2 **Gender and racial/ethnic issues**

To our knowledge there is no literature addressing gender or race related interactions with adjuvant therapy with FOLFOX or bevacizumab or 5-FU + LV. Some studies have suggested possible gender interactions with treatment using other adjuvant chemotherapy regimens. In the NSABP R-01 study, in male patients only, there was increased DFS with MOF over no adjuvant therapy.[56] However, in NSABP C-01, which used the same chemotherapy regimen, no sex interaction was found.[57] Two other studies conducted by NCCTG have demonstrated contrasting sex interaction in the chemotherapy effect.[2,57] In the first study[2] there was an increase in DFS in females treated with 5-FU + LEV. In contrast, in the second study,[58] there was a benefit in males treated with 5-FU + LEV. Furthermore, several recent colorectal studies using 5-FU chemotherapy demonstrated no interactions in the treatment effect by gender.[59-61]

In summary, in the majority of the studies, no gender interactions have been identified, and in the few studies where such interactions have surfaced, subset analyses (with their inherent limitations) were performed. Therefore, one can reasonably conclude that there is no strong evidence for a treatment interaction by gender with 5-FU based chemotherapy. Especially with 5-FU + LV or FOLFOX or bevacizumab, no information exists pointing to a treatment interaction by gender.

To our knowledge, no literature exists demonstrating a differential effect of adjuvant chemotherapy within racial/ethnic groups of patients with colon cancer. Therefore, there is no evidence either for or against the possibility of racial/ethnic group differences in treatment effect for this study.

Based on accrual in our previous NSABP colon protocols, we expect about 55% of the patients in this study to be male and 45% to be female. In similar studies, the racial/ethnic composition for this study population is approximately 85% white; <1% American Indian or Alaskan Native; 3% Asian or Pacific Islander; 8% black, not of Hispanic origin; 3% Hispanic; and <1% other. It is anticipated that this distribution will be maintained for Protocol C-08. Because of the sample size limitations, we will not be able to compare the effects separately for different cultural or racial groups. Analyses will be performed to test for gender differences in treatment effect.

The gender, racial, and ethnic composition of the 2,632 patient group will be as follows:

TABLE 19. Expected gender, racial, and ethnic composition of C-08.

Ethnic Category	**Sex/Gender**		
	Female	**Male**	**Total**
Hispanic or Latino	31	63	94
Not Hispanic or Latino	1121	1417	2538
Ethnic Category: Total of all subjects	**1152**	**1480**	**2632**
Racial Category	**Sex/Gender**		
	Female	**Male**	**Total**
American Indian or Alaskan Native	4	2	6
Asian	43	40	83
Black or African American	102	92	194
Native Hawaiian or other Pacific Islander	2	0	2
White	1001	1346	2347
Racial Category: Total of all subjects	**1152**	**1480**	**2632**

Ethnic Categories: **Hispanic or Latino** – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race.

Not Hispanic or Latino

Racial Categories: **American Indian or Alaskan Native** – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.

Black or African American – a person having origins in any of the black racial groups of Africa.

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

Potential for enrollment of minority patients in this study is enhanced through the NSABP Minority Initiative Program, which disseminates information and provides opportunities for greater participation by under represented racial and ethnic groups.

17.0 PUBLICATION INFORMATION

The publication or citation of study results will be made in accordance with the publication policy of the NSABP that is in effect at the time the information is to be made publicly available.

The bevacizumab and oxaliplatin supplied by CTEP, DCTD, NCI used in this protocol are provided to the NCI under Collaborative Agreements (CRDA, CTA) between Genentech, Inc., Sanofi-Synthelabo, Inc. [hereinafter referred to as "Collaborators"] and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" contained within the terms of award, apply to the use of bevacizumab and oxaliplatin in this study:

17.1 Bevacizumab and oxaliplatin may not be used for any purpose outside the scope of this protocol, nor can bevacizumab and oxaliplatin be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for bevacizumab and oxaliplatin 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.*

17.2 For a clinical protocol where there is an investigational Agent used in combination with another 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 "Multiple-Party Data."):

17.2.1 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 the NCI's participation in the proposed combination protocol.

17.2.2 Each Collaborator shall agree to permit use of the Multi-Party Data from the 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.

17.2.3 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.

17.3 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.

17.4 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 the Collaborator's wish to contact them.

17.5 Any data provided to Collaborator(s) for phase III studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

17.6 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 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
E-mail: 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.

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APPENDIX A

TNM NOMENCLATURE AND STAGING FOR COLORECTAL CANCER

TNM Nomenclature

Tumor (T)

T_X	Primary tumor cannot be assessed
T_0	No evidence of primary tumor
T_{is}	Carcinoma in situ: intraepithelial or invasion of lamina propria*
T_1	Tumor invades submucosa
T_2	Tumor invades muscularis propria
T_3	Tumor invades through the muscularis propria into the subserosa or into non-peritonealized pericolic or perirectal tissues
T_4	Tumor directly invades other organs or structures and/or perforates visceral peritoneum**,***

**Note:* T_{is} includes cancer cells confined within the glandular basement membrane (intraepithelial) or lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.

***Note*: Direct invasion in T_4 includes invasion of other segments of the colorectum by way of the serosa; e.g., invasion of sigmoid colon by a carcinoma of the cecum.

***Tumor that is adherent to other organs or structures, macroscopically, is classified T_4. However, if no tumor is present in the adhesion, microscopically, the classification should be pT_3. The V and L substaging should be used to identify the presence or absence of vascular or lymphatic invasion.

Nodes (N)

N_X	Regional lymph nodes cannot be assessed
N_0	No regional lymph node metastasis
N_1	Metastasis in 1 to 3 regional lymph nodes
N_2	Metastasis in 4 or more regional lymph nodes

Note: A tumor nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule is classified in the pN category as a regional lymph node metastasis if the nodule has the form and smooth contour of a lymph node. If the nodule has an irregular contour, it should be classified in the T category and also coded as V1 (microscopic venous invasion) or as V2 (if it was grossly evident), because there is a strong likelihood that it represents venous invasion

Metastasis (M)

M_X	Distant metastasis cannot be assessed
M_0	No distant metastasis
M_1	Distant metastasis

Staging

	T	***N***	***M***	***Dukes****
Stage 0	T_{is}	N_0	M_0	–
Stage I	T_1 T_2	N_0 N_0	M_0 M_0	A A
Stage II A *II B*	T_3 T_4	N_0 N_0	M_0 M_0	B B
Stage III A *III B* *III C*	$T_1 – T_2$ $T_3 – T_4$ Any T	N_1 N_1 N_2	M_0 M_0 M_0	C C C
Stage IV	Any T	Any N	M_1	–

**Note*: Dukes B is a composite of better ($T_3N_0M_0$) and worse ($T_4N_0M_0$) prognostic groups, as is Dukes C (any TN_1M_0 and any TN_2M_0)

APPENDIX B

DETERMINATION OF PERFORMANCE STATUS AND MENOPAUSAL STATUS

1.0 Performance Status Key

ECOG or Zubrod Scale		Karnofsky Score
0	Fully active; able to carry on all pre-disease performance without restriction	90-100%
1	Restricted in physically strenuous activity but ambulatory	70-80%
2	Ambulatory and capable of self-care, but unable to carry out any work activities	50-60%
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours	30-40%
4	Completely disabled	10-20%

2.0 Menopausal Status Determination

The following criteria will be used to define postmenopausal:

- A prior documented bilateral oophorectomy, **or**
- A history of at least 12 months without spontaneous menstrual bleeding, **or**
- Age 55 or older with a prior hysterectomy, **or**
- Age 54 or younger with a prior hysterectomy without oophorectomy (or in whom the status of the ovaries is unknown), with a documented FSH level demonstrating confirmatory elevation in the lab's postmenopausal range.

Women failing to meet one of these criteria will be classified as premenopausal.

APPENDIX C

01/12/05

PROCEDURES FOR ORDERING SERUM COLLECTION KITS FROM COVANCE CENTRAL LABORATORY SERVICES, INC., AND FOR COLLECTING, PROCESSING, AND SHIPPING SPECIMENS FOR ANTI-BEVACIZUMAB ANTIBODY, PHARMACOKINETICS, AND OVARIAN FUNCTION TESTING

Please note: Instructions for collection of serum samples for future, unspecified research and shipment to the NSABP Serum Bank at Baylor can be found in Appendix D.

1.0 ORDERING SERUM COLLECTION KITS FROM COVANCE

Coordinators must submit the initial kit order at the time they start the IRB review process to allow sufficient time for the kits to arrive at their sites. Kits will take approximately 7 working days to arrive in the U.S. and Canada, and approximately 14 working days to arrive at International sites.

Kits are individualized by type and time point to be collected. Resupply will be automatic and will include replacement kits for baseline collections as well as specific kits. The resupply kits will automatically be shipped about 2 weeks prior to the protocol-specified time points after the initial specimen(s) for a patient has been sent to Covance.

Please note (for all sites):

- The address designated for the initial kit shipment will be the address to which **all future resupplies for kits and kits for subsequent visits will be sent**; therefore, please plan accordingly for your preferred mechanism of distribution.

- Shelf life for these kits is approximately 6 months.

1.1 Initial orders for NSABP sites

To order **initial** serum kit supplies, NSABP coordinators **must** use the online order process available in the Members' Area of the NSABP Web site by following the links to *Coordinator Online, Study Management, Drug Ordering and Protocol Specific Procedures.*

The online order process allows NSABP sites to have the kits shipped to main institutions and/or directly to one or more satellite sites. Coordinators may adjust maximum and minimum inventory levels for sites based on accrual expectations. Covance will send a fax to each site requesting shipping and contact information. This is a Covance policy; the NSABP cannot supply this information directly to Covance.

1.2 Initial orders for CTSU sites

To order **initial** serum kit supplies, CTSU coordinators *must* use the NSABP C-08 Covance Serum Specimen Kit Order Form available online in the Members' Area of the CTSU Web site under *Site Registration Documents* for NSABP Protocol C-08. Before the initial order is sent, the coordinator will receive a faxed request from Covance requesting shipping information to initialize the Covance database. This information will be used to ship the initial kit inventory, all resupply kits, and kits for samples that are to be submitted for specific time points after the initial sample submission. **If there are any**

changes to shipping addresses or contact information during a CTSU site's participation in NSABP C-08, you must alert Covance of these changes.

1.3 **Replacement kits and subsequent orders for NSABP and CTSU sites**

There are several important differences between the kit replacement policies that Covance employs and those of the other NSABP serum labs:

- Once an initial shipment has been ordered, coordinators can request additional kits if the initial kit inventory will not meet the needs of imminent accrual or if the kits are nearing the expiration date by calling **1-800-327-7270** or by using the *Additional Kits/Material Order Form* found in the *Covance Central Laboratory Services Manual for Protocol NSABP C-08*.
- Kit replacement is automatic, but replacement occurs when the inventory on site reaches a set minimum amount. Replacement shipments will contain enough kits to meet a predetermined maximum amount of inventory permitted at a site.
- Kit replacements and kits for samples that are to be submitted for specific time points after the initial sample submission are always sent to the site where the initial kits were shipped.
- Kits for subsequent visits should not be ordered online. These are sent approximately 2 weeks before the patient is expected to need the kit. The shipment date is based on data received when the initial kit is submitted to Covance.
- Requests for changes in minimum and maximum inventory limits are made by calling Covance at **1-800-327-7270**. Sites need to allow 7 working days for the Covance system to be updated and for additional kits to be received.
- The minimum number for a kit type cannot be less than two.

1.4 **Inventory limits**

- Initial order:
  - 4 kits for collection of baseline serum antibody and pharmacokinetic samples
  - 2 kits to be used in the event of allergic reactions (these are identified by Covance as kits for an unscheduled visit)
  - 2 kits for collection of samples for testing of ovarian function

- Resupply orders:

Kit Type	Minimum Order	Maximum Order
Serum Antibody and Pharmacokinetic Testing	4	7
Ovarian Function Testing	2	3
Unscheduled Visit	2	3

2.0 COLLECTION OF PROTOCOL-SPECIFIC SERUM SAMPLES (REFER TO PROTOCOL SECTIONS 7.2.2 AND 7.2.3)

Serum samples for bevacizumab antibody testing, pharmacokinetic testing, and ovarian function testing will be submitted to and processed by Covance Central Laboratory Services, Inc.

2.1 Serum collection kits

There are different vials and instructions for the serum antibody testing, the pharmacokinetic testing, and the ovarian function testing:

- *Serum antibody and pharmacokinetic kits*: These are identified by scheduled time intervals.
  - Baseline
  - 3 months post-bevacizumab dose
  - 6 months post-bevacizumab dose
  - Unscheduled (to be used for allergic reactions)
- Ovarian function kits:
  - (FSH/Beta-HCG) kits for the five collection points are interchangeable

2.2 Serum samples for all Group 2 patients

Serum samples for detecting the incidence of antibodies to bevacizumab and the pharmacokinetic analysis of post-treatment serum levels of bevacizumab will be collected for **all Group 2 patients** at the following time points:

- Baseline (after entry, before therapy begins)
- 3 months following the end of bevacizumab therapy
- 6 months following the end of bevacizumab therapy
- Within 2 weeks of a patient experiencing a ≥ grade 3 allergic reaction attributed to treatment with bevacizumab

2.3 Serum samples for all premenopausal women

Serum samples for ovarian function testing will be collected from **all premenopausal women** who consent to this collection at the following time points:

- Baseline (after entry, before therapy begins)
- 6 months from study entry
- 12 months from study entry
- 18 months from study entry
- 24 months from study entry

See Protocol Tables 5 and 6 for additional details.

07/27/05 3.0 **PROCESSING AND SHIPPING PROCEDURES**

Refer to the Covance manual for country-specific instructions on the collection, processing, and shipping of these samples.

Detailed instructions for collecting, processing, and shipping specimens for serum pharmacokinetic testing, antibody testing, and ovarian function testing are found in the *Covance Central Laboratory Services Manual for NSABP C-08*. Hard copies of this lab manual will be sent with each initial kit order. In addition, this lab manual will be available electronically in the Members' Area of the NSABP Web site by following the links to ***Treatment Trial Information, Protocols, C-08, Training/Special Documents.***

Covance Central Laboratory
8211 SciCor Drive
Indianapolis, IN 46214-2985
Phone: 1-800-327-7270
Fax: (317) 616-2358

APPENDIX D

PROCEDURE FOR COLLECTING, PROCESSING, AND SHIPPING BLOOD AND SERUM SPECIMENS

A. **Supplies, equipment, and facilities**

The following supplies will be provided for each patient to each clinical site by the NSABP Serum Bank at Baylor:	**The clinical sites must have on hand the following supplies and equipment:**
• 10 ml evacuated red-top vacutainer tubes (3) • 10 ml yellow-top vacutainer tube (1) (containing 3 ml ACD) • 7 ml polypropylene Sarstedt sample vials (3) • polyfoam container including Ziplock bags, foam pad, absorbent material, and U-Tek cold pack • patient identification labels • preprinted airbills for specimen shipments • corrugated cardboard boxes – must be used with each shipment • diagnostic specimen envelope	• disposable gloves • alcohol swabs • sterile gauze pads or cotton swabs • 21-gauge vacutainer needle, 1-1/2" (multiple-sampling) • pipets and pipeting system • vacutainer holder • tourniquet • refrigerator or ice bucket with crushed ice • centrifuge capable of accommodating 10 mL vacutainer tubes • needle disposal containers • biohazard containers • waterproof black markers • Ziplock bags • Package tape • NSABP Form BNK *(specimen documentation form)*

For problems with supplies or requests for additional supplies, please contact the NSABP Serum Bank at the telephone number provided under "Information Resources," page v.

B. **Timing of specimen collections**

Blood specimens are to be collected at the following time points:

- Sample 1: At baseline (following randomization prior to chemotherapy).
- Sample 2: Time of first recurrence.

C. **Sample collection procedures**

Four vacutainer tubes of blood are to be drawn for these specimens. Tubes will be provided by the NSABP Serum Bank for this purpose.

Procedures:

Please refer to your institutional policies and procedures for drawing blood specimens. The following are specific procedures related to the collection of specimens for transport to the NSABP Serum Bank.

1. Assemble the vacutainer tubes and vials required for the collection. These include:

   – three 10-mL red-top vacutainer tubes (plain, without silica or polymer)
   – one 10-mL yellow-top ACD vacutainer tube
   – three 7-mL polypropylene Sarstedt sample vials

2. Label the above tubes and vials with patient identification labels provided by the NSABP Serum Bank.

3. Completely fill the three red-top vacutainer tubes and the yellow-top ACD vacutainer tube with blood, according to your institutional procedure for blood specimen collection.

4. Place the yellow-top tube on ice or in the refrigerator.

5. Place the three red-top tubes upright in the test tube rack; allow to sit at room temperature for approximately 1 hour for clot to form before the tubes are centrifuged. The blood from patients with abnormal clotting due to disease or from those receiving anticoagulant therapy will require a longer time for complete clot formation. *Do not refrigerate tubes before centrifugation.*

6. If using a refrigerated centrifuge, set temperature of centrifuge to 25ºC. Balance centrifuge carriers containing the vacutainer tubes using a top-loading balance. Fill a fourth reusable tube with distilled water to serve as a balance tube. Make sure that tubes are properly seated in the carriers.

7. Load the carriers onto the centrifuge rotor. If either a swinging bucket rotor or a fixed angle bucket rotor is used, **centrifuge tubes at 1000-1200 g for 15 minutes**. *Do not exceed 1300 g in a fixed angle bucket rotor or 2200 g in a swinging head bucket rotor when centrifuging glass vacutainer tubes.*

8. While tubes are being centrifuged, sort the empty labeled Sarstedt vials in a row of a test-tube rack.

9. Allow the centrifuge to come to a complete stop. Carefully open the centrifuge, taking care to avert your face from the opening. (Avoid inhaling escaping air.) Inspect carriers for tube breakage. Remove carriers from centrifuge and place on table. Carefully remove vacutainer tubes from carriers and sort into the test-tube rack, matching each red-top tube with the appropriately labeled Sarstedt vial.

10. Pick up the first red-top tube, verifying identification against the labeled Sarstedt vial. Hold the tube so the stopper is pointing away from your face. Gently pry the stopper out, using a pulling force with the forefinger and a pushing force with the thumb. Discard stopper in a biohazard container.

11. Using a transfer pipet, carefully transfer serum from the first tube into the Sarstedt vial. The clot/serum interface will be very tight so that serum can be carefully pipetted off to within a few millimeters of the interface. Remove as much of the serum as possible. Cap the Sarstedt vial and return it to the test-tube rack. Discard the tube with remaining clot and the transfer pipet into a biohazard container. Repeat this procedure with the two additional red-top tubes.

12. The yellow-top tube does not require any processing before shipping.

D. **Shipping procedures**

Both serum and blood specimens should be shipped the same day as collected to the NSABP Serum Bank. To ensure the integrity of the specimens, the mailers must contain a refrigerant pack to maintain a cool temperature during shipping.

In the event that a blood sample needs to be collected on a Friday, process the blood and store the serum in the refrigerator until Monday when it should be shipped. For the yellow-top ACD tube, refrigerate the sample unprocessed; the ACD tube will support blood cells.

Polyfoam containers are provided with a foam insert to cushion the vials/tubes. Cold packs are provided; these must be frozen at -20º C overnight before shipping. One cold pack must be placed in the lid of the polyfoam container; the polyfoam container lid is designed to accommodate this. The vials/tubes must be placed in a Ziplock bag along with the absorbent material, before inclusion in the polyfoam container. Fold and place the Form BNK in a second Ziplock bag. Be sure that the bags are securely closed before placing in the polyfoam container. The polyfoam container ***must*** be sealed completely, placed inside a cardboard box ***and*** then in a diagnostic lab pack or it ***will not*** be accepted for shipment. A completed Form BNK must be included in the polyfoam container.

An account has been established with an overnight carrier for priority "Overnight Air Shipment" of specimens to this laboratory. ***Clinics should ship on Monday through Thursday*** so that shipments do not arrive on the weekend.

As shipments are received in the NSABP laboratory, the mailers will be opened, emptied, and returned with the cold packs to the clinic from which they were sent. Shipping containers will be returned by surface mail and may require a week to arrive at the clinic from which they were sent.

Since overnight carriers may vary and the specific details required for specimen shipment could change over the course of the study, the NSABP Serum Bank will provide more detailed instructions with specimen kits when they are shipped to the institutions. Please review those instructions carefully before mailing specimens.

Stepwise procedures:

1. Place a frozen U-Tek cold pack in the cover of the insulated polyfoam container. Place the foam pad in the polyfoam container.

2. Carefully place the three Sarstedt vials in a Ziplock bag; wipe any moisture from the outside of the yellow-top tube and place this in the Ziplock bag. Seal the bag and place in the polyfoam container next to the ice pack. (The tube should be "sandwiched" between the refrigerant pack and the foam pad.)

3. ***Complete the NSABP Form BNK, place in a Ziplock bag, and enclose in the polyfoam*** container. Seal the polyfoam container. Place the polyfoam container inside the cardboard box and seal the cardboard box. Place the cardboard box inside the diagnostic lab pack. Close the lab pack and seal.

4. Fill out the overnight carrier airbill; check all information for accuracy.

5. Arrange for priority overnight shipping. Specify that these are diagnostic specimens.

6. Ship the package immediately. Please note that blood and serum should be shipped on Monday through Thursdays only so that delivery is made to the NSABP Specimen Bank on a weekday.

   CANADIAN SITES PLEASE NOTE: If you are shipping on a Thursday, please contact the NSABP Serum Bank by fax at (713) 798-1642 and provide the tracking number of your shipment. Serum Bank personnel can then arrange for Saturday delivery if your shipment is delayed in Customs and does not arrive on Friday as scheduled.

08/02/07

Shipments must be sent to the following address, using the preprinted airbill.

Attn: Baylor College of Medicine Breast Center
NSABP Serum Bank, Room N1220
One Baylor Plaza
Houston, TX 77030

APPENDIX E

CANCER TRIALS SUPPORT UNIT (CTSU) INSTRUCTIONS

These instructions supplement the protocol for CTSU participants. The protocol is to be followed in areas not described in this appendix.

1.0 PATIENT ENTRY FOR CTSU INVESTIGATORS

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 Website or by calling the PMB at (301) 496-5725 Monday through Friday between 8:30 AM and 4:30 PM Eastern time. Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documents to the CTSU Regulatory office before they can enroll patients. All forms and documents associated with this study can be downloaded from the NSABP C-08 Web page on the CTSU Member Website (http://members.ctsu.org).

Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and all pertinent forms and documents are approved and on file with the CTSU.

Requirements for NSABP C-08 ***site registrations***:

- CTSU IRB Certification
- IRB/Regulatory Approval Transmittal Sheet

07/27/05

Requirements for patient enrollment on NSABP C-08:

- Patient must meet all inclusion criteria and no exclusion criteria should apply.
- Patient has signed the consent.
- All baseline laboratory and pre-study evaluations performed.
- Patient completed baseline Form HT-B.

07/27/05

CTSU Procedures for Patient Enrollment: Contact the CTSU Patient Registration Office by calling 1-888-462-3009 and leave a voice mail message to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, i.e., within one hour, call the Registrar cell phone at 1-301-704-2376. Complete the following forms:

- CTSU Patient Enrollment Transmittal Form
- Form A (Registration Form) with necessary attachments
- Copy of the signed and dated consent form

01/12/05
02/24/05

Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 7:00 p.m., Mon-Fri, Eastern Time (excluding holidays). For same day patient registrations to NSABP C-08, forms must be submitted to the CTSU by 3:30 p.m. Eastern Time. The CTSU registrar will check the investigator and site information provided to ensure that all regulatory requirements have been met. The registrar will also check the forms for completeness and follow-up with the site to resolve any discrepancies. Once investigator eligibility is confirmed

and enrollment documents are reviewed for completeness, the CTSU registrar will contact the NSABP to obtain assignment of a treatment arm and a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will convey this information to the enrolling site and follow up with a confirmation via e-mail or fax.

04/21/06 2.0 **DRUG ORDERS FOR CTSU INVESTIGATORS**

CTSU investigators should refer to Section 12.0 for detailed instructions on drug ordering, preparation, administration, and accountability.

bevacizumab – obtain through PMB

oxaliplatin – obtain through PMB

5-FU – obtain commercially

leucovorin – obtain commercially

CTSU investigators should refer to Section 12.0 for detailed instructions on drug ordering, preparation, administration, and accountability. Completed Clinical Drug Requests (NIH-986) should be submitted to the PMB by fax (301) 480-4612 or mailed directly to the Pharmaceutical Management Branch.

Drug may not be transferred from one protocol to another protocol. All other transfers (e.g., a patient changes from one CTSU investigator to another CTSU investigator) must be approved in advance by the PMB and the CTSU must then be informed of the change. The CTSU will then inform the NSABP Biostatistical Center of the transfer.

08/02/07 3.0 **SUBMISSION OF PATHOLOGY MATERIALS BY CTSU INVESTIGATORS**

With the patient's consent, investigators must submit pathology materials along with the completed Form BLK directly to the **NSABP Biostatistical Center**. This should be done after the patient is randomized but within 3 months of randomization (see Protocol Section 7.1).

08/02/07 4.0 **SERUM COLLECTION BY CTSU INVESTIGATORS**

4.1 **Serum collection for banking and future research**

CTSU will ship supplies for serum collection to the CTSU site at time of patient registration. Subsequent serum collection kits will be sent to the CTSU site by the NSABP Serum Bank. CTSU investigators should follow protocol directions for collection of serum and blood (see Section 7.2.1 and Appendix D). Specimens should be shipped the same day as collected to the **NSABP Serum Bank**. Clinics should schedule specimen shipments to occur on Monday – Thursday so as not to be received on the weekend. See Appendix D for the NSABP Serum Bank address. A completed NSABP Form BNK transmittal must accompany all shipments.

07/27/05 4.2 **Serum collection for immunogenicity testing, pharmacokinetics analysis, and evaluation of ovarian function by Covance Central Laboratory Services, Inc. on behalf of Genentech, Inc.**

Covance will ship supplies for serum collection for immunogenicity testing, pharmacokinetics analysis, and evaluation of ovarian function to the CTSU sites. To order initial serum kit supplies and for information on replacement kits and subsequent orders, refer to the instructions in Appendix C. CTSU investigators should follow the protocol directions for serum collection. (See Sections 7.2.2 and 7.2.3 and Appendix C.)

02/24/06
07/27/05
08/02/07

5.0 DATA SUBMISSION FOR CTSU INVESTIGATORS

All case report forms (CRFs) associated with this study must be downloaded from the NSABP C-08 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.

Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and other documents directly to the NSABP Biostatistical Center. The preferred method of sending data is via fax at 412-622-2111. Do not include a cover sheet for faxed data.

The NSABP Biostatistical Center will send query notices and delinquency reports directly to the site for reconciliation. Please send query responses and delinquent data to the NSABP Biostatistical Center and do not copy the CTSU Data Operations. If the query is sent with a fax transmittal form, return the data to the fax number on the transmittal form, otherwise fax to 412-624-1082.

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 NSABP Biostatistical Center.

6.0 ADVERSE EVENT (AE) REPORTING BY CTSU INVESTIGATORS

02/24/05
07/27/05

Specific reporting requirements for NSABP C-08 are found in protocol Section 13.0. For general information regarding adverse event reporting, please refer to Appendix F. The Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 is required for reporting adverse events for protocol C-08. A link to the CTCAE version 3.0 is available on the CTSU Member Website. CTSU investigators should employ definitions of adverse events as described in Section 13.1 and Appendix F of this protocol. All expedited reporting must be conducted within the time frames specified in Tables 14 and 15 (Protocol Section 13.3), and all completed forms for both expedited and routine AE reporting must be submitted as outlined in Section 13.0.

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

02/24/05
07/27/05
08/02/07

6.1 Routine reporting

CTSU institutions should refer to both Section 13.4 of the protocol and the NSABP protocol-specific routine reporting of adverse events form (Form AE) for instructions regarding routine adverse event reporting. If indicated, supporting documentation must be included with Form AE submission. Form AE is to be completed by the CTSU institution and sent to the NSABP Biostatistical Center. Include on Form AE those events that have been reported via AdEERS.

01/12/05
02/24/05
07/27/05

6.2 Expedited reporting

- CTSU institutions should refer to Section 13.3 and Tables 14 and 15 of the protocol for instructions regarding expedited adverse event reporting requirements.
- Contact the C-08 Research Nurse Specialist at the NSABP Biostatistical Center (refer to Information Resources, page iv) for questions regarding completion of reports, the need for supporting documentation, and submission time constraints.
- Follow the instructions in Section 13.3 when AdEERS reporting is required. Access the AdEERS electronic web based application and complete it fully and accurately. AdEERS reports are submitted electronically to the NSABP Lead Group, and available supporting documentation is faxed to the NSABP Biostatistical Center at **412-622-2113** at the time of the AdEERS submission. Include the patient's study number and the AdEERS ticket number on each page of supporting documentation.
- The NSABP Lead Group submits the AdEERS report to the NCI.
- Remember that events that have been reported via AdEERS must also be reported on Form AE.

07/27/05
08/02/07

6.3 Secondary AML/MDS/ALL reporting

Refer to protocol Section 13.3.7. CTSU investigators will submit the NCI Secondary AML/MDS Report Form and supporting documentation to the NSABP Biostatistical Center which will then forward the information to the NCI.

07/27/05
08/02/07

6.4 Reporting second primary malignancies

All second primary malignancies (including AML/MDS/ALL) are to be reported on NSABP Follow-up Form F; supporting documentation for the diagnosis must be submitted. CTSU investigators will submit the Form F and supporting documentation to the NSABP Biostatistical Center.

07/27/05

6.5 Pregnancy occurring while the patient is on protocol therapy

If a patient (or the sexual partner of a male patient) becomes pregnant while receiving protocol therapy, notify the NSABP Clinical Coordinating Division.

08/02/07

7.0 REGULATORY AND MONITORING

7.1 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 Registered Member Web site.

7.2 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-US HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU Web site.

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.

7.3 Clinical Data Update System (CDUS) monitoring

This study will 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.

APPENDIX F

INFORMATION BASICS FOR ADVERSE EVENT REPORTING

Included in this appendix is general information required for adverse event reporting. Please refer to the section of this protocol "Adverse Event Reporting Requirements" for specific instructions regarding expedited and routine adverse event reporting.

1.0 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. Additionally, the timely reporting of serious adverse events is required by FDA regulations and is addressed in the investigator registration FDA Form 1572. Because of the medical importance of serious and/or unexpected adverse events, the responsible physician should review any expedited report prior to submission to the NSABP.

2.0 DEFINITIONS FOR ADVERSE EVENT REPORTING

2.1 Investigational agent

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

2.2 Commercial agents

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source or distributed by the NCI or other distributor.

2.3 Investigational combination therapy

This study includes both investigational and commercial agents. When an investigational agent is administered concurrently with a commercial agent(s) and an adverse event occurs that is expected for the commercial agent(s), but is not listed for the investigational agent, the adverse event should be considered expected for the combination. However, ***if based on clinical judgment, the investigator believes the adverse event was possibly, probably, or definitely related to the investigational agent rather than the commercial agent***, the adverse event should be considered unexpected for the combination.

3.0 ADVERSE EVENT ASSESSMENT

Reporting requirements are determined by the assessment of the following adverse event characteristics: the *type* or nature of the event; the *grade* (severity); the *relationship to the study therapy* (attribution); *prior experience* (expectedness) of the adverse event; and whether the patient has received an *investigational or commercial agent or both*.

The recommended assessment steps include:

07/27/05

Step 1 *Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0*. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov). If assistance is needed, contact the NSABP Clinical Coordinating Division or the Research Nurse Specialist at the NSABP Biostatistical Center. All appropriate treatment locations should have access to a copy of the CTCAE Version 3.0.

Step 2 *Grade* the severity of the adverse event using the NCI CTCAE Version 3.0.

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* if the protocol treatment given any time prior to the adverse event included an *investigational agent, a commercial agent(s), or a combination of investigational and commercial agents.*

Step 5 *Determine the prior experience of the adverse event. Expected* events are those that have been previously identified as resulting from administration of the investigational agent or the commercial agent(s) being given in combination with the investigational agent. For expedited reporting purposes, an adverse event is considered *unexpected* when either the type of event or the severity of the event is *not* listed in the investigator's brochure and/or the drug package insert of the agent(s) being administered.

01/12/05

4.0 PROTECTING PATIENT CONFIDENTIALITY

Remove patient names and identifiers such as social security number, address, telephone number, etc., from reports and supporting documentation. All telephone calls and written reports must include the protocol number, and the patient's study number, and when associated with an AdEERS report, the AdEERS ticket number.

APPENDIX G

04/21/06

URINE PROTEIN/CREATININE (UPC) RATIO INSTRUCTIONS

1.0 Calculation of UPC ratio

Since proteinuria is a recognized toxicity of therapy with bevacizumab, NSABP Protocol C-08 requires screening for proteinuria ≥ 1 gm of protein per 24 hours. Since collection of a 24-hour urine specimen for protein is inconvenient for screening purposes, screening for proteinuria will be done using a random (spot) urine collection to obtain a urine protein/creatinine (UPC) ratio.

While some chemistry laboratories may report the actual UPC ratio (either as a protein/creatinine ratio or an albumin/creatinine ratio), others may report the total urine protein (or albumin) and the urine creatinine as separate results, generally reported in milligrams per deciliter (mg/dL). In this case, the UPC Ratio is calculated by using a simple ratio, dividing the protein (or albumin) by the creatinine.

Example:

Total urine protein (or albumin) ÷ urine creatinine = UPC Ratio

46.5 mg/dL (protein) ÷ 1501.1 mg/dL (creatinine) = 0.0309 (UPC Ratio)

2.0 UPC ratio and 24-hour urine collection requirements

UPC ratio is to be obtained prior to study entry and at various time points throughout the study (see Tables 5 and 6). ***The UPC ratio is a calculated estimate of grams of protein per 24 hours.*** Therefore, if the ratio is < 1, then the amount of protein in a 24-hour urine specimen is assumed to be < 1 gm per 24 hours. For the purposes of the C-08 study, if the urine protein/creatinine ratio is ≥ 1 at any time, then a 24-hour urine collection for protein is required (see Sections 5.1.4 and 6.0 [Tables 5 and 6]). *Reminder: Patients with ≥ 1 gm of protein/24 hours confirmed by a 24-hour urine collection on pre-entry evaluation are not eligible for this trial.*

3.0 Recording the UPC ratio on C-08 data forms

The UPC ratio should be recorded to the nearest tenth or to one decimal point. Rounding of the value is permitted. If the number being rounded has a 5, 6, 7, 8, or 9 in the hundredth spot, round the number up. If the number in the hundredth spot is 0, 1, 2, 3, or 4, round the number down.

Example:

A UPC ratio of 0.0309 would be rounded down to 0.0 and *recorded as shown below.* (Do not write outside the boxes provided.)

Urine Protein/Creatinine Ratio [ ] [0] . [0]

Examples of rounding the UPC ratio:

0.167 is rounded up to 0.2
0.132 is rounded to 0.1
0.03 is rounded down to 0.0
0.07 is rounded up to 0.1

APPENDIX H

NSABP C-08 Sample Consent Form

NSABP PROTOCOL C-08: A Phase III Clinical Trial Comparing Infusional 5-Fluorouracil (5-FU), Leucovorin, and Oxaliplatin (mFOLFOX6) Every Two Weeks with Bevacizumab to the Same Regimen without Bevacizumab for the Treatment of Patients with Resected Stages II and III Carcinoma of the Colon

Consent Version: April 21, 2006
Consent Addendum #1 Version: May 17, 2005 (Only for Group 2 patients enrolled before local IRB approval of Amendment #3.)
Consent Addendum #2 Version: October 25, 2007 (Only for Group 2 patients receiving bevacizumab within 3 months of local IRB approval of Amendments #6 and #7.)
To be attached to Protocol Version: October 25, 2007

07/27/05

Instructions to Local Institutional Review Boards Regarding
Local IRB Review of Multicenter Clinical Trials

In order to conform to OHRP guidelines (effective November 9, 1992) regarding local IRB review of multicenter clinical trials, and to provide local IRBs with flexibility in conforming to local standards, the NSABP provides the following instructions regarding the IRB approval process of this multicenter clinical trial.

The protocol and sample consent form provided by the NSABP have been reviewed and approved by the Division of Cancer Treatment and Diagnosis, National Cancer Institute. Local IRBs and the investigator are permitted to make changes to the consent form; however, the editorial changes must not alter the overall content or the intent of the information in the sample consent form. Should an investigator or local IRB delete or make a substantive modification of the information contained in the risks or alternative treatments sections of the consent form, this must be justified in writing by the investigator or the IRB and then approved by the IRB. Also, the NSABP Operations Center requires that, similarly, the NSABP also be notified of substantive changes in the consent form section regarding consent to collect and store samples for possible future testing. Of primary concern are text changes that could potentially impact the future usage of the banked samples. The IRB is responsible for reflecting in the IRB minutes the justification for, and approval of, such deletions or modifications. **The investigator is responsible for forwarding copies of such IRB-approved changes with their justifications to the NSABP Operations Center Division of Regulatory Affairs immediately.** It is the responsibility of the principal investigator and the IRB to determine what constitutes a substantive change. Any conflict between the two groups concerning this decision would be resolved at the NSABP Operations Center.

Upon receipt of these documents at the NSABP, Operations Center staff will review and approve the changes and their justifications with input (as needed) from the Quality Assurance staff and government agencies.

NSABP SAMPLE CONSENT

Consent Form
For
A Phase III Clinical Trial Comparing Infusional 5-Fluorouracil (5-FU), Leucovorin, and Oxaliplatin (mFOLFOX6) Every Two Weeks with Bevacizumab to the Same Regimen without Bevacizumab for the Treatment of Patients with Resected Stages II and III Carcinoma of the Colon

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

Why have I been asked to take part in this research study?

You are being asked to take part in this study because you have colon cancer that has been removed by an operation. Even though your doctor has removed the tumor, there is a chance that cancer cells have spread elsewhere in your body. The operation may not have permanently cured your cancer.

Who is conducting the study?

The National Surgical Adjuvant Breast and Bowel Project (NSABP) is conducting this study.

(The NSABP institution must supply appropriate information as to who is conducting the trial locally.)

Why is this research study being done?

01/12/05 Studies have shown that using chemotherapy (drugs given to fight cancer) after surgery can lower the chance of the cancer returning in patients with tumors that invade through the bowel wall (Stage II) or that involve the lymph nodes in the area (Stage III). The purpose of this study is to compare the effects (good and bad) from a combination of chemotherapy drugs when given with and without a new drug called bevacizumab. The chemotherapy given in this study is 5-fluorouracil (5-FU), leucovorin, and oxaliplatin. This chemotherapy has been tested in patients with your stage of colon cancer. Patients treated with this chemotherapy have fewer recurrences in the first 3 years after treatment. This chemotherapy is now being used in practice for patients with your stage of colon cancer. Bevacizumab is a new biologic therapy drug being studied for treating colon cancer. We want to see if adding bevacizumab to the chemotherapy is better for treating the stage of colon cancer you have. We also want to see if adding bevacizumab will help prevent the cancer from coming back.

Another reason for doing this study is to gather more information about the safety and effectiveness of bevacizumab. This drug has been shown to be helpful in treating colon cancer that has spread elsewhere in the body (Stage IV cancer). The U.S. Food and Drug Administration (FDA) considers the use of bevacizumab to be investigational for treating Stage II and Stage III colon cancer.

(Note: Centers outside of the U. S. must insert the applicable country and government oversight agencies in place of the U.S. and the FDA where appropriate throughout the consent form.)

For all patients who receive bevacizumab: Researchers will also study certain effects of bevacizumab. These studies are not part of regular cancer care. They are being done for the purpose of this study. They will include checking to see how much bevacizumab remains in your blood over a long period of time. They will also check your blood to see if you develop any antibodies to bevacizumab. (Antibodies are substances in the blood that your body makes to fight off a foreign substance.) In studies to date, no patients have developed antibodies to bevacizumab.

How many people will take part in the study?

About 2,632 patients will take part in the study.

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

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

- medical history and physical exam
- blood tests (including a pregnancy test for women of childbearing potential)
- urine tests
- chest x-ray or chest CT scan
- enema and/or endoscopic exam (The enema will use a substance so your colon can be examined by x-ray. These procedures will allow an exam of your bowel.)

In addition, you will be checked to see if you have an enlarged liver or blood tests that show abnormal liver function. If you do, then a liver scan, sonogram, abdominal CT scan, or MRI scan will be done if your doctor thinks it is needed.

During the study: If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will be "randomized" into one of the two study groups: Group 1 or Group 2. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in either of the two groups. Patients in

Group 1 will receive the drugs 5-FU, leucovorin, and oxaliplatin. Patients in Group 2 will receive bevacizumab, in addition to 5-FU, leucovorin, and oxaliplatin.

If you are in Group 1: Leucovorin and oxaliplatin will be given at the same time into a vein. This will take 2 hours. Then you will receive an injection of 5-FU into a vein. Another dose of 5-FU will continue to be given to you through a small portable pump for the next 46 hours. This process will be repeated 14 days later. (The 14 days between the first day you receive your chemotherapy drugs and the next time you receive them is called a cycle. You will receive 12 cycles of chemotherapy over about 6 months.)

If you are in Group 2: You will receive the same chemotherapy and follow the same schedule as Group 1. However, you will also receive bevacizumab (by injection into a vein) on day 1 of each cycle of chemotherapy before you get your chemotherapy. After your chemotherapy is done, you will continue to receive bevacizumab once every 2 weeks for another 6 months.

For both Groups 1 and 2: Your doctor will need to put a temporary tube into a vein in your chest or your arm. This tube will be attached to a small portable pump. The drug 5-FU will be given using this pump. The small size of the pump allows it to be attached to your clothing so that it can be used without restricting most of your movements and activities. You will wear this pump at home for the 46-hour period.

GROUP 1	**GROUP 2**
Oxaliplatin, 5-FU, and leucovorin *These drugs are given every 14 days for 12 cycles = about 6 months.*	**Oxaliplatin, 5-FU, and leucovorin** *These drugs are given every 14 days for 12 cycles = about 6 months.* + **Bevacizumab** *Bevacizumab is given every 14 days for 12 months, beginning with the first dose of oxaliplatin, 5-FU, and leucovorin.*

You will need the following tests and procedures. They are part of regular cancer care unless noted otherwise.

During the first year after entering the study, all patients will have the following tests and procedures performed:

- *a physical exam* every 2 weeks before chemotherapy and at 6, 9, and 12 months after starting therapy. Patients in Group 2 will also have a physical exam every 6 weeks before their bevacizumab injection.

- *blood tests* every 2 weeks before chemotherapy and at 6 and 12 months after starting therapy. Patients in Group 2 will also have a blood test before they begin chemotherapy and every 6 weeks before their bevacizumab injection. Patients in Group 2 may also have a blood test to look at bevacizumab antibody levels if they have an allergic reaction to bevacizumab. Antibody testing is not part of regular cancer care. It is done for the purpose of the study. The results will not affect your care.
- *urine tests* every 6 weeks before chemotherapy. Patients in Group 2 will also have a urine test every 6 weeks during their bevacizumab therapy. If your urine test contains an abnormal amount of protein, you will then need to collect your urine for 24 hours. If you need to do this, your study doctor or nurse will let you know what you need to do. (Note: The urine tests are not part of regular cancer care. They are being done for the purpose of this study.)
- *an enema with x-ray and/or an endoscopic exam* at about 12 months after starting therapy.
- You will be checked to see if you have an enlarged liver or blood tests that show abnormal liver function at 12 months after you begin your therapy. If you do, then a liver scan, sonogram, abdominal CT scan, or MRI scan will be done if your doctor thinks it is needed.

During 2-5 years after entering the study, all patients will have the following tests and procedures performed:

- *a physical exam* will be performed every 3 months during year 2, and every 6 months during years 3-5.
- *blood tests* will be performed every 6 months during years 2-5. Patients in Group 2 will have a blood test at 3 months and 6 months after completing bevacizumab therapy. (Note: These two blood collections for Group 2 patients are not part of regular cancer care. They are being done for the purpose of the study.)
- *urine tests*: If your last urine test in year 1 contained an abnormal amount of protein, then urine tests will be performed every 3 months during the 12 months after you complete your therapy. If your urine test contains an abnormal amount of protein, you will then need to collect your urine for 24 hours. If you need to do this, your study doctor or nurse will let you know what you need to do. (Note: The urine tests are not part of regular cancer care. They are being done for the purpose of this study.)
- *an enema with x-ray or endoscopic exam* every 1-3 years during years 2-5, depending on the findings at the time of the exam.
- You will be checked to see if you have an enlarged liver or blood tests that show abnormal liver function at your annual visit. If you do, then a liver scan, sonogram, abdominal CT scan, or MRI scan will be done if your doctor thinks it is needed.

After the 5th year on the study, a physical exam will be required yearly. Additionally, you will need to have an enema with x-ray and/or endoscopic exam every 1-3 years depending on the findings at the time of the previous exam.

How long will I be on the study?

Chemotherapy for all patients will last about 6 months. If you are assigned to also receive bevacizumab, your bevacizumab treatment will begin on the first day of your chemotherapy and will last for 1 year. Even if you need to skip some of your bevacizumab doses, treatment will only last for 1 year from your first treatment. You will be asked to visit your study doctor for follow-up exams for at least 5 years.

We would like to keep track of your medical condition for the rest of your life. Keeping in touch with you and checking on your condition yearly helps us to look at the long-term effects of the study.

Can I stop being in the study?

Yes, you can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study drugs can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

You can choose to withdraw one of two ways. In the first, you can stop your study treatment, but still allow the study doctor to follow your care. In the second, you can stop your study treatment and not have any further contact with the study staff.

Can anyone else stop me from being in the study?

The study doctor may stop you from taking part in this study at any time if he or she believes it is in the best interest for your health, if you do not follow the study rules, or if the study is stopped by the NSABP.

What side effects or risks can I expect from being in the study?

You may have side effects while on this study. Most of these are listed here, but there may be other side effects that we cannot predict. Side effects will vary from person to person. Everyone taking part in the study will be carefully watched for any side effects. However, doctors do not know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medications to help lessen some of the side effects. Many side effects go away soon after you stop taking your study drugs. In some cases, side effects may be very serious, long-lasting, or may never go away. *There is also a risk of death.*

You should talk with your study doctor about any side effects that you may have while taking part in the study.

During the study, we will do blood and urine tests to see if the dose of some of the drugs you are receiving during your therapy should be changed or delayed. The tests will also help monitor any side effects you may have. You will not need to be hospitalized unless you have serious side effects.

Risks and side effects related to the chemotherapy (5-FU, leucovorin, and oxaliplatin)

01/12/05 *Likely effects*

These side effects occur in **10% or more** of patients receiving 5-FU, leucovorin, and oxaliplatin:

- Diarrhea
- Nausea
- Vomiting
- Loss of appetite
- Dehydration
- Irritation of intestines
- Abdominal pain or cramps
- Sores in mouth, throat, and the esophagus, which is the tube that goes from the mouth to the stomach
- Low white blood cell count (may make you more likely to get infections)
- Low platelet count that may lead to bleeding
- Low red blood cell count (anemia) (can cause tiredness, weakness, and shortness of breath)
- Fever
- Cough
- Changes in blood tests that may indicate liver injury
- Infection
- Fatigue
- Nerve problems that are usually temporary, but some may be long-lasting. These may be made worse by exposure to cold temperature and cold objects
  - Pain, tingling, burning, or numb feeling (pins and needles) in hands, feet, or area around mouth or throat, which may cause problems walking or performing the activities of daily living.
  - Trouble swallowing or saying words, jaw tightness, odd feelings in the tongue, chest pressure, or a feeling of not being able to swallow or breathe without having any physical reason for this.
- Temporary hair loss
- Nail changes
- Skin darkening
- Time away from work

01/12/05
04/21/06

Less likely effects

These side effects may occur **in 3-9%** of patients receiving 5-FU, leucovorin, and oxaliplatin:

- Gastrointestinal ulcers and bleeding
- Bowel wall changes (that may require hospitalization)
- Intestinal blockage
- Constipation
- Flu-like symptoms such as fevers, chills, and muscle aches
- Watery eyes
- Nasal stuffiness
- Allergic reaction (including itching, hives, skin rash, fever, chills, muscle stiffening, sinus congestion, or swelling or puffiness of the face, especially eyelids)
- Fever with a low white blood cell count
- Blood clots
- Dizziness
- Eye problems (including redness or irritation)
- Difficulty sleeping
- Shortness of breath
- Headache
- Rash
- Blood tests that may indicate kidney damage
- Blistering, peeling, redness, swelling, tingling, numbness, and/or pain of the palms of hands and bottoms of feet
- Inflammation of the veins
- Taste changes
- Changes (high or low) in blood pressure
- Rapid heartbeat
- Pain in muscles, bones, joints
- Mood changes (including depression)
- Weight loss
- Hot flashes/flushing
- Hiccups
- Involuntary movements

01/12/05

Rare but serious effects

These side effects are **rare but serious**, occurring in **less than 3%** of patients receiving 5-FU, leucovorin, and oxaliplatin:

- Confusion or memory loss
- Slurred speech
- Poor coordination and balance
- Changes in the lungs (including inflammation, thickening, scarring, and possible lung failure)
- A breakdown of red blood cells and kidney failure known as the hemolytic uremic syndrome
- Skin and tissue damage in the area surrounding the catheter where the chemotherapy drug is injected
- Severe allergic reaction including shortness of breath, low blood pressure, wheezing, chest tightness and severe breathing problems
- Liver damage that may be permanent, including a serious form called "veno-occlusive disease" which can cause swelling of the abdomen, painful swelling of the liver, yellowing of the skin
- Problems with hearing
- Visual changes (including blindness usually lasting less than a minute)
- Heart attack or chest pain
- Irregular heartbeat
- Clots that form in the blood and use up the substances needed to stop bleeding

Diarrhea that occurs at the same time as low white blood cell counts can lead to very serious, life-threatening infection. On rare occasions, this can be fatal. Diarrhea can also be a sign of other serious intestinal problems. It is very important that you tell the study staff if you are having diarrhea so they can watch over your condition. You may need to be hospitalized to receive supportive care.

Side effects of bevacizumab

Likely effects
These side effects occur in **10% or more** of patients receiving bevacizumab:

- Nose bleeds
- High blood pressure
- Watery eyes
- Skin and nail changes (including dryness, itching, rash, discoloration, ulcers, or peeling)
- Sores in mouth and/or throat
- Taste changes
- Abnormal levels of protein in the urine (which may indicate kidney damage)
- Shortness of breath
- Mild to moderate bleeding in the gastrointestinal tract (serious and life-threatening bleeding events were rare)

Less likely effects
04/21/06 These side effects may occur in **3-9%** of patients receiving bevacizumab:

- Gastrointestinal upset (which may include gas, heartburn, constipation, diarrhea, nausea, vomiting, or loss of appetite)
- Headache
- Pain in the chest area
- Low white blood cell count (may make you more likely to get infections)
- Changes in blood tests that indicate possible kidney damage
- Low platelet count that might interfere with clotting
- Low sodium and/or potassium levels that might make you feel weak or dizzy
- Weight loss
- Confusion
- Poor coordination and balance
- Cough
- Frequent urination
- Voice changes (hoarseness)
- Blood clots in veins
- Tiredness/weakness
- Flu-like symptoms, such as fevers, chills, muscle aches, joint pain, and stiffness

05/17/05 Blood clots in your arteries which may cause stroke or heart attack or other problems. Several studies comparing chemotherapy with bevacizumab to chemotherapy alone have been done in patients with advanced cancers. Side effects of each study were looked at together. Problems due to blood clots in arteries were seen in about 2% of patients receiving chemotherapy alone, and about 4.5% of patients receiving bevacizumab with chemotherapy. Patients who were 65 or older, or those with past problems with blood clots in their arteries, appeared to be at greatest risk. Problems due to blood clots in the arteries were seen in about 2.9% of patients 65 or older receiving chemotherapy alone, and about 8.5% of patients 65 or older receiving bevacizumab with chemotherapy. Patients who were both 65 or older and reported a history of past problems

with blood clots in their arteries appeared to be at even higher risk, although further study is required before an estimate of the risk can be provided. These conditions can be life-threatening or fatal.

Rare but serious effects
These side effects are **rare but serious**, occurring in **less than 3%** of patients receiving bevacizumab:

- Bleeding in various parts of the body leading to disability (including stroke) or death (especially in lung cancer patients). *You should report any abnormal bleeding to your study doctor.*
- Serious stomach and/or bowel problems. A few patients have had a breakdown of tissue at the site where their bowel was reattached after removal of the tumor. A few patients have also had a hole form in their stomach or bowel wall. Both of these problems can lead to very serious infection and will require surgery to repair.

02/24/05
- Allergic reaction including: fever, chills, rash, hives, flushing, low blood pressure, swelling, and shortness of breath

02/24/05
- Reaction to the infusion including: fever, chills, hives, rash, joint pain, shortness of breath, low or high blood pressure, muscle stiffening, and sweating may occur during the infusion and last about 24 hours
- Kidney damage
- Coughing up blood
- Heart problems (including irregular heartbeats, changes in blood pressure, fluid collections surrounding the heart, chest pain, and possibly heart attack or heart failure)
- Infection
- Lung problems
- Reversible changes in liver function tests that may indicate liver damage

04/21/06
- Severe high blood pressure that can have an effect on brain function and can be life-threatening

04/21/06
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) is a medical condition related to leakiness of blood vessels in the brain. RPLS can cause headaches, confusion, vision changes or blindness, and seizure, as well as changes in brain scans. This condition is usually temporary but in very rare cases, it is potentially life-threatening and may have long-term effects on brain function.

Risk related to wound healing: There have been reports of patients on bevacizumab who had delayed healing of their surgical wounds. Therefore, if you need additional surgery for any reason while on bevacizumab, tell your doctor. Your doctor may choose to temporarily stop then restart your bevacizumab therapy to avoid any possible risk.

Risks related to fertility and pregnancy: The drugs in this study may affect the way a woman's ovaries work and her ability to get pregnant. The drugs in this study can affect an unborn baby. Therefore, women should not become pregnant and men should not father a baby while on this study. (Men and women in Group 2 should continue to take precautions for at least 3 months after their last dose of bevacizumab.) Both male and female patients should ask about counseling and more information about preventing pregnancy. Female patients who feel they

might be pregnant, even though they practiced birth control, must notify the study doctor immediately. A pregnancy test may be performed. Male patients should also inform the study doctor immediately if their sexual partners become pregnant while the patient is receiving treatment. Women should not breastfeed a baby while on this study, and, if they are in Group 2, for at least 3 months after their last dose of bevacizumab.

Doctors do not know for sure how bevacizumab may affect unborn children or children nursed by mothers who received bevacizumab. We do not know how long after stopping bevacizumab that you safely can become pregnant, father a child, or nurse a child. A period of at least 3 months is recommended, but we do not know if this is actually best. It is best to discuss your concerns with your doctor.

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

Are there benefits to taking part in this study?

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

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

Your other choices may include:

- Getting treatment or care for your cancer without being in this study
- Taking part in another study
- Getting no treatment

All the drugs used in this study are available without being on the trial. Although bevacizumab is commercially available in the United States, it is not approved for treatment of patients with your stage of colon cancer. The FDA considers use of bevacizumab in this setting to be investigational.

Please talk with your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. Organizations that may look at and/or copy your medical records for research, for quality assurance, and data analysis include:

- the National Surgical Adjuvant Breast and Bowel Project (NSABP);
- the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG), the sponsor of this trial in Canada;
- Genentech, Inc., which is supplying the study drug *bevacizumab* through the NCI;
- Sanofi-Synthelabo Inc., which is supplying the study drug *oxaliplatin* through the NCI;
- your local Institutional Review Board (IRB), a group of people who review the research study to protect your rights;
- the Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials; and

02/24/05
04/21/06

- government agencies, including the NCI or its authorized representatives, the FDA, the Office for Human Research Protections (OHRP), and the Irish Medicines Board. These agencies may review the research to see that it is being done safely and correctly.

What are the costs of taking part in this study?

You and/or your health plan/insurance company will need to pay for all of the costs of treating your cancer in this study except for those described below in this section. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment. Medicare should be considered a health insurance provider.

01/12/05

Genentech will provide you with the bevacizumab free-of-charge for this study through the National Cancer Institute. Bevacizumab is the common name for the commercial drug Avastin. The bevacizumab used in this trial, however, is for use in research studies only and may be made at locations different from those where Avastin is made. Although some differences may exist, bevacizumab for research use and the commercial drug, Avastin, are manufactured by a similar process, meet similar standards for final product testing, and are expected to be very similar in safety and effectiveness.

Sanofi-Synthelabo will provide you with the oxaliplatin free-of-charge through the National Cancer Institute. However, you or your health plan will need to pay for costs of the supplies and personnel who give you the drugs. Every effort will be made to ensure adequate supplies of both the bevacizumab and oxaliplatin, free-of-charge, for all patients. Either bevacizumab or oxaliplatin may become commercially available for your stage of colon cancer during this study. If this happens, there is a possibility that you and/or your health plan may have to pay for the

drug needed to complete the study. Your study doctor will discuss this with you if this occurs. 5-FU and LV will not be provided for free with this study.

Neither you nor your healthcare insurer will be charged for the cost of the blood and urine tests done solely for the purpose of the C-08 study. This includes the following tests:

- urine tests done after you enter the study, and
- blood tests to look at bevacizumab antibody levels and the amount of bevacizumab in the blood done for patients in Group 2 during years 1 and 2.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site. Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

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

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

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

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

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

The Data Monitoring Committee (DMC), an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study. You may be asked to sign another consent form in response to new information.

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

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____***(insert doctor's name and phone number).***

For questions about your rights while taking part in this study, call the _____ ***(insert the institution's name)*** Institutional Review Board (IRB) (a group of people who review the research to protect your rights) at _____ ***(insert IRB phone number).***

(If your institution is using the NCI Central IRB, insert the following sentence: **You may also call the Operations Office of the NCI Central Institutional Review Board [CIRB] at 888-657-3711 [from the continental U.S. only].)**

Additional tests for the NSABP C-08 study

The following section of the informed consent form is about additional research studies that may be done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be part of the main study even if you say "no" to taking part in these additional studies.

Consent for use of blood and tissue for future research

About using blood and tissue for future research: The NSABP would like to keep some of the tissue that was taken during your colon surgery and some of the blood that is taken during the study but is not used for other tests. If you agree, the blood and tissue samples will be kept and may be used in future research to learn more about cancer and other diseases. The blood and tissue samples will be given only to researchers approved by the NSABP. Any research study using your samples must also be approved by an IRB. The research that may be done with your blood and tissue samples is not designed to specifically help you. It might help people who have cancer and other diseases in the future. Reports about research done with your samples will not be given to you or your doctor. These reports will not be put in your health records. The research using your blood and tissue samples will not affect your care.

Things to think about: The choice to let the NSABP keep the blood and tissue samples for future research is up to you. No matter what you decide to do, it will not affect your care in this study. If you decide now that your blood and tissue samples can be kept for research, you can change your mind at any time. Just contact your study doctor and let him or her know that you do not want the NSABP to use your blood and tissue samples and they will no longer be used for research. Otherwise, they may be kept until they are used up, or until the NSABP decides to destroy them.

In the future, people who do research with your blood and tissue samples may need to know more about your health. While the NSABP may give them reports about your health, they will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes blood and tissue samples are used for genetic research (about diseases that are passed on in families). Even if your blood and tissue samples are used for this kind of research, the results will not be told to you and will not be put in your health records.

Your blood and tissue samples will be used only for research and will not be sold. The research done with your samples may help to develop new products in the future, but you will not get paid.

Benefits and risks: The possible benefits of research from your blood and tissue include learning more about what causes cancer and other diseases, how to prevent them and how to treat them. The greatest risk to you is the release of information from your health records. The NSABP will protect your records so that your name, address, and phone number will be kept private. The chance that this information will be given to someone else is very small. There will be no cost to you for any blood or tissue collected and stored by the NSABP.

Making your choice: Please read each sentence below and think about your choice. After reading each sentence, circle "yes" or "no." If you have questions, please talk to your doctor or nurse. Remember, no matter what you decide to do about the storage and use of your blood and tissue samples, you may still take part in the C-08 study.

By signing this form, you are agreeing that:

1. Your blood and tissue samples may be kept by the NSABP for use in future research to learn about, prevent, detect, or treat cancer.

   YES NO

2. Your blood and tissue samples may be used for research about other health problems (for example: causes of heart disease, osteoporosis, diabetes).

   YES NO

3. Your study doctor (or someone he or she chooses) may contact you in the future to ask you to take part in more research.

   YES NO

<u>The following research substudy only applies to female patients who are premenopausal:</u>*
*(*Your study doctor or his or her staff will tell you if this substudy applies to you.)*

Consent for blood tests to look at ovarian function

We want to find out how the drugs used in the study affect a woman's ovaries. If you are premenopausal, we would like to collect a blood sample five times. A sample will be collected before you begin your therapy, then every 6 months during the 2 years you are on the study. When possible, the blood will be collected at the same time as tests that are being done to

monitor your care. These blood samples will help us to see if the study drugs have an effect on your ovaries.

On behalf of Genentech, Inc., a central laboratory will test your blood samples. Neither you nor your doctor will receive the results of this testing. The testing will not affect your therapy or care during the study. There is no benefit to you from this testing. These samples are for research only; they are not necessary for your care. The greatest risk to you is the release of information from your health records. The NSABP will protect your records so that your name, address, and phone number will be kept private. The chance that this information will be given to someone else is very small. There will be no cost to you for this testing.

This testing will help Genentech, Inc. evaluate the safety of bevacizumab for patients like you. Genentech, Inc. will not be able to identify you because the blood samples they receive will be coded. The coded results will be sent to the NSABP for analyses. The blood samples will be destroyed after the testing and analyses are complete. They will not be used by Genentech, Inc. or the NSABP for any other purpose.

You may choose whether or not your blood samples can be collected and tested. No matter what you decide to do, it will not affect your care in this study. You may still take part in the C-08 study. If you have questions, please talk with your doctor or nurse.

Please circle "yes" or "no" below.

By signing this form, you are agreeing that:

4. Your blood samples may be collected and sent to Genentech, Inc. for testing to find out if bevacizumab has an effect on ovaries.

   YES NO

Where can I get more information?

- You may call the National Cancer Institute's (NCI's) Cancer Information Service at:

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

- You may also visit the NCI Web site at http://cancer.gov
- For the NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials
- For the NCI's general information about cancer, go to: http://cancer.gov/cancerinfo
- You may also visit the NSABP Web site at http://www.nsabp.pitt.edu

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

(NSABP institutions may insert or attach a list of materials that they can provide locally to patients regarding clinical trials, drug information, the institution/investigator, and/or the NSABP.)

Signatures

I have been given a copy of all sixteen pages of this form. I have read the consent form or it has been read to me. This information was explained to me and my questions were answered.

I agree to take part in this research study.

_____	_____
Date	Patient's signature
_____	_____
Date	Signature of person conducting the informed consent discussion

NSABP SAMPLE CONSENT FORM ADDENDUM #1

Consent Form Addendum #1 for A Phase III Clinical Trial Comparing Infusional 5-Fluorouracil (5-FU), Leucovorin, and Oxaliplatin (mFOLFOX6) Every Two Weeks with Bevacizumab to the Same Regimen without Bevacizumab for the Treatment of Patients with Resected Stages II and III Carcinoma of the Colon

[This information was not provided in the original document that patients signed. It is provided here as new information for patients who have received bevacizumab.]

New information about the NSABP C-08 study

When you entered the NSABP C-08 study, the NSABP promised to tell you about new information that might affect your participation in the trial. You are being told this new information because you are receiving bevacizumab.

You were told in the original consent form you signed that the drug, bevacizumab, may cause blood clots in your arteries. These blood clots may cause a stroke or heart attack. Several studies comparing chemotherapy with bevacizumab to chemotherapy alone have been done in patients with advanced cancers. Side effects of each study were looked at together. Problems due to blood clots in the arteries were seen in about 2% of patients receiving chemotherapy alone, and about 4.5% of patients receiving bevacizumab with chemotherapy. Patients who were 65 or older, or those with past problems with blood clots in their arteries, appeared to be at greatest risk for these problems.

The company that makes bevacizumab has continued to look at the results of these studies. They found that problems due to blood clots in the arteries were seen in about 2.9% of patients 65 or older receiving chemotherapy alone, and about 8.5% of patients 65 or older receiving bevacizumab with chemotherapy. Patients who were both 65 or older *and* reported a history of past problems with blood clots in their arteries appeared to be at even higher risk, although further study is required before an estimate of the risk can be provided. These conditions can be life-threatening or fatal.

Because of this new information, the NSABP has changed the study rules about who may join the NSABP C-08 study. Originally, patients who had a heart attack, angina (chest pain), or problems from blood clots in arteries in the past 6 months were not able to join the NSABP C-08 study. Now, patients cannot have had those problems in the 12 months before they join. Originally, patients could not have had symptoms of blood circulation problems in their legs or feet within the past 6 months unless these were mild symptoms caused by exercise. Now, patients who have any symptoms of blood circulation problems in their legs and feet cannot join the study even if these symptoms are related to exercise.

You should discuss your past health and the benefits and risks of bevacizumab with the researcher ***(insert name and phone number here)*** or with your regular doctor. They can help you decide if you should continue the bevacizumab. If the NSABP receives more information at any time about bevacizumab, the NSABP will tell you and your doctor.

Signatures

I have been given this new information that was not in the original consent form.

_____	_____
Date	Patient's Signature
_____	_____
Date	Signature of person conducting the informed consent discussion

NSABP SAMPLE CONSENT FORM ADDENDUM #2

Consent Form Addendum #2
for
A Phase III Clinical Trial Comparing Infusional 5-Fluorouracil (5-FU), Leucovorin, and Oxaliplatin (mFOLFOX6) Every Two Weeks with Bevacizumab to the Same Regimen without Bevacizumab for the Treatment of Patients with Resected Stages II and III Carcinoma of the Colon

[This information was not provided in the original consent form that patients signed. It is provided here as new information to be given to patients who are currently receiving bevacizumab or whose last dose of bevacizumab was within 3 months of the local approval of Amendments #6 and #7.]

New information about side effects related to bevacizumab:

When you joined the NSABP C-08 study, the NSABP promised to tell you about new information that might affect your care during participation in the trial. The NSABP would like to inform you of some additional side effects related to the use of bevacizumab.

You were told in the original consent form you signed that the drug bevacizumab may cause wound healing problems for patients who undergo surgery while receiving the drug. There have also been a few reports of patients receiving bevacizumab in other trials who developed complications with wound healing due to skin problems such as leg ulcers. These wound healing problems have been associated with infections that may take a long time to heal. Therefore, if you develop any skin problems, such as open sores or wounds, tell your study doctor.

Since you signed the original consent form, there have also been reports of patients receiving bevacizumab who experienced the following side effects:

- In addition to bowel perforation, perforation of other organs (rare, occurring in less than 3% of patients receiving bevacizumab).
- Fistula (an abnormal connection between parts of body systems such as the digestive, respiratory, urinary, and reproductive systems) that may require surgery (rare, occurring in less than 3% of patients receiving bevacizumab)
- High blood pressure of the blood vessels in the lungs (rare, occurring in less than 3% of patients receiving bevacizumab)
- Decreased red blood cell count that may cause tiredness and shortness of breath (less likely, occurring in 3-9% of patients receiving bevacizumab)
- Allergy-type symptoms like stuffy nose and sneezing (less likely, occurring in 3-9% of patients receiving bevacizumab)

If you have questions, you should discuss this with your study doctor ***(insert name and phone number here)***. If the NSABP receives more information at any time about bevacizumab that may affect you, the NSABP will tell you and your doctor.

Signatures

I have been given this new information that was not in the original consent form. I have been given a copy of this form.

_____	_____
Date	Patient's Signature
_____	_____
Date	Signature of person conducting the informed consent discussion