North Central Cancer Treatment Group

Randomized Phase III Trial of mFOLFOX7 or XELOX Plus Bevacizumab Versus 5-Fluorouracil/Leucovorin or Capecitabine Plus Bevacizumab as First-line Treatment in Elderly Patients with Metastatic Colorectal Cancer

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√Study contributor(s) not responsible for patient care.

Drug Availability
Commercial Agents: 5-fluorouracil, leucovorin, capecitabine, bevacizumab, oxaliplatin
IND #110231: Exempt

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NCI Version Date: November 29, 2011
# Cancer Trials Support Unit (CTSU)

## Address and Contact Information

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<tr>
<td><strong>The CTSU Public website is located at:</strong> <a href="http://www.ctsu.org">www.ctsu.org</a></td>
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<tr>
<td><strong>The CTSU Registered Member website is located at</strong> <a href="http://members.ctsu.org">http://members.ctsu.org</a></td>
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| **To submit site registration documents:** CTSU Regulatory Office  
1818 Market Street, Suite 1100  
Philadelphia, PA 19103  
Phone: 1-866-651-CTSU  
Fax: 215-569-0206 |
| **For patient enrollments:** Please refer to patient enrollment in Section 6.0 for instructions on using the OPEN system. All site staff (CTSU, NCCTG, and CALGB sites) will use OPEN to enroll patients to this study. |
| **Submit study data directly to NCCTG unless otherwise specified in the protocol:** NCCTG Operations Office  
NW Clinic 3-24  
200 First Street SW  
Rochester MN 55905  
Attention: QAS for N0949  
Note: NCCTG sites will submit all forms via NCCTG Remote Data Entry System, except for the Physician Fluoropyrimidine Treatment Decision Form, which will be faxed to the NCCTG Registration Office at (507) 284-0885 (see Section 6.39g).  
Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions. |

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://www.ctsu.org](https://www.ctsu.org). Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol.

CTSU sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.

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<td><strong>For patient eligibility or treatment-related questions</strong></td>
<td>Contact the NCCTG Research Base Quality Assurance Specialist (listed in Protocol Resources table on next page).</td>
</tr>
<tr>
<td><strong>For questions unrelated to patient eligibility, treatment, or data submission</strong></td>
<td>Contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or <a href="mailto:ctsucontact@westat.com">ctsucontact@westat.com</a>. All calls and correspondence will be triaged to the appropriate CTSU representative.</td>
</tr>
<tr>
<td><strong>For detailed information on the regulatory and monitoring procedures for CTSU sites</strong></td>
<td>Please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members’ website <a href="https://www.ctsu.org">https://www.ctsu.org</a></td>
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### Protocol Resources

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| Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission | Carol A. Leonard  
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Fax: (507) 284-9628  
E-mail: mcnamara.patricia@mayo.edu |

*No waivers of eligibility per NCI*
Schema

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Addendum 3

**Schema**

**Randomization**

**Arm A**
Fluoropyrimidine + bevacizumab

**Arm B**
Fluoropyrimidine/oxaliplatin + bevacizumab

Physician decision for fluoropyrimidine\(^1\)

**Arm C** \(^2\)
5-FU/LV + bevacizumab

**Arm D** \(^3\)
Capecitabine + bevacizumab

**Arm E** \(^2\)
mFOLFOX7 + bevacizumab

**Arm F** \(^3\)
XELOX + bevacizumab

Continue treatment until PD, unacceptable toxicity, patient withdrawal

Observation (28-42 days)

Event Monitoring (5 years)

**Neurotoxicity Assessment**
(Neurotoxicity Symptom Experience Diary)
Baseline → prior to every cycle → Observation Phase

**QoL Assessments**
(Fatigue/Uniscale, LASA, EQ-5D, WIWI\(^4\))
Baseline → every 3 months → Observation Phase

**Geriatric/Frailty Assessments**
(CSGA, Rockwood CSHA-CFS, NCCTG Brief Frailty Inventory)
Baseline → Observation Phase

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\(^1\)Following randomization, direct assignment to appropriate arm will be based on physician decision for fluoropyrimidine. **No crossover will be allowed.**

\(^2\)cycle = 14 days

\(^3\)cycle = 21 days

\(^4\)WIWI Questionnaire to be completed during Observation Phase only

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1.0 Background

1.1 Advanced Colorectal Cancer in the Elderly

In the United States, colorectal cancer (CRC) is a major health issue. CRC is the third most common cancer in both men and women and the second most frequent cause of cancer-related death in men and women combined. For 2009, it is estimated 146,970 new cases will be diagnosed, and 49,920 deaths will occur from colon and rectum cancer (Jemal et al. 2009). Approximately 19% of colon and rectum cancer cases are diagnosed as advanced stage disease, which has a 5-year relative survival rate of 11.6% (Altekruse et al. 2010).

Over the past 10 years, newer combination therapies for the adjuvant treatment of advanced CRC have significantly improved median overall survival (OS) rates, which are approaching two years. However, the majority of cancer research, in general, has been conducted on younger patient groups with elderly patients being significantly underrepresented in clinical trials (Hutchins et al. 1999). The current mean age of CRC patients in treatment trials is 60 years old (Rosati 2005). However, from 2002-2006, the median age at diagnosis was 71 years of age and the median age at death was 75 years of age for CRC patients (Horner et al. 2009). The fastest growing cohort of cancer patients are >65 years old and it is predicted that within 20 years, more than 75% of new CRC cases, and 85% of CRC deaths will be in patients over the age of 65 (Rosati and Bilancia 2008). In a retrospective analysis of colorectal phase II or III cooperative group clinical trials active from 1997-2000, 73% of the newly diagnosed late stage colorectal cancer cases were elderly; however, only 41% of the patients in late-stage clinical trials were elderly (Lewis et al. 2003). In addition to decreased number of older participants, clinical trials generally include only elderly patients with few comorbidities and good performance status (PS); therefore, the “normal” elderly population of CRC patients is not truly represented. Yet, despite the magnitude of this problem, treatment of elderly advanced CRC patients still remains a challenge.

Clinical studies have defined “elderly” as ranging from 65 to 85 years of age (Papamichael et al. 2009). Although the problem exists that there is no standard definition of “elderly”, many researchers consider 70 years of age an appropriate cut off definition for “elderly” patients in clinical trials (Folprecht et al. 2008). Given median age of diagnosis with colorectal cancer of 70 (Altekruse et al. 2010) and data showing similar efficacy and side effect profile among patients 70-75 years of age to their younger counterparts (Goldberg et al. 2006; Folprecht et al. 2008), we advocate using 75 years of age as an appropriate cut off point in advanced colon cancer, allowing enrollment of patients age 70-74 to encourage enrollment but limited to no greater than 25% of the cohort. The cohort of patients age 70-74 will provide descriptive benchmarks for toxicity, efficacy, and quality of life (QoL) comparison with the older group of patients >74 years of age as well as with the patients enrolled in the parallel Japanese trial which will enroll patients age 70 and higher.

Besides chronological age, several other issues exist that may influence treatment decisions for elderly patients: 1) age-related physiological changes, such as decreased renal and liver function, may affect drug metabolism and toxicity, 2) chronologic age may not necessarily correlate with physiological changes or functional status, 3) limited information is available related to tolerance and efficacy of chemotherapy in older individuals, 4) a disproportionate number of elderly patients are ineligible because of protocol exclusion criteria based on comorbidities or functional status, 5) increased comorbidities may reduce clinical benefit and
increase treatment toxicities, as well as affect overall survival (OS), 6) concerns about the susceptibility of elderly patients to the chemotherapy complications may compromise their quality of life, and 7) elderly patients have a diminished life expectancy (Carreca et al. 2005; Bruce et al. 2007; Rosati and Bilancia 2008). Consequently, as the mCRC patient population increases and as mCRC therapy options improve, there will be a greater need to validate and optimize palliative treatment standards for elderly and/or poor PS patients with mCRC, with prevention of treatment-related toxicities being one of the biggest challenges due to the heterogeneity of this population.

1.2 Clinical Trials of Elderly Patients with Metastatic Colorectal Cancer (mCRC)

1.21 Fluoropyrimidines (5-FU/Capecitabine) As Single Agent Therapy

Fluoropyrimidines, such as 5-FU, have been one of the most effective cytotoxic agents for treating mCRC for the past 40 years. 5-FU is an antimetabolite that interferes with DNA synthesis by inhibiting the enzyme thymidylate synthase (TS) and blocking the methylation reaction of deoxyuridylic acid to thymidylic acid. Also to a lesser extent, 5-FU can be incorporated into RNA; thus, inhibiting the formation of nuclear RNA (Pinedo and Peters 1988). Addition of a folate co-factor, leucovorin (LV), forms a stable ternary complex with the enzyme that prolongs the inhibition of TS, thereby enhancing 5-FU cytotoxicity (Mini et al. 1990). In a meta-analysis of 3,300 patients randomized in 19 trials, there was a two-fold increase in tumor response rates (21% vs. 11%) and a small significant increase in OS for 5-FU/LV compared to 5-FU alone (median survival, 11.7 v 10.5 months, P=.004) (Thirion et al. 2004).

Capecitabine, an oral fluoropyrimidine, is metabolized to 5-FU in three enzymatic steps. Oral availability of capecitabine offers improved patient acceptability compared to the traditional intravenous 5-FU/LV due to convenience of treatment at home, reduction in hospital/office visits, and reduced pain and discomfort of intravenous administration. In two phase III mCRC trials, capecitabine compared to 5-FU/LV in the first-line setting achieved a superior response rate (25.7% versus 16.7%, P<0.0002) and at least equivalent median time to disease progression (4.7 months vs. 4.8 months, respectively) and OS (13.1 months vs. 13.0 months, respectively) (Twelves and Group 2002). Patients receiving capecitabine vs. 5-FU/LV also experienced significantly less diarrhea, stomatitis, nausea, alopecia and grade 3 or 4 neutropenia (P <0.001), but increased hand–foot syndrome (Cassidy et al. 2002).

With regards to fluoropyrimidine treatment in elderly mCRC patients, a retrospective pooled analysis of 22 European trials investigating different 5-FU-based regimens from 1982 to 1996 identified a total of 629 elderly patients (≥70 years of age) out of 3825 5-FU-treated patients (Folprecht et al. 2004). The investigators found no significant difference in OS (10.8 months vs. 11.3 months, P=0.31) or in response rate (23.9% vs. 21.1%, P=0.14) between elderly patients and younger patients; however, PFS was slightly extended in elderly patients (5.5 months vs. 5.3 months, P=0.01). In both age groups, response rate, OS, and PFS were significantly increased in patients treated with infusional 5-FU compared with patients treated with bolus 5-FU.
In a second pooled analysis of four North Central Cancer Treatment Group (NCCTG) trials testing 5-FU with or without LV, 1748 advanced CRC patients were divided into four quartile-based age groups, ≤55, 56-65, 66-70, and >70 years of age (D’Andre et al. 2005). No significant difference was found in median OS (12 months in patients ≤55 years vs. 10.4 months in patients >70 years, P=0.42) or in median time to progression (range 5.3 to 6.5 months in the four age groups, P=0.25). The response rates (range 27%-30%) did not differ by age group (2-sided; P=0.90), although response rate was significantly lower for patients with higher performance status scores (30% for score of 0/1; 17% for 2/3; 2-sided; P=0.001). Compared to patients ≤65 years of age, patients older than 70 years of age had modestly higher rates of ≥ grade 3 toxicity overall (53% vs. 46%, P=0.01) and higher rates of diarrhea (21% vs. 16%, P=0.01), stomatitis (17% vs. 13%, P=0.03), and infection (4% vs. 2%, P=0.02). Toxicity rates were similar between patients 66-70 years of age and patients older than 70 years of age.

Prospectively, researchers have shown that 5-FU is well tolerated in elderly mCRC patients (Mattioli et al. 2001). Sixty-two previously untreated advanced CRC patients aged ≥ 70 years were enrolled in a study assessing activity and toxicity of the de Gramont schedule. Median age was 75 years (range 70-88 years). Response rate was 20%, median PFS was 5 months, and OS was 13 months. Treatment was very well-tolerated. The only ≥grade 3 hematological toxicity observed was anemia (grade 3, 3%); there were no ≥grade 3 non-hematological toxicities (Mattioli et al. 2001).

In addition, researchers have demonstrated that oral capecitabine is also well tolerated in elderly mCRC patients (Feliu et al. 2005; Petrioli et al. 2008). In the study by Petrioli et al., 29 elderly patients (>75 years of age) received continuous 2000 mg daily of capecitabine. There were no grade 4 toxicities observed and only one patient had grade 3 nausea and vomiting and one patient had grade 3 diarrhea. The response rate was 22.2%, the median time to progression was 4.4 months, and the median survival was 9.5 months (Petrioli et al. 2008). In a second study by Feliu and colleagues, 51 elderly patients (≥70 years of age) received 1,250 mg/m2 twice per day on days 1-14 of a three week cycle. Overall response rate was 24%, median time to disease progression was 7 months, and median overall survival was 11 months. Six patients (12%) experienced grade 3 and 4 adverse events, with the most common events being diarrhea, hand-foot syndrome, and thrombocytopenia (Feliu et al. 2005).

The studies described above demonstrate the efficacy and tolerability of first-line fluoropyrimidine-based regimens in treating elderly mCRC patients, with response rates ranging from 22.2%-29%, median time to progression ranging from 4.4-7 months, and median overall survival ranging 9.5-13.1 months.
1.22 Oxaliplatin in Combination with Fluoropyrimidines

Oxaliplatin has shown limited activity in colorectal cancer as a single agent compared to 5-FU/LV (Rothenberg et al. 2003); however, oxaliplatin combined with infusional 5-FU/LU exhibits a synergistic effect. Two phase III trials have compared 5-FU/LV plus oxaliplatin with 5-FU/LV as first-line therapy for patients with advanced colorectal cancer (de Gramont et al. 2000; Giacchetti et al. 2000). In these studies, there was a significant increase in response rates (approximately 50%) and PFS (range 8.7-9 months), but no significant improvement in median OS (range 16.2-19.9 months). Grade 3/4 neutropenia (41.7% vs. 5.3%) and diarrhea (11.9% vs. 5.3%) were more common in the oxaliplatin-containing treatment arms (de Gramont et al. 2000). On January 9, 2004, the U.S. Food and Drug Administration approved oxaliplatin for injection (Eloxatin™, a trademark of Sanofi-aventis.), for use in combination with infusional 5-FU/LV for the initial treatment of advanced colorectal cancer (http://www.cancer.gov/cancertopics/druginfo/fda-oxaliplatin#Anchor-Initia-

Several retrospective analyses have examined the combination of a fluoropyrimidine plus oxaliplatin as first-line treatment in elderly patients with mCRC (Twelves et al. 2005b; Goldberg et al. 2006; Figer et al. 2007; Arkenau et al. 2008; McKibbin et al. 2008). In a national, retrospective chart review of 520 patients, McKibbin et al. compared the proportion of younger (age ≤65 years, n=239) versus older (age >65 years, n=281) advanced CRC patients receiving first-line doublet chemotherapy (fluoropyrimidine with either oxaliplatin or irinotecan). Eighty four percent of the younger patients compared to 58% of elderly patients received first-line doublet chemotherapy (P<0.001), demonstrating that elderly patients were less likely to receive first-line doublet chemotherapy compared to younger patients. Further analyses of patients > 70 years of age (n=205) and >75 years of age (n=125), showed that initial treatment with doublet chemotherapy continues to decrease as patients age (53% and 42%, respectively). Specifically with regards to treatment with a fluoropyrimidine with or without oxaliplatin, 58% and 14% of the younger patients received oxaliplatin plus a fluoropyrimidine or fluoropyrimidine alone, respectively compared to 43% (P<0.001) and 39% (P<0.001) of the older patients receiving oxaliplatin plus a fluoropyrimidine or fluoropyrimidine alone. Thus, as patient age increased, use of combination treatment decreased. There were no significant differences between younger and older patients with regards to treatment delays, dose modifications, or treatment discontinuation in patients treated with fluoropyrimidine either alone or with oxaliplatin (all P>0.2). Moreover, there were no differences in adverse event toxicity between younger and older patients treated with fluoropyrimidine alone. In contrast, increased neutropenia (P=0.03) was observed in the younger patients and increased diarrhea (P<0.01), dehydration (P=0.03), and neurotoxicity (P=0.02) was observed in the older patients. Finally, there was a significant difference in median survival time between the elderly (19.1 months) and the younger (24.5) patients (P<0.01). However, in a proportional hazards model which included age, performance status (PS) score, and initial doublet therapy, the adjusted hazard ratio for elderly patient mortality was 1.19 (P=0.03); however, initial doublet therapy did not significantly reduce the HR, but PS score of 2 or 3 compared to 0 or 1 independently predicted a higher risk for mortality.
In a phase II study, mCRC patients were treated with first-line oxaliplatin 130 mg/m² intravenously on day 1 followed by oral capecitabine 1,000 mg/m² twice daily for 14 days every 3 weeks (XELOX) (Twelves et al. 2005b). There were 52 younger patients (< 65 years of age) and 44 older patients (≥ 65 years of age) enrolled in this study. XELOX efficacy and safety profile was similar between the younger and older patients. Both age groups received a median of 8 cycles with response rates of 58% and 52% in younger versus older patients, respectively. There was no significant difference in time to disease progression (P=0.85) and OS (P=0.65) in younger versus older patients. The safety profile, which included incidence of adverse events (including grade 3/4), dose reductions, and withdrawals because of adverse events, were similar between the patients < 65 years of age and the patients ≥ 65 years of age.

Goldberg and coauthors performed a retrospective analysis of four adjuvant clinical trials (n=3,742) comparing the safety and efficacy of 5-FU/LV plus oxaliplatin (FOLFOX4) administered bimonthly in younger patients and older patients (≥70 years of age, n=614). One of these studies examined FOLFOX4 in Stage II/III CRC patients (Andre et al. 2004), whereas the other studies used FOLFOX4 as 1st line (de Gramont et al. 2000; Goldberg et al. 2004) and 2nd line (Rothenberg et al. 2003) treatment in advanced CRC patients. There was no increase in severe neurologic adverse events (14% vs. 12%; P=0.37), diarrhea (11% vs. 13%; P=0.38), nausea/vomiting (9% vs. 7%; P=0.38), infection (5% vs. 4%; P=0.57), overall incidence of grade ≥ 3 toxicity (63% vs. 67%; P=0.15), or 60-day mortality (1.1% vs. 2.3%; P=0.20) in elderly patients compared to younger patients, respectively. However, grade ≥3 neutropenia (43% v 49%; P = .04) and thrombocytopenia (2% v 5%; P = .04) were both significantly higher in older patients. Odds ratios for response rates (in advanced disease) ranged from 1.65-7.22 in favor of FOLFOX4, and FOLFOX4 was associated with improved progression or recurrence free-survival (hazard ratio, 0.70 for younger patients and 0.65 for older patients; P=0.42), and improved OS (hazard ratio, 0.77 for younger and 0.82 for older patients; P=0.79). Overall, FOLFOX4 safety profile and efficacy in elderly patients (≥70 years of age) with CRC was similar to that observed in younger patients (<70 years of age) (Goldberg et al. 2006).

In the OPTIMOX1 study, 620 patients, including an exploratory cohort of 37 patients aged 76-80, were randomized to receive first-line treatment with either FOLFOX4 (LV 200 mg/m² followed by 5FU bolus 400 mg/m² and 22-hour infusion 600 mg/m² on 2 consecutive days with oxaliplatin 85 mg/m² on Day 1) every 2 weeks (arm A, n=20 elderly patients), or FOLFOX7 (a new oxaliplatin stop-and-go strategy; LV 400 mg/m² followed by a 5FU 46-hour infusion 2400 mg/m² and oxaliplatin 130 mg/m² on Day 1, every 2 weeks) for 6 cycles, maintenance with 12 cycles of simplified 5FU/LV, and reintroduction of FOLFOX7 for 6 cycles (arm B, n=17 elderly patients). The overall response rate was 59.5% (65% in arm A and 53% in arm B), median PFS was 9.0 months (7.6 months in arm A and 9.4 months in arm B), and median OS was 20.7 months (14.0 months in arm A and 25.1 months in arm B) in the older patient cohort. This was comparable to that observed in the younger patients: overall response rate 59%, PFS 9.0 months (P=0.63), and OS 20.2 months (P=0.57). There was a trend for older patients to experience increased overall grade 3 or 4 toxicity than younger patients (65% versus 48%, P=0.06), mainly due to increased neutropenia [41% (55% in arm A and 24% in arm B) vs. 24%, P=0.03] and neurotoxicity [22% (4 patients in each arm) vs. 11%, P=0.06] (Figer et al. 2007).
Finally, in a more recent retrospective analysis of a phase III trial, Arkenau and colleagues (Arkenau et al. 2008) compared younger (n=336) and elderly patients aged ≥70 years of age (n=140) receiving first-line treatment with either 5-FU/LV/oxaliplatin (FUFOX) or capecitabine/oxaliplatin (XELOX). The response rate was 52% versus 49% and median PFS was 7.5 months and 7.7 months (P=0.54; HR, 1.07; 95% CI, 0.86-1.34) between the younger (<70 years of age) and elderly (≥70 years of age) patients, respectively. In elderly patients, there was no difference between length of FUFOX (7.9 months) or XELOX (7.6 months) chemotherapy treatment and the median OS when treated with FUFOX (14.4 months) versus XELOX (14.2 months). However, median OS in elderly patients was 14.4 months versus 18.8 months in younger patients (P=0.013; HR, 1.37; 95% CI, 1.07-1.76). Both treatments were well tolerated with grade 3/4 toxicities being similar between the younger and older cohorts, although more gastrointestinal and fewer neurosensory side effects were observed in the elderly compared to the younger group of patients.

Several studies have prospectively examined the use of fluoropyrimidines with oxaliplatin in the first-line setting in elderly patients with mCRC (Comella et al. 2005; Mattioli et al. 2005; Feliu et al. 2006; Arkenau et al. 2008; Sastre et al. 2009). Mattioli et al. (Mattioli et al. 2005) examined the feasibility, efficacy, activity of daily living (ADL) and instrumental activity of daily living (IADL) of first-line treatment with 5-FU/LV and bi-fractionated oxaliplatin regimen in elderly patients with mCRC. Seventy seven evaluable patients, median age 75 years, received oxaliplatin 45 mg/m², LV 200 mg/m², 5-FU 400 mg/m² and 22 h continuous infusion of 5-FU 600 mg/m² i.v. on days 1 and 2, every 2 weeks. Overall response rate was 51%, with 7 CR and 32 PRs. Canadian NCI grade 3/4 toxicities included neutropenia (32%), diarrhea (10%), sensory neuropathy (6%), mucositis (4%), and fatigue (4%). In addition, these researchers showed that ADL and IADL scores did not change significantly during treatment (Mattioli et al. 2005).

Two studies have examined the combination of capecitabine and oxaliplatin alone. In the study by Comella and coworkers, mCRC patients aged 70-81 years (n=35), were treated with a combination of oxaliplatin (i.v. over 2 h on day 1) and capecitabine (orally twice a day from day 2 to day 15). For the first cycle, starting doses were 85 mg/m² for oxaliplatin, and 2000 mg/m² per day for capecitabine. Alternated dose escalations for both drugs were planned over the first three cycles for each patient. Overall response rate (two patients with CR and 12 with PR) was 40%, median PFS was 6.9 months, and OS was 14.1 months. There were no grade 4 adverse events and 10 (29%) cases of grade 3 toxicity (any type) were reported, including neuropathy (11%), diarrhea (9%), abdominal symptoms (pain, nausea, or vomiting) (6%) patients, and hand and foot syndrome (3%) (Comella et al. 2005). In a second study by Feliu et al., fifty patients with mCRC aged ≥70 years received 130 mg/m² oxaliplatin on day 1 followed by oral capecitabine 1000 mg/m² twice daily on days 1-14 every 3 weeks. Thirty percent had PR, and 6% had CR, with an overall response rate was 36%. The median times to PD and OS were 5.8 months and 13.2 months, respectively. Grade 3/4 adverse events were observed in 28% patients: 22% diarrhea, 16% asthenia, 14% nausea/vomiting, 6% neutropenia, 6% thrombocytopenia, and 4% hand-foot syndrome. There was one treatment-related death from diarrhea and sepsis (Feliu et al. 2006).
Finally, Sastre et al. compared first-line treatment of fluoropyrimidine plus oxaliplatin between elderly versus young mCRC patients in a Phase III trial. Patients (n=348) were randomized to capecitabine 1000 mg/m² (12 h), days 1-14, plus oxaliplatin 130 mg/m² day 1, every 3 weeks (XELOX) or weekly infusional 5-FU 2250 mg/m² over 48 h plus bimonthly oxaliplatin 85 mg/m² (FUOX). Overall response rate was 34.9% and 44.7% for patients ≥70 years and patients <70 years, respectively (P=0.081). There was no difference in time to progression (TTP; 8.3 months and 9.6 months, P=0.114) and in median OS (16.8 months and 20.5 months, P=0.74) between patients ≥70 years and patients <70 years of age, respectively. With XELOX, grade 3/4 diarrhea was higher in elderly patients compared to younger patients (25% vs. 8%, respectively, p=0.005). For FUOX, only paresthesia was significantly lower in patients ≥70 years (53%) versus patients <70 years (71%) of age (P=0.032) (Sastre et al. 2009).

The studies described above demonstrate addition of oxaliplatin to fluoropyrimidine-based (i.e., 5-FU or capecitabine) therapy is generally well tolerated, and compared to fluoropyrimidine alone, improved response rates (range 34.9%-59.5%), increased median PFS (range 5.8-9.0 months), and increased median OS (range 13.2-20.7 months) are observed in elderly patients with mCRC.

1.23 Bevacizumab in Combination with Fluoropyrimidine ± Oxaliplatin

1.231 Bevacizumab

It is well established that new tumor blood vessel growth (angiogenesis) for delivery of oxygen and nutrients to cancer cells is essential for solid tumor growth and invasion (Folkman 1971). Normal blood vessels are highly ordered structures consisting of endothelial cells (ECs), pericytes, and a basement membrane, which are tightly regulated by a balance of pro- and anti-angiogenic factors (Jain 2003; Shojaei and Ferrara 2008). However, tumors exhibit an imbalance between these pro- and anti-angiogenic factors resulting in tumor vasculature that is structurally and functionally abnormal (Jain 2001; Jain 2003; Jain 2005; Shojaei and Ferrara 2008). Structurally within the tumor vessels, the ECs have an irregular morphology, pericytes are missing or loosely attached, and the basement membrane thickness is irregular or loosely attached to the ECs and pericytes, making the vasculature architecture appear dilated, tortuous, sac-like, and leaky (Jain 1988; Jain 1994; Morikawa et al. 2002; Baluk et al. 2003; Winkler et al. 2004; Jain 2005; Shojaei and Ferrara 2008). In addition, proliferating tumor cells compress the tumor blood vessels, also contributing to the aberrant morphology (Padera et al. 2004). These structural abnormalities affect vascular function by impairing blood flow and increasing vessel hyperpermeability (Jain 1994; Baish and Jain 2000; Jain 2001; Yang et al. 2005; Fukumura and Jain 2007). Taken together, these structural and functional blood vessel abnormalities, along with the fact that tumors lack functional lymphatic vessels, result in a significant increase in interstitial fluid pressure (IFP) within the tumor, creating a physiological barrier that impedes drug delivery to the tumor (Jain 2001; Heldin et al. 2004; Jain 2005; Yang et al. 2005; Fukumura and Jain 2007). In addition to increased IFP,
heterogeneic blood flow in the tumor vascular network can induce hypoxia and acidosis within the tumor, thus affecting the efficacy of radiation and cytotoxic therapies, as well as altering the regulation of pro- and anti-angiogenic factors (Jain 2001; Jain 2005; Yang et al. 2005; Fukumura and Jain 2007).

Several pro- and anti-angiogenesis factors have been identified, with vascular endothelial growth factor (VEGF), also known as vascular permeability factor, being the most potent mediator of angiogenesis (Folkman 1995). VEGF is released by tumor cells in a paracrine manner to activate the proliferation of neighboring EC (Dvorak et al. 1995; Ferrara and Davis-Smyth 1997). VEGF binds to two potential receptors, VEGFR1 (Flt-1) and VEGFR2 (KDR), which are present exclusively on vascular EC. Ligand-receptor binding initiates a cascade of phosphorylation events triggering a variety of signaling processes including EC proliferation, migration, survival, vascular permeability, and extracellular matrix remodeling. Researchers have shown that blocking VEGF signaling can revert tumor vasculature back to a “normalized” state by restoring the balance of pro- and anti-angiogenic factors, decreasing leakiness and IFP, and improving blood flow and tumor oxygenation, which can aid in enhanced drug delivery to the tumor (Jain 2001; Jain 2005).

In most human cancers, elevated VEGF expression positively correlates with microvessel density and is associated with worse prognosis. Bevacizumab, a recombinant humanized version of a murine anti-human VEGF monoclonal antibody, has been clinically tested as a single agent and in combination with cytotoxic chemotherapy in treatment of a number of metastatic solid tumor types, including colorectal cancer (Hurwitz et al. 2004; Kabbinavar et al. 2005b; Giantonio et al. 2007; Hochster et al. 2008; Saltz et al. 2008). Neutralizing antibodies, such as bevacizumab which directly targets the angiogenic signaling molecule VEGF, demonstrate tumor vasculature can transiently revert back to a normalized state (Yuan et al. 1996; Jain 2001; Tong et al. 2004; Winkler et al. 2004; Jain 2005). Both preclinical and clinical studies have shown that anti-angiogenic treatment, which normalizes tissue vasculature, exhibits synergistic therapeutic effects when combined with cytotoxic therapy, thus improving delivery and efficacy of radiotherapy and cytotoxic drugs (Wildiers et al. 2003; Tong et al. 2004; Willett et al. 2004; Huber et al. 2005; Jain 2005; Willett et al. 2005; Yang et al. 2005). Several phase III trials have demonstrated that the combination therapy with bevacizumab and FOLFOX chemotherapy results in statistically significant increased PFS in metastatic CRC patients independent of KRAS status (Ince et al. 2005; Giantonio et al. 2007; Bokemeyer et al. 2008; Saltz et al. 2008). Thus, the majority of mCRC patients in the United States currently receive first-line therapy with oxaliplatin combined with 5-FU and bevacizumab.
1.232 Relevant Clinical Trials with Elderly Patients

Results from the Bevacizumab Regimens: Investigation of Treatment Effects and Safety (BRiTE) observational cohort study demonstrated the median OS in the overall BRiTE population was 25.1 months and that continuation of bevacizumab beyond first disease progression was associated with improved OS (HR, 0.48; P<0.001) (Grothey et al. 2008a). Researchers have subsequently performed a subgroup analyses of elderly patients (≥65 years of age) that were enrolled in the BRiTE study (Sugrue et al. 2007; Kozloff et al. 2008a; Kozloff et al. 2008b). Of the 1953 patients enrolled in BRiTE, 896 patients (45.9 %) were ≥65 years of age (533 patients were 65-74 years of age, 363 patients were ≥75 years of age, and 161 patients were ≥80 years of age). In this subgroup analysis, administration of FOLFOX (61.3% vs. 37.9%) and post-progression treatment with bevacizumab (38.6% vs. 22.4%) decreased, while administration of bolus 5-FU/LV (3.2% vs. 21.1%) increased as patients aged. The BRiTE study demonstrated bevacizumab-targeted safety and PFS were comparable between elderly and younger patients, despite the reduced use of FOLFOX/bevacizumab and increased use of fluoropyrimidine/bevacizumab treatment. However, median OS was lower in elderly patients (≥65 years of age) compared to younger patients (<65 years of age). In multiple regression analyses including various baseline factors, age was not a significant factor for predicting incidence of GI perforation, bleeding/wound healing complications or adverse toxic events in patients treated with bevacizumab. Median PFS was 10.2, 9.7, 9.8, and 9.2 months and median OS was 28.0, 21.3, 19.5, and 17.3 months for patients <65, 65-74, ≥75, and ≥80 years of age, respectively. Multivariate analyses showed that the median OS differences could be due to poorer baseline performance status, a decrease in overall exposure to chemotherapy agents, and a significantly lower percentage of elderly patients receiving second-line therapy compared with the younger cohort. Results from this subgroup analyses demonstrate that age alone should not be a deterrent for providing bevacizumab-containing treatment in elderly mCRC patients (Sugrue et al. 2007; Kozloff et al. 2008a; Kozloff et al. 2008b).

Additionally, pooled efficacy data from two placebo-controlled studies were retrospectively analyzed for OS, PFS, and objective response (Kabbinavar et al. 2009). Metastatic CRC patients ≥65 years of age were randomized to receive first-line treatment with bevacizumab plus fluorouracil-based chemotherapy (n = 218) or placebo plus fluorouracil-based chemotherapy (n = 221). Median OS (19.3 months vs. 14.3 months) and median PFS (9.2 months vs. 6.2 months) were statistically improved in patients treated with bevacizumab plus chemotherapy compared to patients treated with placebo plus chemotherapy, respectively. However, there was no difference in objective response rates (34.4% vs. 29.0%) in patients treated with bevacizumab plus chemotherapy compared to patients treated with placebo plus chemotherapy, respectively (Kabbinavar et al. 2009).
Although there hasn’t been a clinical trial prospectively examining bevacizumab in combination with fluoropyrimidine with or without oxaliplatin specific to the elderly population, one randomized, phase II trial compared 5-FU/LV plus bevacizumab (n=104) or placebo (n=105) as first-line therapy in mCRC patients who were considered non-optimal candidates for treatment with irinotecan first-line treatment (Kabbinavar et al. 2005b). Enrolled patients had one of the following characteristics: ≥ 65 years of age, Eastern Cooperative Oncology Group performance status (ECOG PS) 1 or 2, serum albumin ≤ 3.5 g/dL, or prior abdominal/pelvic radiotherapy. Eighty percent of the patients enrolled in this study were ≥65 years of age; 80/105 (76%) in the FU/LV/placebo cohort and 88/104 (85%) in the FU/LV/bevacizumab cohort were elderly patients. Overall, median PFS was statistically significant (9.2 months vs. 5.5 months, P=0.0002) and there were trends in response rate (26% vs. 15.2%, P=0.055) and duration of response (9.2 months vs. 6.8 months; P=0.088) in FU/LV/bevacizumab compared to FU/LV/placebo patients, respectively. There was no statistically significant difference in median OS between the FU/LV/bevacizumab patients and the FU/LV/placebo patients (16.6 months vs. 12.9 months, respectively, P=0.16). Not surprisingly, grade 3 hypertension was more common with bevacizumab treatment (16% vs 3%).

Finally, a small, single institution phase II study of 16 patients with mCRC ≥70 years of age demonstrated the feasibility and efficacy of a combination of capecitabine plus bevacizumab in this elderly patient population with TTP of 9.5 months and OS of 21.2 months (Puthillath et al. 2009).

1.3 Current Clinical Trial in Elderly Patients

1.3.1 Treatment Rationale

There are several FDA-approved first-line treatment options for mCRC patients, with the preferred options being combination 5-FU and oxaliplatin (FOLFOX) or irinotecan (FOLFIRI), with or without bevacizumab. The majority of mCRC patients in the United States currently receive first-line therapy with oxaliplatin combined with 5-FU/LV (FOLFOX) and bevacizumab, with limited available data evaluating the efficacy of monoclonal antibodies, such as bevacizumab and cetuximab, in the elderly patient population. Recently, an International Society of Geriatric Oncology (SIOG) task force provided the following recommendations: 1) fit, elderly mCRC patients benefit from systemic treatment, 2) continuous infusion versus bolus 5-FU is more effective and less toxic, 3) combination chemotherapy, with or without bevacizumab, should be the treatment of choice, 4) dose reduction according to creatinine clearance is necessary when capcitabine is administered, and 5) data for cetuximab and panitumumab treatment in the elderly is lacking and these antibodies should be used according to their licensed indication (Papamichael et al. 2009). In support of these recommendations, the studies described above clearly demonstrate fit, elderly mCRC patients benefit from combination treatment with fluoropyrimidine, oxaliplatin, and bevacizumab chemotherapy and this combination therapy is reasonably well tolerated, at least to the same extent as younger patients. Thus, age alone should not prevent elderly patients from receiving standardized chemotherapy or limit elderly patient participation in clinical trials. However, the
studies described above in elderly mCRC patients generally have excluded the unfit/frail, elderly population; therefore, this study fills an important need by providing therapeutic options for this growing underrepresented population, where historically, studies have been lacking.

As described above, retrospective analyses of first-line treatment with bevacizumab plus fluorouracil-based chemotherapy have demonstrated similar clinical benefit and safety profile between younger and older patients (Sugrue et al. 2007; Kozloff et al. 2008a; Kozloff et al. 2008b; Kabbinavar et al. 2009). Addition of bevacizumab to fluoropyrimidine-based treatment demonstrated an increase in median OS (19.3 months) and median PFS (9.2 months), but no significant difference in objective response rates (34.4%) (Kabbinavar et al. 2009). Based on these studies, the SIOG recommendations for treatment of elderly mCRC patients, and lack of studies in the frail, elderly population, this study will randomize mCRC patients \( \geq 70 \) years of age (patients 70-74 years limited to 25% of the study population) to receive either fluoropyrimidine-based therapy with oxaliplatin (i.e., modified FOLFOX7 [mFOLFOX7] or XELOX) plus bevacizumab or fluoropyrimidine (i.e., 5-FU/LV or capecitabine) plus bevacizumab (without oxaliplatin).

### 1.3.2 Treatment Efficacy and Safety

While oxaliplatin has been shown to be tolerable in elderly patients (Goldberg et al. 2006), it is associated with higher toxicity than fluoropyrimidine alone, and it is unclear if oxaliplatin is really needed to optimize efficacy in context of bevacizumab-based therapy (Kabbinavar et al. 2005a). Recent results of BRiTE registry suggest similar efficacy in terms of PFS for elderly patients compared with a younger cohort in spite of reduced use of FOLFOX + bevacizumab in favor of fluoropyrimidine + bevacizumab treatment (Kozloff et al. 2008b). Oxaliplatin-induced sensory neurotoxicity, which is cumulative in nature and often dose-limiting, is conceivably a serious concern in particular in elderly and frail patients. This toxicity limits the duration of oxaliplatin-based therapy so that in recent trials, which did not limit oxaliplatin-containing treatment cycles, more patients discontinued therapy due to neurotoxicity than due to tumor progression (Green et al. 2005; Saltz et al. 2008; Hecht et al. 2009). In a trial with first-line PFS as primary endpoint, this effect could conceivably compromise the interpretation of results and interfere with identifying whether the experimental arm was truly superior to the control arm in terms of delaying tumor progression. Allowing investigators to determine when oxaliplatin should be discontinued in view of emerging toxicity could lead to unbalanced distribution of duration of oxaliplatin between treatment arms, again potentially compromising the comparability of outcome measures between the regimens. Trials which mandated the discontinuation of oxaliplatin after a predefined number of cycles have been successfully conducted with clear evidence that this strategy does not compromise the overall outcome of therapy with regard to response rate, PFS and OS (Tournigand et al. 2006; Maindrault-Goebel et al. 2007; Punt et al. 2008; Grothey et al. 2008b). We therefore strongly recommend the discontinuation of oxaliplatin after eight treatment cycles of mFOLFOX7 (16 weeks) and after 5-6 treatment cycles of XELOX (15-18 weeks) when a planned cumulative dose of 680 mg/m\(^2\) (mFOLFOX7) or 650-780 mg/m\(^2\) (XELOX) oxaliplatin has been administered. In an analysis of N9741, this cumulative dose was found to be well tolerated and it was noted that almost all patients eventually classified as responders on the trial already had a response at this time point (Green et al. 2005; Saltz et al. 2008; Hecht et al. 2009).
Information from the BRiTE study indicated that besides a strong trend toward a higher rate of arterial thromboembolic events (ATE), bevacizumab-targeted safety data between elderly (≥65 years of age) and younger patients (<65 years of age) was comparable. ATEs following treatment with bevacizumab were more likely to occur in patients ≥65 years of age (P=0.082), patients who had a previous history of ATE (P=0.060), or patients with both risk factors (P=0.052) (Scappaticci et al. 2007). In addition to ATE, other common bevacizumab-related toxicities to monitor during the treatment of patients enrolled in this study include hypertension, gastrointestinal perforations, proteinuria, bleeding, wound healing complications, and bowel perforation (Brochure 2008).

1.33 Neurotoxicity Assessments

The healthcare research team (physician, institutional nurse, or certified research assistant [CRA]) will evaluate the patient for neurotoxicity at baseline, before starting a cycle of treatment, and 28-42 days following treatment termination. Oxaliplatin-specific scale grade (grade 0-none, grade 1-sensory symptoms of short duration, grade 2-sensory symptoms persisting between cycles, or grade 3-sensory symptoms causing functional impairment) will be evaluated and recorded on the Evaluation/Treatment Form and peripheral sensory neuropathy grade will be evaluated and recorded on the Adverse Event Form per the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grading. Standardized questions have been developed to assist in classifying patient-reported symptoms to determine peripheral sensory neuropathy grade (see Appendix III).

In addition, the patient will complete a Neurotoxicity Symptom Experience Diary (Appendix VI) at baseline, before starting a cycle of treatment (Appendix VIII), and 28-42 days following treatment termination (Appendix X). This tool will be used to characterize and quantify patient-reported neurotoxicity. A new booklet will be given to the patient for each treatment cycle and at the observation visit after patient discontinues treatment.

1.34 Patient Reported Outcomes – Adverse Events (PRO-CTCAE)

Recent literature has demonstrated differences in assessment of adverse events by patients and clinicians (Huschka et al. 2007; Sloan et al. 2007; Basch et al. 2009). In response to these findings NCI funded the development of a patient-reported outcome version of the CTCAE (contract HHSN261200800043C). Led by Dr. Ethan Basch, a multi-site team has developed the PRO-CTCAE which is presently undergoing validation testing within a number of studies including cooperative group trials and a primary validation study (MC1091). Support and oversight for the PRO-CTCAE contract is provided by representatives from NCI's Division of Cancer Control and Population Sciences, Division of Cancer Prevention, Community Oncology and Prevention Trials Research Group, Division of Cancer Treatment and Diagnosis, and the Center for Bioinformatics. The NCI is also working collaboratively with the Food and Drug Administration (FDA) to develop the PRO-CTCAE and to assure that the PRO-CTCAE will be compliant with the Medical Dictionary for Regulatory Activities (MedDRA). The PRO-CTCAE platform will be developed to be fully interoperable with caAERS, CDUS, and the caBIG Study Calendar, fully integrated...
with CTCAE v4, and mapped to MedDRA. The NCCTG has incorporated the PRO-CTCAE into a number of its trials in order to facilitate the incorporation of the patient perspective into adverse event assessment and to improve the precision with which such assessments are made.

Included in this study, patients will complete a subset of nine PRO-CTCAE (relabeled as Patient Reported Outcomes- Adverse Events for patients) items related to the expected adverse events related to this trial, namely neuropathy, nausea, diarrhea, hand/foot syndrome, and fatigue. These additional questions will take no longer than 5 minutes to complete and are included in the patient booklets in Appendices VI, VIII, and X.

1.4 Geriatric/Frailty Assessment and Quality of Life (QoL) Tools

1.41 Geriatric/Frailty Assessments

1.411 Cancer Specific Geriatric Assessment (CSGA)

Clearly, chronological age alone should not be considered the determining factor for the appropriateness of any particular treatment regimen, but patient’s performance status (PS), extent of comorbidity, as well as overall health must also be evaluated for determining optimal chemotherapy treatment options for these aging patients. In support of this, a pooled analysis of four NCCTG studies (n=1748), found PS, but not age, to be predictive of dose intensity, response rate, time to progression, and OS in advanced CRC patients (D'Andre et al. 2005). Moreover, comorbidities interfere with PS assessment (i.e., either Karnofsky or Eastern Cooperative Oncology Group); thus, PS may not be a reliable measurement in older versus younger patients (Balducci and Beghe 2000). Furthermore, physician assessment may not fully incorporate factors influencing functional status of older patients (Wedding et al. 2007). Therefore, careful consideration and evaluation of geriatric parameters should be integrated into the decision-making process to maximize treatment benefit.

Accordingly, a multidimensional evaluation tool for older patients, a comprehensive geriatric assessment (CGA), has become a useful aid for thoroughly reviewing and identifying issues in older cancer patients that may affect cancer treatment and evaluating these issues for tailoring the treatment of fit, vulnerable, or frail elderly patients (Balducci and Beghe 2000; Extermann and Hurria 2007; Brunello et al. 2009). Geriatric assessment allows for a derivation of life expectancy, physical function and reserve (Balducci 2007; Wedding et al. 2007). Functional status, a component of geriatric assessment, predicts survival, chemotherapy toxicity, postoperative morbidity, and mortality in several studies (Extermann and Hurria 2007). The composite assessment however can be time-consuming and labor-intensive and has not yet been shown to guide care in a prospective randomized trial.
The International Society of Geriatric Oncology (SIOG) created a task force that systematically reviewed the use of a CGA in cancer patients, and found there is strong evidence supporting CGA utilization and that a CGA may: 1) detect many problems missed by a regular oncologic assessment, 2) improve function and reduce hospitalization in elderly cancer patients, 3) improve patient survival, and 4) predict morbidity and mortality in older patients (Extermann et al. 2005; Extermann and Hurria 2007). Consequently, prospective trials utilizing a CGA to thoroughly identify, evaluate, and manage the treatment of elderly mCRC patients are justified.

The Cancer Specific Geriatric Assessment (CSGA) developed by Hurria et al is a more brief geriatric assessment developed in 40 cancer patients ≥ 65 years (Hurria et al. 2005). It includes seven domains reflective of the Comprehensive Geriatric Assessment developed by Balducci (Balducci 2005). The seven domains are as follows: (1) Functional status, (2) Comorbidity, (3) Cognition, (4) Psychologic, (5) Social functioning, (6) Social support, (7) Nutrition. Functional status includes 6 sub-domains as follows: (a) Activities of Daily Living, (b) Instrumental Activities of Daily Living, (c) Karnofsky Physician-Rated Performance Rating Scale, (d) Karnofsky Self-Reported Performance Rating Scale, (e) Timed Up and Go, (f) number of falls in the last six months. The nutrition domain includes 2 sub-domains of body mass index and percent of unintentional weight loss in the last six months. This abbreviated tool is a written questionnaire that has been evaluated for feasibility in a pilot study of 43 patients with cancer, mean age 74, the majority of whom had stage IV disease. Nearly 80% of this cohort completed the CSGA without assistance in an average time of 27 minutes (Hurria et al. 2005). The CSGA has been validated in written-format in a multi-center clinical trial and is being validated in computer-format in two simultaneous individual center trials. A predictive model for grade 3 or higher toxicity has been developed based on this study in the general older cancer population [Hurria, personal communication, CALGB spring meeting June 2010]. Factors noted to be predictive of grade 3 or higher toxicity included the following: hemoglobin (male: <11, female: <10), creatinine clearance (Jelliffe – ideal wt <34), falls in last 6 months (≥1), hearing impairment (fair or worse), physical limitation in walking 1 block, assistance required in medication intake, and decreased social activity. External validation in specific older cancer populations is warranted.

1.4111 CSGA – Patient Assessment

In addition to demographic information (marital status, household composition, employment status, and level of education; Section A in Patient Questionnaire), the following components of the CSGA will be assessed by the patient:

1.41111 Functional status (Section B through Section D in Patient Questionnaire) – Functional status is captured by 6 subdomains: Instrumental Activities of Daily Living (IADL), Activities of Daily Living (ADL), Karnofsky Physician-Rated Performance Rating Scale (KPPS), Karnofsky Self-
reported Performance Rating Scale (KPS), Timed Up and Go (TUG), and number of falls in last 6 months. The IADL is a subscale of the Older American Resources and Services Multidimensional Functional Assessment Questionnaire (OARS MFAQ) which was developed to assess level of function and has been validated among over 6,000 community-dwelling older persons (Fillenbaum and Smyer 1981; Fillenbaum 1985). The IADL subscale consists of questions rated on a three point Likert scale of independence in performing the activity. Normative data are available based on 2,146 elderly community residents (Fillenbaum 1985). The ADL is a subscale of the Medical Outcomes Study (MOS) Physical Health Scale. The scale includes items on vigorous activities (running, lifting heavy items) as well as basic activities (bathing and dressing). Items are rated on a three point Likert scale of independence of performing the activity. The total score is calculated by transforming mean averages into a 0 to 100 scale with higher scores indicating better functioning. Karnofsky Self-Reported Performance Rating Scale (KPS) assesses the patient’s perception of their performance status and is significantly related to morbidity and mortality from chronic illness (Wingard et al. 1991). The number of falls in the last 6 months will be assessed given their association with limitations in mobility and balance, possible correlation with neurologic impairment and subsequent risk of injury. The KPS and TUG will be performed by a trained member of the research team (physician, institutional nurse, or CRA) and are described below in Section 1.4112.

1.4112 Medication review (Section F in Patient Questionnaire) – Patients are asked to list the number and names of prescribed and over-the-counter medicines taken on a daily basis.

1.4113 Comorbidity (Section F in Patient Questionnaire) – The Physical Health Section subscale of the Older Americans Resource Scale (OARS) is used to assess the number and type of concurrent medical conditions a patient has and the degree to which they interfere with daily activities rated on a three point Likert scale. Additionally, data on the number of medications used is collected. This measure correlates well with the need for additional supportive services (Fillenbaum and Smyer 1981).

1.4114 Psychologic (Section G in Patient Questionnaire) – The Health Questionnaire is a 17 item scale evaluating the degree of emotional well-being (Stewart and Ware 1992). Items are rated on a six point Likert scale and correlates with patient levels of emotional distress. The mean score is transformed to a 0 to 100 scale with higher numbers indicating greater
levels of distress.

1.41115 Social Functioning (Section H in Patient Questionnaire) – The Social Activity subscale of the Medical Outcomes Study (MOS) Social Activity Limitations Measure is a 4 item scale evaluating the impact of physical or emotional problems on social activities (Stewart and Ware 1992). Items are rated on a five point Likert scale and correlates with patient levels of distress, pain and social limitations. The mean score is transformed to a 0 to 100 scale with higher numbers indicating greater levels of support.

1.41116 Social Support (Section I in Patient Questionnaire) – The Emotional/Information and Tangible subscales are two of four scales on the 20-item Medical Outcomes Study (MOS) Social Support Survey measuring a patient’s perception of available social support using a five point Likert scale (Stewart and Ware 1992).

1.41117 Questions Concerning the Questionnaire (Section J in Patient Questionnaire) - The final questions survey patient satisfaction with the CSGA.

1.4112 CSGA – Research Team Assessment

While the majority of the CSGA is patient-reported, three of the seven domains are performed by the research team – Karnofsky Physician-Rated Performance Rating Scale (KPPS), Timed Up and Go (TUG), and cognition via the Blessed Orientation-Memory-Concentration (BOMC) Test. These instruments will be administered by a trained member of the research team (physician, institutional nurse, or CRA). Training for conduction of the research team portion of the CSGA and supervision of the patient portion of the CSGA is provided through a webinar video posted on the CTSU website. Although this training is strongly recommended, it is not mandatory. The final slide of the 20-minute long video is a certification of training; please complete the certificate and email or fax it to the N049 research protocol specialist listed in the Protocol Resources section on page 3.

1.41121 Karnofsky Physician-Rated Performance Rating Scale (KPPS) (Section II in the Research Team Questionnaire) is a global measure of physical functional status (Karnofsky and Burchenal 1948). Patients are given a score on a numerical scale of 0 to 100.

1.41122 The Timed Up and Go (TUG) test (Section II in the Research Team Questionnaire) assess the time required for a patient to rise from a seated position, walk briskly 10 feet, turn and walk back and resume a seated position. Patients receive a score of 1 for each of the following: the use of arms to get up, unsteady steps, or time exceeding 10 seconds.
to complete the test. A higher score is correlated with functional dependence and mortality (Rockwood et al. 2000; Shumway-Cook et al. 2000; Nordin et al. 2006; Nordin et al. 2008).

1.41123 The Blessed Orientation-Memory-Concentration (BOMC) test (Sections III and IV in the Research Team Questionnaire) consists of 6 questions designed to screen for gross cognitive impairment (Katzman et al. 1983). Scores of $\geq 11$ indicate possible cognitive impairment, rendering the patient-reported data unreliable. Such data will not be used in the final data analysis. Physicians treating patients with scores of $\geq 11$ will be notified of the possible need for further cognitive evaluation as medically indicated.

1.41124 Nutrition (Section V in the Research Team Questionnaire) - Data on percentage of unintentional weight loss and body mass index will be collected. Unintentional weight loss is calculated as follows: Percent unintentional weight loss = (weight lost in last 6 months/baseline body weight) x 100. Body mass index (BMI) is calculated as follows: Body mass index = weight/(height)$^2$.

1.41125 Questions Concerning the Questionnaire (Section VI in Research Team Questionnaire) - The final questions survey research team satisfaction with the CSGA.

1.412 Rockwood Canadian Study of Health and Aging Clinical Frailty Scale (CSHA-CFS) (Rockwood et al. 2007)

Rockwood has demonstrated that a simple single-item measure of frailty consistent with the Extermann CGA recommendations can be prognostic for morbidity and mortality in elderly patients (Rockwood et al. 1999; Ravaglia et al. 2008). Although relatively new, his Canadian Study of Health and Aging Clinical Frailty Scale (CSHA-CFS) has sufficient preliminary data to suggest its use in the present study. It has been compared favorably to the 70-item CGA approach recommended by Extermann and others (Rockwood et al. 2007).

1.413 NCCTG Brief Frailty Inventory

The inclusion of a simple single-item frailty assessment and related activities of daily living impact assessment, the NCCTG Brief Frailty Inventory, will allow for further validation of the CSGA measure and allow us to explore the relative merit of a single-item versus a more detailed measure, as we have demonstrated in numerous other NCCTG studies (Sloan et al. 2007).

1.42 Quality of Life (QoL) Assessments
1.421 Fatigue/Uniscale Assessments

The Fatigue/Uniscale Assessments, a QoL tool routinely used in NCCTG treatment studies, will be used to measure QoL. Evidence has arisen indicating that baseline single-item assessments of fatigue and overall quality of life are strong prognostic indicators for survival in cancer patients, independent of performance status. This evidence was derived from two separate meta-analyses recently presented at ASCO, the first involving 23 NCCTG and Mayo Clinic Cancer Center oncology clinical trials, the second involving 43 clinical trials. Routine inclusion of these measures should be considered similar to that of including performance status, either as stratification or prognostic covariates (Tan et al. 2008; Sloan et al. 2009).

1.422 Linear Analog Self Assessment (LASA)

The Linear Analog Self Assessment (LASA) will be used to measure overall health-related QoL by assessing overall quality-of-life, mental well-being, physical well-being, and fatigue. LASA items have been validated as general measures of global QoL dimensional constructs in numerous settings (Grunberg et al. 1996; Gudex et al. 1996; Hyland and Sodergren 1996; Bretscher et al. 1999). A series of LASA items have been constructed and validated for use in multiple studies with similar populations (Bretscher et al. 1999). Dr. Sloan and colleagues have done extensive research on the application of single-item LASA measures for assessing a wide variety of patient reported outcomes including fatigue, peripheral neuropathy, hot flash activity, and anxiety. These single-item assessments have become the most-used assessment in all NCI-sponsored cancer control studies (Buchanan et al. 2005). Normative data have been obtained from various clinical populations enrolled in NCCTG clinical trials and from healthy participants attending an NCCTG annual meeting. Normative results indicate that, for example, in assessing overall QoL on a 0-100 point scale, healthy volunteers will average about 82, hospice patients will average 78, advanced cancer patients will average somewhere between 60 and 75, newly diagnosed patients will average between 50 and 60, and internal medicine residents will average 44. A score below 50 is indicative of a need for immediate exploration and intervention for the QoL deficit (Sloan et al. submitted). Due to recent research by NCCTG investigators (PI: Sloan), the NCCTG has decided to include LASA measures for overall QoL and fatigue in all future phase II and phase III clinical trials as an independent prognostic factor independent of performance status.

1.423 EQ-5D

The EQ-5D is a validated self-report, standardized measurement of health outcome used in a variety of clinical settings (Anderson et al. 1996; Conner-Spady et al. 2005; Wilson et al. 2006).

1.424 Was It Worth It (WIWI) Questionnaire

We have devised an assessment to provide researchers with feedback
regarding patient satisfaction related to their participation in clinical research, the Was It Worth It (WIWI) Questionnaire. This questionnaire is minimalist and efficient, asking only four key questions. These items are routinely included in NCCTG phase II and phase III treatment clinical trials and have indicated, among other things, that patient satisfaction is related to perceived quality of life and is unrelated to treatment outcome (Atherton et al. 2008).

1.43 Geriatric/Frailty and Quality of Life Assessment Study: Prognostic Ability and Between-arm Comparison

We hypothesize that the geriatric/frailty and QoL assessments will provide prognostic information. Specifically, the geriatric/frailty assessments will provide independent prognostic information with inferior PFS and OS, increased overall grade 3 and higher toxicity and decreased QoL for vulnerable and frail older patients. The QoL assessments will provide independent prognostic information with an inferior PFS and OS for those with poor baseline QoL (defined as a score of 5 or less on the SDS overall QoL question) (Sloan et al. 2007). The geriatric/frailty and QoL assessment data will be captured independently by both groups and will be available for analysis by both groups. The CALGB will have access to response rate, survival, toxicity, and QoL data for purposes of testing the proposed hypotheses.

The neurotoxicity, PRO-CTCAE, geriatric/frailty, and QoL instruments used in this study are described in detail above (Sections 1.33, 1.34, 1.41, and 1.42, respectively) and will only be mandatory for patients who are fluent in reading and speaking English. Neurotoxicity assessments and PRO-CTCAE will be completed at baseline, prior to every cycle during active treatment, and 28-42 days after termination of study treatment. Geriatric/frailty assessments will be performed at baseline and 28-42 days after termination of study treatment. QoL assessments will be performed at baseline, every three months during active treatment, and 28-42 days after termination of study treatment. Enrolled patients in the US cohort will complete the following assessments via the Patient Questionnaire Booklet at the time points indicated:

- Baseline Assessments (Appendix VI):
  - Neurotoxicity: Neurotoxicity Symptom Experience Diary
  - PRO-CTCAE
  - Geriatric/frailty: CSGA
  - Geriatric/frailty: NCCTG Brief Frailty Inventory
  - QoL: Fatigue/Uniscale Assessments
  - QoL: LASA
  - QoL: EQ-5D

- Active Treatment, Current Cycle Assessments (Appendix VIII):
  - Neurotoxicity: Neurotoxicity Symptom Experience Diary
  - PRO-CTCAE

- Active Treatment, Every 3 Months Assessments (Appendix IX):
  - QoL: Fatigue/Uniscale Assessments
  - QoL: LASA
- QoL: EQ-5D

- Observation Phase Assessments (Appendix X):
  - Neurotoxicity: Neurotoxicity Symptom Experience Diary
  - PRO-CTCAE
  - Geriatric/frailty: CSGA
  - Geriatric/frailty: NCCTG Brief Frailty Inventory
  - QoL: Fatigue/Uniscale Assessments
  - QoL: LASA
  - QoL: EQ-5D
  - QoL: WIWI Questionnaire

A trained member of the research team (physician, the institutional nurse, or CRA) will complete the following assessments for enrolled patients in the US cohort via the Research Team Questionnaire Booklet at the time points indicated:

- Baseline Assessments (Appendix VII):
  - Geriatric/frailty: CSGA
  - Geriatric/frailty: CSHA-CFS

- Observation Phase Assessments (Appendix XI):
  - Geriatric/frailty: CSGA
  - Geriatric/frailty: CSHA-CFS

1.5 Assessment of Pharmacogenetic Markers to Predict Tumor Response and Toxicity

We will collect pretreatment tumor specimens and blood products (i.e., plasma, serum, DNA, and white blood cells) for the following purposes: 1) DNA will be used to analyze relevant pharmacogenetic markers that may predict toxicity and/or tumor response, 2) pretreatment tissues will be collected for KRAS and BRAF status analysis (if KRAS and BRAF status is not available from the submitting institution) and for future studies to evaluate the association of tissue-based biomarkers and outcome, and 3) serially collected plasma and serum specimens (i.e., baseline, after 6 weeks of treatment, and at the time patient discontinues treatment) will be collected for future studies to analyze pharmacokinetics and circulating biomarkers prior to and during therapy, and to assess these alterations with outcome. (Detailed instructions regarding blood and tissue biospecimen collections are further outlined in Sections 14.0 and 17.0, respectively.)

Tumor response and adverse event variability in patients treated with therapeutic agents is influenced by genetics; therefore, it has become increasingly important to identify and develop predictive markers to guide the individualization of drug therapy. For example, the recent recognition of KRAS mutation status as a predictor of response to epithelial growth factor receptor inhibitors has allowed these inhibitors to be used in a more selective manner in colorectal cancer (Khambata-Ford et al. 2007). Thus, we hypothesize that polymorphic variants in molecular targets of the therapeutic agents used in this trial (i.e., fluoropyrimidines, bevacizumab, and oxaliplatin) and genes known to potentiate the aging process (e.g., insulin/insulin-like growth factor-I [IGF-I] axis) will be correlated with efficacy and/or tolerability of drug treatment.
Candidate gene pathway analyses and whole genome scans are common approaches for the identification of germline polymorphisms that contribute to a given phenotype. Most pharmacogenetic analyses have taken a candidate gene approach that utilizes biological data to guide the selection of drug response genes in a pathway. Pharmacogenetic studies of fluoropyrimidine, bevacizumab, and oxaliplatin molecular targets to be analyzed include, but are not limited to, \textit{DPYD} (van Kuilenburg 2004), \textit{TYMS} (Marsh 2005; Gibson 2006), \textit{VEGF} (Schneider et al. 2008), \textit{VEGFR2/KDR} (Schneider et al. 2008), \textit{XRCCI} (Stoehlmacher et al. 2001), \textit{XPD} (Park et al. 2001), and \textit{GSTP1} (Stoehlmacher et al. 2002; Grothey et al. 2005). Pharmacogenetic analyses of genes involved in the insulin/IGF-I pathway (Bonafe and Olivieri 2009; Salminen and Kaarniranta 2010) will include, but are not limited to, \textit{IGF-I}, \textit{IGF-IR} (Bonafe et al. 2003), \textit{PI3KCB} (Bonafe et al. 2003), \textit{NF-\textbf{\char12}B} (Sun and Zhang 2007), \textit{Foxo1a} (Lunetta et al. 2007) and \textit{TP53} (Bonafe and Olivieri 2009).

The candidate gene approach described above, which utilizes biological data to guide the selection of drug response genes in a pathway, is limited by our knowledge of the mechanisms underlying the phenotypes. In contrast, a genome-wide approach collects SNP data across the entire human genome and has significant power to detect common variants that confer a modest risk for a complex phenotype (Botstein and Risch 2003). The relatively large size of NCCTG N0949 and robust response and toxicity phenotype data that will be available make it an ideal sample set for whole genome analysis. In addition, the identification of SNPs that contribute to response and toxicity of the widely used drugs studied in NCCTG N0949 will lead to additional studies to understand the mechanism for these associations and to investigate the application of genetic information for the optimization of cancer therapy. The primary objective of this study is to identify novel SNPs variants associated with drug induced peripheral neuropathy. In addition, we aim to identify SNPs associated with other toxicity (e.g., hypertension) and clinical outcome (e.g., DFS or OS), identify copy number variants (CNV) associated with clinical outcome and conduct a cancer risk study using public controls. Finally, we will use this cohort to independently validate SNPs identified in completed (e.g., CALGB 80303, 40101 and 90401) and ongoing CALGB genome-wide association studies (GWAS).

2.0 Goals

2.1 Primary

To compare the progression-free survival (PFS) of elderly patients with metastatic colorectal carcinoma who are randomized to receive fluoropyrimidine-based therapy plus bevacizumab, with or without oxaliplatin.

2.2 Secondary

2.21 In a prospectively planned pooled analysis with a similar trial to be conducted by the Japanese Clinical Oncology Group (JCOG), evaluate and compare the overall survival (OS) of elderly patients with metastatic colorectal carcinoma who are randomized to receive fluoropyrimidine-based therapy plus bevacizumab, with or without oxaliplatin.

2.22 To assess and compare response rates and adverse events of elderly patients with metastatic colorectal carcinoma randomized to receive fluoropyrimidine-based therapy plus bevacizumab, with or without oxaliplatin.

2.3 Correlative Research
2.31 To evaluate the quality of life (QoL) in elderly patients with metastatic colorectal carcinoma randomized to receive fluoropyrimidine-based therapy plus bevacizumab, with or without oxaliplatin.

2.32 To determine whether a geriatric/frailty assessment predicts overall ≥grade 3 toxicity to chemotherapy, and is associated with PFS, OS, overall QoL, hospitalization, dose modification (delay or reduction), or discontinuation of chemotherapy due to toxicity, morbidity, or mortality in elderly patients with metastatic colorectal cancer randomized to receive fluoropyrimidine-based therapy plus bevacizumab, with or without oxaliplatin.

2.33 Determine whether a geriatric/frailty assessment tool can identify a subgroup of elderly patients which benefit from oxaliplatin-based chemotherapy as first-line treatment of metastatic colorectal carcinoma.

2.34 To analyze relevant pharmacogenetic markers in tissue and blood that may predict toxicity and/or tumor response in elderly patients with metastatic colorectal carcinoma randomized to receive fluoropyrimidine-based therapy plus bevacizumab, with or without oxaliplatin.

2.35 To evaluate the association of tissue-based biomarkers (e.g., KRAS and BRAF status) and outcome in elderly patients with metastatic colorectal carcinoma randomized to receive fluoropyrimidine-based therapy plus bevacizumab, with or without oxaliplatin.

2.36 To analyze pharmacokinetics and circulating biomarkers prior to and during therapy, and to assess these alterations with outcome in elderly patients with metastatic colorectal carcinoma randomized to receive fluoropyrimidine-based therapy plus bevacizumab, with or without oxaliplatin.

3.0 Patient Eligibility

3.1 Randomization – Inclusion Criteria

3.11 Age ≥ 70 years (age 70-74 years limited to no greater than 25% of the whole study population and eligibility will be modified at the time this benchmark is reached).

3.12 Patients must have metastatic colorectal cancer that has been histologically or cytologically confirmed. Confirmation may be from either the primary tumor or a metastasis.

3.13 Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0, 1, or 2. ECOG PS criteria are on the NCCTG website at https://ncctg.mayo.edu/ncctg/forms/NonProtocolSpecificForms.

3.14 The following laboratory values obtained ≤14 days prior to randomization.
- Absolute neutrophil count (ANC) ≥ 1,500/mm³
- Peripheral Platelet Count (PLT) ≥ 100,000/mm³
- Hemoglobin (HgB) > 9.0 g/dL
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
- Aspartate transaminase (AST) ≤ 2.5 x ULN (≤ 5 x ULN for patients with liver involvement)
- Alkaline phosphatase ≤ 3 x ULN (≤ 5 x ULN for patients with liver involvement)
- Creatinine ≤ 1.5 x ULN
- INR <1.5 x ULN unless patients are receiving anti-coagulation therapy. Patients receiving prophylactic anti-coagulation therapy with an agent such as warfarin or heparin are allowed to participate if INR ≤3.0.
- UPC ratio <1 or urine dipstick <2+. NOTE: Urine protein must be screened by urine analysis for Urine Protein Creatinine (UPC) ratio or by dipstick. For UPC ratio ≥1.0 or urine dipstick ≥2+, 24-hour urine protein must be obtained and the level should be <1000 mg.

3.15 Life expectancy ≥ 3 months.

3.16 Ability to complete questionnaire(s) by themselves or with assistance.

3.17 Provide informed written consent.

3.18 Willing to provide mandatory blood samples for correlative research purposes (see Sections 6.0 and 14.0).

3.2 Randomization – Exclusion Criteria

3.21 The following because this study involves agents whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:
- Men of childbearing potential who are unwilling to employ adequate contraception

3.22 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of the safety and adverse events of the prescribed regimens.

3.23 Immunocompromised patients (other than that related to the use of corticosteroids) including patients known to be HIV positive with CD4<100 cells/uL.

3.24 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.25 Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

3.26 Other active malignancy ≤ 3 years prior to randomization. EXCEPTIONS: Non-melanotic skin cancer or carcinoma-in-situ of the cervix. NOTE: If there is a history of prior malignancy, patients must not be receiving other specific treatment (other than hormonal therapy) for this prior cancer.

3.27 Prior chemotherapy, radiation therapy, immunotherapy, or biological therapy for recurrent or metastatic colorectal cancer. (NOTE: Prior chemotherapy or radiotherapy is permitted if they had been administered as adjuvant or neoadjuvant therapy and a complete surgical resection of the original colorectal cancer had been achieved.)

3.28 Progressive disease ≤12 months of completing oxaliplatin-containing adjuvant therapy.
3.29a Prior radiation to >30% of the bone marrow at any time.

3.29b Calculated creatinine clearance <60 mL/minute.

TO CALCULATE CREATININE CLEARANCE (CrCl) from SERUM CREATININE:

\[
CrCl = \frac{(140 - \text{age}) \times \text{wt. in kg} \times 0.85 \text{ (female)}}{72 \times \text{serum creatinine}} \text{ OR } \frac{\text{X 1.00 (male)}}{}
\]

**Note:** If calculated creatinine clearance does not meet eligibility requirement, a 24 hour urine can be collected for a creatinine clearance, and the patient can be enrolled if measured creatinine clearance \(\geq 60\) mL/minute.

3.29c Known central nervous system or brain metastasis that are either symptomatic or untreated. Note: If a patient has a resection of the metastasis and is no longer symptomatic, the patient is eligible for the study. Note: Patients with neurological symptoms must undergo a CT scan/MRI of the brain to exclude brain metastasis.

3.29d New York Heart Association (NYHA) classification III or IV congestive heart failure. (This form is on the NCCTG website https://ncctg.mayo.edu/ncctg/forms/NonProtocolSpecificForms/).

3.29e Inadequately controlled hypertension (systolic blood pressure of >150 mmHg or diastolic pressure >100 mmHg on anti-hypertensive medications).

3.29f Major surgical procedures, open biopsy or significant traumatic injury ≤28 days prior to randomization or anticipation of need for elective or planned major surgical procedure during the course of the study.

3.29g Core biopsy or other minor surgical procedures ≤7 days prior to randomization. NOTE: Placement of a vascular access device is allowed.

3.29h Active or recent hemoptysis (≥½ teaspoon of bright red blood per episode) ≤30 days prior to randomization.

3.29i History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess ≤6 months prior to randomization.

3.29j Serious, non-healing wound, active ulcer, or untreated bone fracture. NOTE: Patients with fractures secondary to metastatic disease are eligible after appropriate radiotherapy.

3.29k History of hypertensive crisis or hypertensive encephalopathy.

3.29l Patient has experienced any arterial thromboembolic events, including but not limited to myocardial infarction, stroke, transient ischemic attack (TIA), cerebrovascular accident, or unstable angina ≤6 months prior to randomization or congestive heart failure requiring use of ongoing maintenance therapy for life-threatening ventricular arrhythmias.
3.29m Significant vascular disease (e.g., aortic aneurysm, aortic dissection) or recent peripheral arterial thrombosis ≤6 months prior to randomization.

3.29n Evidence or history of bleeding diathesis (greater than normal risk of bleeding) or coagulopathy (in the absence of therapeutic anticoagulation), any hemorrhage/bleeding event >Grade 3 ≤4 weeks prior to randomization. Patients with full-dose anticoagulants are eligible provided the patient has been on a stable dose, at least 2 weeks, of low molecular weight heparin or warfarin and has an INR range 2-3. Aspirin doses >325 mg daily are not allowed.

3.29o Known hypersensitivity to any of the components of 5-fluorouracil/leucovorin, capecitabine, oxaliplatin, or bevacizumab.

3.29p Clinically significant peripheral neuropathy at the time of randomization (defined in the NCI Common Terminology Criteria for Adverse Events [CTCAE] v4.0 as ≥ grade 2 neurosensory or neuromotor toxicity).
### 4.0 Test Schedule

<table>
<thead>
<tr>
<th>Tests and procedures</th>
<th>≤14 days prior to randomization</th>
<th>At baseline (before start of treatment)</th>
<th>Weekly for first 42 days</th>
<th>Prior to each new cycle (± 3 days)</th>
<th>At PD, withdrawal, or removal</th>
<th>Observation (28-42 days after termination of study treatment)</th>
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</thead>
<tbody>
<tr>
<td>History and physical exam, including weight, pulse, temperature, ECOG performance status (PS)</td>
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<td>Adverse event assessment</td>
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<td>Blood pressure</td>
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<td>Blood Pressure Diary (Appendix IV)</td>
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<td>ANC, WBC, PLT, HgB</td>
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<td>Total bilirubin, alkaline phosphatase, AST, LDH, glucose, electrolytes (Mg, Na, K, calcium), creatinine, albumin</td>
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<td>Coagulation PT/INR</td>
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<td>Urinalysis for proteinuria (either by UPC ratio or dipstick)</td>
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<td>CT or MRI for tumor measurement</td>
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<td>CT or MRI (head)</td>
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<td>Chest x-ray</td>
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<td>Physician Fluoropyrimidine Treatment Decision Form</td>
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<td>Patient Capecitabine Medication Diary (Appendix V)</td>
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<td>Tests and procedures</td>
<td>≤14 days prior to randomization</td>
<td>At baseline (before start of treatment)</td>
<td>Weekly for first 42 days</td>
<td>Prior to each new cycle (± 3 days)</td>
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<td>Observation (28-42 days after termination of study treatment)</td>
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<td>Mandatory blood sample (see Section 14.0)</td>
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<td>Optional tissue sample (see Section 17.0)</td>
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<td>Patient Questionnaire Booklet – Active Treatment, Every 3 Months (Appendix IX)</td>
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<td>Patient Questionnaire Booklet – Observation Phase (Appendix X)</td>
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1. Cycle length for Arm C and Arm E is 14 days and cycle length for Arm D and Arm F is 21 days.
2. Prior to each cycle of treatment and 28-42 days after treatment discontinuation (because of the long half-life of bevacizumab, all patients [including those who have left the study because of progressive disease, unacceptable adverse events, patient refusal, investigator’s decision to remove patient, etc.] must have an adverse event assessment at this time point).
3. Hypertension will be monitored through routine evaluation of blood pressure prior to each bevacizumab treatment. Blood pressure should be measured weekly during the first 42 days of treatment and thereafter monitored prior to each new cycle after that. Patients may return to the treating location, have the measurement taken at their local physician’s office, or take the measurement themselves (either at home or by some other method such as a patient-operated machine at a drug store). If blood pressure measurements are not taken at the treating location, patient should record the measurement in the Blood Pressure Diary (see Appendix IV) and should be instructed to contact the treating physician if it is elevated. Patient should bring the completed Blood Pressure Diary to their next scheduled visit to the treating location. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with bevacizumab.

Footnotes continued on next page.
4. Patients with full-dose anti-coagulants are eligible provided the patient has been on a stable dose, at least 2 weeks, of warfarin or low molecular weight heparin and has an INR range 2-3. To be repeated prior to cycle 3 only and if clinically indicated.

5. Urinalysis for proteinuria will be monitored by either urine protein creatinine (UPC) ratio (see Appendix XII) or dipstick at baseline and every other cycle (every 4 weeks for Arm C and Arm E patients or every 6 weeks for Arm D and Arm F patients) and 24-hour collection should be done if indicated. Patients discovered to have ≥2+ proteinuria on dipstick analysis at baseline should undergo a 24-hour urine collection and must demonstrate ≤1 g of protein in 24 hours to be eligible. The 24-hour urine collection may be done by a local medical doctor.

6. Tumor measurement should be ≤28 days prior to registration.

7. Use same imaging modality throughout the study.

8. Should be conducted within 4 days before planned treatment every 6 weeks per Section 11.1 (i.e., prior to every 3 cycles for Arms C and E and prior to every 2 cycles for Arms D and F).

9. Patients with neurological symptoms must undergo a CT scan/MRI of the brain ≤14 days prior to randomization to exclude brain metastasis.

10. Not necessary if CT chest is performed for tumor measurement.

11. The Physician Fluoropyrimidine Treatment Decision Form must be submitted ≤7 days after patient randomization. Treatment cannot begin prior to randomization and must begin ≤14 days after submission of the Physician Fluoropyrimidine Treatment Decision Form.

12. The diary must begin the day the patient starts taking capecitabine, if applicable, and must be completed per protocol and returned to the treating institution OR compliance must be documented in the medical record by any member of the care team.

13. Mandatory blood draws will be collected at baseline prior to study treatment (after randomization), after 6 weeks of treatment (i.e., after cycle 3 for Arm C and Arm E patients and after cycle 2 for Arm D and Arm F patients), and at time patient discontinues treatment. Kits are required for this collection (Note: Mayo Clinic Rochester will use Special Study Cards).

14. To be submitted ≤30 days following randomization.

15. Patient Questionnaire Booklets: Please obtain a starter supply of all necessary booklets before registering patients. Booklets should be ordered from CTSU by completing the CTSU Supply Request Form. Patient Questionnaire Booklets (which will only be mandatory for patients who are fluent in reading and speaking English) and Research Team Questionnaire Booklets must be used; copies are not acceptable for this submission. The Research Team Questionnaire Booklet must be completed prior to the patient completing their Booklet. Questionnaire Booklets are to be completed during the scheduled clinic visits indicated in the table above and returned to their nurse or physician. A CRA Training Module webinar video is posted on the CTSU website to assist research staff complete and administer questionnaires. Although this training is strongly recommended, it is not mandatory. The final slide of the 20-minute long video is a certificate of training; please complete the certificate and email or fax it to the N0949 research protocol specialist listed in the Protocol Resources section on page 3.

16. To be completed every 3 months during active treatment.

R. Research funded (see Section 19.0).
5.0  Stratification and Grouping Factors

5.1  Stratification Factors (Used for randomization to Arms A-B)

5.11 Age (years): ≥85 vs. 80-84 vs. 75-79 vs. 70-74

5.12 ECOG Performance Status (PS): 0-1 vs. 2

5.13 Number of metastatic sites: 1 vs. >1

5.2  Grouping Factors (Used for direct assignment to physician declared fluoropyrimidine-based treatment. These four treatments are named as treatment “Arms”, despite the primary endpoint of the study being the direct comparison of Arm A (i.e., fluoropyrimidine + bevacizumab, Arms C+D) to Arm B (i.e., fluoropyrimidine/oxaliplatin + bevacizumab, Arms E+F).

5.21 Arm C: 5-fluorouracil/leucovorin + bevacizumab

5.22 Arm D: capecitabine + bevacizumab

5.23 Arm E: mFOLFOX7 (5-fluorouracil/leucovorin + oxaliplatin) + bevacizumab

5.24 Arm F: XELOX (capecitabine + oxaliplatin) + bevacizumab

6.0  Registration/Randomization Procedures – All Site Staff (NCCTG, CALGB, and CTSU institutions)

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

6.1  Investigator Registration

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

6.2  Site Registration Requirements – IRB Approval

6.21 Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org. Requirements for N0949 site registration:
6.22 In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually). If the necessary documentation is not submitted in advance of attempting patient randomization, the randomization will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

6.23 When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the CTSU is no longer necessary.

6.3 Patient Randomization

6.31 Patient randomization can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as ‘approved’ in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

6.32 All site staff (NCCTG, CALGB, and CTSU Sites) will use the OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members’ side of the website at https://www.ctsu.org.

6.33 Prior to accessing OPEN, site staff must verify the following:

- All eligibility criteria must have been met within the protocol stated timeframes. Site staff should use the randomization forms provided on the NCCTG or CTSU web site as a tool to verify eligibility.

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

6.34 Access Requirements for Oncology Patient Enrollment Network (OPEN)

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

6.342 To perform randomizations, the site user must have been assigned the ‘Registrar’ role on the relevant Group or CTSU roster.

6.343 To perform randomizations on protocols for which you are a member of the Lead Group (i.e., NCCTG), you must have an equivalent ‘Registrar’ role on the Lead Group (i.e., NCCTG) roster. Role assignments are handled through the Groups in which you are a member.

6.344 To perform randomizations to trials accessed via the CTSU mechanism (i.e., non-Lead Group randomizations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature.
under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

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

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

6.35 **Correlative Research**

6.351 A mandatory correlative research component for blood is part of this study, the patient will be automatically registered onto this component (see Sections 3.18 and 14.0).

6.352 An optional correlative research component for tissue is part of this study. There will be an option to select if the patient is to be registered onto this component (see Section 17.0).

- Patient has/has not given permission to give his/her tissue sample(s) to NCCTG for research testing planned as part of this study.

6.36 Patient has/has not given permission to store and use his/her sample(s) for use in future research to learn about, prevent, or treat cancer.

6.37 Patient has/has not given permission to store and use his/her sample(s) for use in future research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer’s disease, or heart disease).

6.38 Patient has/has not given permission for NCCTG to give his/her stored sample(s) for use in future research to outside researchers.

6.39a Treatment on this protocol must commence at the accruing membership under the supervision of a CTSU, NCCTG, or CALGB member physician.

6.39b Treatment cannot begin prior to randomization and must begin $\leq 14$ days after submission of Physician Fluoropyrimidine Treatment Decision Form. Note: *The Physician Fluoropyrimidine Treatment Decision Form must be submitted $\leq 7$ days after patient randomization.*

6.39c Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.39d All required baseline symptoms (see Section 10.3) must be documented and graded.

6.39e Blood draw kit is available on site.
6.39f  Patient Questionnaire Booklets and Research Team Questionnaire Booklets are available on site; copies are not acceptable for this submission.

Note:  Once the above conditions have been met, access the OPEN website and follow the instructions for enrollment.

6.39g  The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors. The values of the stratification factors will be recorded. Following randomization, the Physician Fluoropyrimidine Treatment Decision Form must be completed within 7 days of randomization and submitted to the Registration Office at (507) 284-0885. Treatment must begin within 14 days of submission of this form. The patient then will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups (Pocock and Simon 1975).

Arm A:   fluoropyrimidine + bevacizumab

Arm B:   fluoropyrimidine/oxaliplatin + bevacizumab

6.39h  Following randomization, direct assignment to appropriate arm will be based on physician decision for fluoropyrimidine. **No crossover will be allowed.**

Arm C:   5-fluorouracil/leucovorin + bevacizumab all on day 1; repeated every 14 days

Arm D:  capecitabine twice daily on days 1-14 + bevacizumab on day 1; repeated every 21 days

Arm E:  mFOLFOX7 (5-fluorouracil/leucovorin + oxaliplatin) + bevacizumab all on day 1; repeated every 14 days.

Arm F:  XELOX (capecitabine twice daily on days 1-14 + oxaliplatin on day 1) + bevacizumab on day 1; repeated every 21 days.
7.0 Protocol Treatment

7.1 Treatment Schedule - Use actual weight or estimated dry weight if fluid retention
The order of drug administration is at the discretion of the individual sites. All regimens are standard of care.

7.11 Control Arm – Arm C or Arm D
Note: Following randomization, direct assignment to appropriate arm will be based on physician decision for fluoropyrimidine. No crossover will be allowed.

Control arm (Arm C): 5-Fluorouracil/leucovorin + bevacizumab

<table>
<thead>
<tr>
<th>Arm</th>
<th>Agent</th>
<th>Dose Level</th>
<th>Route</th>
<th>Day</th>
<th>ReRx(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Bevacizumab</td>
<td>5 mg/kg</td>
<td>IV infusion over 90 minutes(^b)</td>
<td>1</td>
<td>Every 14 (± 3) days</td>
</tr>
<tr>
<td></td>
<td>Leucovorin</td>
<td>400 mg/m(^2)</td>
<td>IV- 2hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-Fluorouracil</td>
<td>2400 mg/m(^2)</td>
<td>Continuous IV x 46-48 hrs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) If necessary to accommodate holidays, patient schedule, or other justifiable circumstance, the schedule may be modified +/- 3 days.

\(^b\) Infuse the initial dose of bevacizumab over 90 minutes. Follow package insert and institutional clinical practice for subsequent infusion rates. Infusion rate should be a maximum of 90 minutes and a minimum of 10 minutes (Reidy et al., 2007; see Section 15.44).

OR

Control arm (Arm D): capecitabine + bevacizumab

<table>
<thead>
<tr>
<th>Arm</th>
<th>Agent</th>
<th>Dose Level</th>
<th>Route</th>
<th>Day</th>
<th>ReRx(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>Bevacizumab</td>
<td>7.5 mg/kg</td>
<td>IV infusion over 90 minutes(^e)</td>
<td>1</td>
<td>Every 21 (± 3) days</td>
</tr>
<tr>
<td></td>
<td>Capecitabine(^b)</td>
<td>1000 mg/m(^2)/dose(^c)</td>
<td>Orally</td>
<td>Twice a day x 14 days(^d)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) If necessary to accommodate holidays, patient schedule, or other justifiable circumstance, the schedule may be modified +/- 3 days.

\(^b\) Patient must complete a Patient Medication Diary for capecitabine every cycle. The diary must begin the day the patient starts taking capecitabine and be completed every cycle. Patient should bring the completed diary with them to each visit and be given a new diary at that time. Compliance should be documented in the medical record. Patient should NOT make up for missed dose or double up on a dose (see Section 15.392).

\(^c\) Capecitabine available in 150 or 500 mg capsules. Dose should be rounded DOWN appropriately using available capecitabine dosages.

\(^d\) The total number of capecitabine administrations per cycle should be 28. Capecitabine is given on days 1-14 if first dose of capecitabine is given in the AM. Capecitabine is given on days 1-15 if first dose of capecitabine is given in the PM of day 1 with last dose given in the AM of day 15.

\(^e\) Infuse the initial dose of bevacizumab over 90 minutes. Follow package insert and clinical practice for subsequent infusion rates. Infusion rate should be a maximum of 90 minutes and a minimum of 30 minutes (see Section 15.44).
7.12 Experimental Arm – Arm E or Arm F

**Note:** Following randomization, direct assignment to appropriate arm will be based on physician decision for fluoropyrimidine. **No crossover will be allowed.**

### Experimental arm (Arm E): mFOLFOX7 (5-Fluorouracil/leucovorin + oxaliplatin) + bevacizumab

<table>
<thead>
<tr>
<th>Arm</th>
<th>Agent</th>
<th>Dose Level</th>
<th>Route</th>
<th>Day</th>
<th>ReRx^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>Bevacizumab</td>
<td>5 mg/kg</td>
<td>IV infusion over 90 minutes^c</td>
<td>1</td>
<td>Every 14 (± 3) days</td>
</tr>
<tr>
<td></td>
<td>Oxaliplatin</td>
<td>85 mg/m^2</td>
<td>IV- 2hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leucovorin</td>
<td>400 mg/m^2</td>
<td>IV- 2hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-Fluorouracil</td>
<td>2400 mg/m^2</td>
<td>Continuous IV x 46-48 hrs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^a If necessary to accommodate holidays, patient schedule, or other justifiable circumstance, the schedule may be modified +/- 3 days.

^b We strongly recommend the discontinuation of oxaliplatin after eight mFOLFOX7 treatment cycles (i.e. after projected 16 weeks of therapy) when a planned cumulative dose of 680 mg/m^2 oxaliplatin has been administered.

^c Infuse the initial dose of bevacizumab over 90 minutes. Follow package insert and institutional clinical practice for subsequent infusion rates. Infusion rate should be a maximum of 90 minutes and a minimum of 10 minutes (Reidy et al., 2007; see Section 15.44).

### OR

### Experimental arm (Arm F): XELOX (capecitabine + oxaliplatin) + bevacizumab

<table>
<thead>
<tr>
<th>Arm</th>
<th>Agent</th>
<th>Dose Level</th>
<th>Route</th>
<th>Day</th>
<th>ReRx^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>Bevacizumab</td>
<td>7.5 mg/kg</td>
<td>IV infusion over 90 minutes^f</td>
<td>1</td>
<td>Every 21 (± 3) days</td>
</tr>
<tr>
<td></td>
<td>Oxaliplatin</td>
<td>130 mg/m^2</td>
<td>IV- 2hrs</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Capecitabine</td>
<td>850 mg/m^2/dose (total daily dose 1700 mg/m^2/day)^d</td>
<td>Orally</td>
<td>Twice a day x 14 days^e</td>
<td>1</td>
</tr>
</tbody>
</table>

^a If necessary to accommodate holidays, patient schedule, or other justifiable circumstance, the schedule may be modified +/- 3 days.

^b We strongly recommend the discontinuation of oxaliplatin after 5-6 XELOX treatment cycles (i.e. after projected 15-18 weeks of therapy) when a planned cumulative dose of 650-780 mg/m^2 oxaliplatin has been administered.

^c Patient must complete a Patient Medication Diary for capecitabine every cycle. The diary must begin the day the patient starts taking capecitabine and be completed every cycle. Patient should bring the completed diary with them to each visit and be given a new diary at that time. Compliance should be documented in the medical record. Patient should NOT make up for missed dose or double up on a dose (see Section 15.392).

^d Reduced capecitabine dosing of experimental Arm F compared to control Arm D is based on results from the TREE-2 trial (Hurwitz et al. 2004; Kabbinavar et al. 2005b; Giantonio et al. 2007; Hochster et al. 2008; Saltz et al. 2008). Capecitabine available in 150 or 500 mg capsules. Dose should be rounded DOWN appropriately using available capecitabine dosages.

^e The total number of capecitabine administrations per cycle should be 28. Capecitabine is given on days 1-14 if first dose of capecitabine is given in the AM. Capecitabine is given on days 1-15 if first dose of capecitabine is given in the PM of day 1 with last dose given in the AM of day 15.

^f Infuse the initial dose of bevacizumab over 90 minutes. Follow package insert and clinical practice for subsequent infusion rates. Infusion rate should be a maximum of 90 minutes and a minimum of 30 minutes (see Section 15.44).
7.2 Treatment by a local medical doctor (LMD) is not allowed. Treatment can only be done at an NCCTG, CTSU, or CALGB treatment location. Treatment will be administered on an outpatient basis and patient must return for an evaluation at least every 14 days for Arm C or Arm E patients or at least every 21 days for Arm D or Arm F patients.

7.3 Blood pressure will be taken at baseline, weekly during the first 6 weeks, and prior to every cycle after that. Blood pressure may be taken either at the doctor’s office or using any calibrated electronic device (such as those found at a local drug store or pharmacy). Patient will be provided with a Blood Pressure Diary (Appendix IV) on which to record the measurements. If blood pressure measurements are not taken at the treating location, patient should record the measurement in the Blood Pressure Diary and should be instructed to contact the treating physician if it is elevated. Patient should bring the completed Blood Pressure Diary to their next scheduled visit to the treating location.

7.4 Patient must complete a Patient Capecitabine Medication Diary (Appendix V) for capecitabine every cycle. The diary must begin the day the patient starts taking capecitabine and be completed every cycle. Patient should bring the completed diaries with them to each visit and be given a new diary at that time. Compliance should be documented in the medical record.

7.5 The following patient reported tools will be used to characterize and/or quantify neurotoxicity, geriatric/frailty, and QoL of patients on this trial. Please obtain a starter supply of all necessary booklets before registering patients. Booklets should be ordered from CTSU by completing the CTSU Supply Request Form. Patient Questionnaire Booklets, which will only be mandatory for patients fluent in reading and speaking English, must be used. Appropriate Patient Questionnaire Booklets should be given to the patient for the corresponding time points (see Section 4.0; Appendices VI, VIII, IX, and X).

A CRA Training Module webinar video is posted on the CTSU website to assist research staff complete and administer questionnaires. Although this training is strongly recommended, it is not mandatory. The final slide of the 20-minute long video is a certification of training; please complete the certificate and email or fax it to the N0949 research protocol specialist listed in the Protocol Resources section on page 3.

7.51 Neurotoxicity Assessments (baseline, prior to every cycle, and 28-42 days after termination of study treatment)
   - Neurotoxicity Symptom Experience Diary

7.52 PRO-CTCAE (baseline, prior to every cycle, and 28-42 days after termination of study treatment)
   - PRO-CTCAE

7.53 Geriatric/Frailty Assessments (baseline and 28-42 days after termination of study treatment)
   - CSGA
   - NCCTG Brief Frailty Inventory

7.54 QoL Assessments (baseline, every 3 months, and 28-42 days after termination of study treatment)
   - Fatigue/Uniscale Assessments
- LASA
- EQ-5D
- WIWI Questionnaire (28-42 days after termination of study treatment only)

7.6 The following research team reported tools will be used to characterize and/or quantify neurotoxicity and geriatric/frailty of patients on this trial. Research Team Questionnaire Booklets must be used, copies are not acceptable. Booklets should be ordered from CTSU by completing the CTSU Supply Request Form. The Research Team Questionnaire Booklet should be completed by the physician, institutional nurse, or CRA prior to the patient completing their booklet. Questionnaire booklets should be completed during the schedule clinic visits indicated in Table 4.0 and Appendices VII and XI.

7.6.1 Geriatric/Frailty Assessments (baseline and 28-42 days after termination of study treatment)
- CSGA – Research Team Questionnaire
- CSHA-CFS – Research Team Questionnaire

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table for the first two cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

**Alert**: ADR reporting may be required for some adverse events (See Section 10)

8.1 Dose Levels (Based on Adverse Events in Tables 8.2 – 8.5).

Add 2 Tables 8.1A-D describe the dose reduction guidelines for each study drug for each treatment arm. A reduction of 1 dose level will be to the next lower dose in the table.

<table>
<thead>
<tr>
<th>Table 8.1A Arm C Dose Reduction Guidelines (Based on Adverse Events in Tables 8.2 – 8.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Bevacizumab¹</td>
</tr>
<tr>
<td>Leucovorin¹</td>
</tr>
<tr>
<td>5-FU continuous infusion over 46-48 hours</td>
</tr>
</tbody>
</table>

* Starting dose level.

¹ Dosing of bevacizumab and leucovorin will remain fixed at 100% of recommended dose.

<table>
<thead>
<tr>
<th>Table 8.1B Arm D Dose Reduction Guidelines (Based on Adverse Events in Tables 8.2 – 8.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Table 8.1C Arm E Dose Reduction Guidelines (Based on Adverse Events in Tables 8.2 – 8.5)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Level</th>
<th>0*</th>
<th>-1</th>
<th>-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab 1</td>
<td>7.5 mg/kg</td>
<td>7.5 mg/kg</td>
<td>7.5 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Capecitabine</td>
<td>1000 mg/m²/dose</td>
<td>750 mg/m²/dose</td>
<td>500 mg/m²/dose</td>
<td></td>
</tr>
</tbody>
</table>

* Starting dose level.
1 Dosing of bevacizumab will remain fixed at 100% of recommended dose.

Table 8.1D Arm F Dose Reduction Guidelines (Based on Adverse Events in Tables 8.2 – 8.5)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Level</th>
<th>0*</th>
<th>-1</th>
<th>-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab 1</td>
<td>7.5 mg/kg</td>
<td>7.5 mg/kg</td>
<td>7.5 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Capecitabine (Arm F)</td>
<td>850 mg/m²/dose</td>
<td>650 mg/m²/dose</td>
<td>450 mg/m²/dose</td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin (Arm F)</td>
<td>85 mg/m²</td>
<td>65 mg/m²</td>
<td>50 mg/m²</td>
<td></td>
</tr>
</tbody>
</table>

* Starting dose level.
1 Dosing of bevacizumab and leucovorin will remain fixed at 100% of recommended dose.

8.2 Bevacizumab

**There are no dose reductions in the bevacizumab dose.** If adverse events occur that require omitting bevacizumab, the dose will remain the same once treatment resumes. Any adverse events associated or possibly associated with bevacizumab treatment should be managed according to standard medical practice. Bevacizumab has a terminal half-life of 2 to 3 weeks; therefore, its discontinuation results in slow elimination over several months. There is no available antidote for bevacizumab.

Subjects should be assessed clinically for adverse events prior to, during, and after each infusion. If unmanageable adverse events occur because of bevacizumab at any time during the study, treatment with bevacizumab should be discontinued.

Patients who have an ongoing bevacizumab-related Grade 4 or serious adverse event at the time of discontinuation from study treatment will continue to be followed until resolution of the event or until the event is considered irreversible.

**Infusion Reaction:** Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. Subjects who experience a NCI Common Terminology Criteria for Adverse Events (CTCAE; CTEP Version 4.0) Grade 3
or 4 allergic reaction, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment.

The infusion should be slowed to 50% or less or interrupted for subjects who experience any infusion-associated symptoms not specified above. When the subject’s symptoms have completely resolved, the infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle.

Regardless of the reason for holding study drug treatment, the maximum allowable length of treatment interruption is ≤28 days with the exception of patients who have surgery for bowel obstruction and resection of ANY metastases (see Section 9.2).

8.3 Dose Modifications

**NOTE:** If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for that entire cycle. If that cycle is completed with no further adverse events greater than Grade 2, then the dose may be increased for capecitabine and/or 5-FU only, at the investigator’s discretion, one level at a time, in the following cycles.

**NOTE:** Adverse events requiring a dose-reduction step for any or all drugs beyond the two dose-reduction steps (levels –1 and –2) will be 20% dose reductions from the previous level, if the decision is made for the patient to be kept on study. These dose reductions must be clearly recorded in reported clinical data.

Omit = Treatment is not given for this cycle
Hold/Delay = Treatment can be made up as part of this cycle
Discontinue = Treatment is totally stopped
### Table 8.2 Adverse Events Based on Interval Adverse Event

*Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified.

<table>
<thead>
<tr>
<th>CTCAE System/Organ/Class (SOC)</th>
<th>ADVERSE EVENT</th>
<th>AGENT¹</th>
<th>DOSAGE CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Febrile neutropenia ≥Grade 3</td>
<td>5-FU (or capecitabine) Oxaliplatin</td>
<td>Decrease 5-FU (or capecitabine) and oxaliplatin one dose level at retreatment.</td>
</tr>
<tr>
<td></td>
<td>Hemolytic uremic syndrome² ≥Grade 3</td>
<td>Bevacizumab Oxaliplatin</td>
<td>Hold bevacizumab until resolution. Discontinue oxaliplatin.</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Left ventricular systolic dysfunction ≥Grade 3</td>
<td>Bevacizumab</td>
<td>Discontinue bevacizumab. Continue fluoropyrimidine (and oxaliplatin).</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction³ Any grade</td>
<td></td>
<td>Discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring.</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea Grade 3</td>
<td>5-FU (or capecitabine) Oxaliplatin</td>
<td>Decrease 5-FU (or capecitabine) one dose level at retreatment.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td></td>
<td>Decrease 5-FU (or capecitabine) and oxaliplatin one dose level at retreatment.</td>
</tr>
</tbody>
</table>
| | Epistaxis, esophageal, gastric, lower gastrointestinal, intra-abdominal, and retroperitoneal hemorrhage Grade 3 | Bevacizumab | • Patients who are also receiving full-dose anticoagulation will discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring.  
  • For patients not on full-dose anticoagulation, omit bevacizumab until all of the following criteria are met then resume at same dose:  
    - The bleeding has resolved and hemoglobin is stable.  
    - There is no bleeding diathesis that would increase the risk of therapy  
    - There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.  
  • Patients who experience a repeat Grade 3 hemorrhagic event will discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring.  
<p>| | Grade 4 | | Discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring. |
| | Esophageal, gastric, colonic, and small intestinal obstruction Grade 2 ≥Grade 3 | | Hold until resolution. |
| | Esophageal, gastric, colonic, and small intestinal perforation Any grade | | Discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring. |</p>
<table>
<thead>
<tr>
<th>CTCAE System/Organ/Class (SOC)</th>
<th>ADVERSE EVENT</th>
<th>AGENT</th>
<th>DOSAGE CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders (continued)</strong></td>
<td>Gastrointestinal fistula</td>
<td>Bevacizumab</td>
<td>Discontinue bevacizumab. Continue fluoropyrimidine (and oxaliplatin).</td>
</tr>
<tr>
<td>Mucositis oral</td>
<td>Any grade</td>
<td>5-FU (or capecitabine)</td>
<td>Decrease 5-FU (or capecitabine) one dose level at retreatment.</td>
</tr>
<tr>
<td>≥Grade 3</td>
<td>Oxaliplatin</td>
<td>Decrease oxaliplatin one dose level at retreatment. Decrease both 5-FU and oxaliplatin one dose level at retreatment.</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>Grade 3</td>
<td>5-FU (or capecitabine)</td>
<td>Decrease 5-FU (or capecitabine) one dose level at retreatment.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Oxaliplatin</td>
<td>Decrease oxaliplatin one dose level at retreatment. Decrease both 5-FU and oxaliplatin one dose level at retreatment.</td>
<td></td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td>Allergic reaction</td>
<td>Oxaliplatin</td>
<td>Stop oxaliplatin infusion and institute appropriate measures, including corticosteroid therapy and antihistamines. In a few cases oxygen, plasma expanders and epinephrine may be required. Discontinue oxaliplatin, continue fluoropyrimidine and bevacizumab treatment.</td>
</tr>
<tr>
<td>Grade 2-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Injury, poisoning and procedural complications</strong></td>
<td>Biliary, esophageal, gastric, large intestinal, small intestinal anastomotic leak</td>
<td>Bevacizumab</td>
<td>Hold bevacizumab until healing.</td>
</tr>
<tr>
<td>Grade 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥Grade 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound complication</td>
<td>≥Grade 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥Grade 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>≥Grade 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥Grade 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>Alanine aminotransferase increased ≥Grade 3 (&gt;5.0 x ULN; &gt;5 x ULN for &gt;2 weeks)</td>
<td>5-FU</td>
<td>Decrease 5-FU one dose level at retreatment.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alkaline phosphatase increased ≥Grade 3 (&gt;5.0 x ULN)</td>
<td></td>
<td>Decrease 5-FU one dose level at retreatment.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aspartate aminotransferase increased ≥Grade 3 (&gt;5.0 x ULN; &gt;5 x ULN for &gt;2 weeks)</td>
<td>5-FU (or capecitabine)</td>
<td>Decrease 5-FU one dose level at retreatment.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oxaliplatin</td>
<td>Decrease oxaliplatin one dose level at retreatment.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blood bilirubin increased ≥Grade 2 (&gt;1.5 x ULN)</td>
<td>5-FU (or capecitabine)</td>
<td>Decrease both fluoropyrimidine (5-FU or capecitabine) and oxaliplatin one dose level at retreatment.</td>
</tr>
<tr>
<td></td>
<td>Neutrophil count decreased Grade 3 (&lt;1000; &lt;1.0 x 10e9 /L)</td>
<td>Oxaliplatin</td>
<td>Decrease oxaliplatin one dose level at retreatment.</td>
</tr>
<tr>
<td></td>
<td>Grade 4 (&lt;500; &lt;0.5 x 10e9 /L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Platelet count decreased Grade 3 (&lt;50,000; &lt;50.0 x 10e9 /L)</td>
<td></td>
<td>Decrease oxaliplatin one dose level at retreatment.</td>
</tr>
</tbody>
</table>
**Table 8.2 Adverse Events Based on Interval Adverse Event**

> Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified

<table>
<thead>
<tr>
<th>CTCAE System/Organ/Class (SOC)</th>
<th>ADVERSE EVENT</th>
<th>AGENT(^1)</th>
<th>DOSAGE CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigations (continued)</strong></td>
<td>Platelet count decreased (continued) Grade 4 (&lt;25,000; &lt;25.0 x 10⁹/L)</td>
<td>5-FU (or capecitabine) Oxaliplatin</td>
<td>Decrease 5-FU or capecitabine one dose level, if applicable, and oxaliplatin two dose levels at retreatment.</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td>Hypomagnesemia ≥Grade 2</td>
<td>5-FU Oxaliplatin</td>
<td>Dose reduction is not required unless symptoms are present. If Grade ≥2 after 4 weeks on ongoing magnesium supplementation, discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring.</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>Intracranial hemorrhage Grade 1</td>
<td>Bevacizumab</td>
<td>• Patients who are also receiving full-dose anticoagulation will discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring. • For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: - the bleeding has resolved and hemoglobin is stable - there is no bleeding diathesis that would increase the risk of therapy - there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥Grade 2</td>
</tr>
<tr>
<td></td>
<td>Ischemia cerebrovascular Any grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reversible posterior leukoencephalopathy syndrome Any grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stroke(^7) Any grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transient ischemic attack(^3) Any grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td>Proteinuria ≥Grade 3 (≥3.5 g/24 hr)</td>
<td>Bevacizumab</td>
<td>Omit until proteinuria improves to ≤Grade 2. If no recovery after 14 days, discontinue bevacizumab. Continue fluoropyrimidine (and oxaliplatin).</td>
</tr>
</tbody>
</table>
Table 8.2 Adverse Events Based on Interval Adverse Event

Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified

<table>
<thead>
<tr>
<th>CTCAE System/Organ/Class (SOC)</th>
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<th>DOSAGE CHANGE</th>
</tr>
</thead>
</table>
| Respiratory, thoracic and mediastinal disorders | Bronchopulmonary hemorrhage | Bevacizumab | ● Patients who are also receiving full-dose anticoagulation will discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring.  
● For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met:  
  - the bleeding has resolved and hemoglobin is stable  
  - there is no bleeding diathesis that would increase the risk of therapy  
  - there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence |
| ≥ Grade 2 | Bevacizumab | Discontinue bevacizumab. Continue fluoropyrimidine (and oxaliplatin). |
| Cough | ≥ Grade 3 | Oxaliplatin | Hold oxaliplatin until interstitial lung disease is ruled out. If interstitial lung disease, discontinue oxaliplatin. Continue fluoropyrimidine and bevacizumab treatment. |
| Dyspnea | ≥ Grade 3 | Bevacizumab | Hold bevacizumab until resolution. Hold oxaliplatin until interstitial lung disease is ruled out. If interstitial lung disease, discontinue oxaliplatin. Continue fluoropyrimidine treatment. |
| Hypoxia | ≥ Grade 3 | Oxaliplatin | Hold bevacizumab until resolution. Hold oxaliplatin until interstitial lung disease is ruled out. If interstitial lung disease, discontinue oxaliplatin. Continue fluoropyrimidine treatment. |
| Pneumonitis | ≥ Grade 3 | Oxaliplatin | Hold bevacizumab until resolution. Hold oxaliplatin until interstitial lung disease is ruled out. If interstitial lung disease, discontinue oxaliplatin. Continue fluoropyrimidine treatment. |
| Skin and subcutaneous tissue disorders | Palmar-plantar erythrodysesthesia syndrome | Capecitabine | Decrease capecitabine one dose level at retreatment |
| Vascular disorders | Hypertension | Bevacizumab | See Section 8.5 for management. |
**Table 8.2 Adverse Events Based on Interval Adverse Event**

*Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified.

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<tr>
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<th>ADVERSE EVENT</th>
<th>AGENT</th>
<th>DOSAGE CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular disorders (continued)</td>
<td>Thromboembolic event(^3) (Venous)</td>
<td>Bevacizumab</td>
<td></td>
</tr>
</tbody>
</table>
|                                | Grade 3 OR Grade 4 (asymptomatic) |       | Omit bevacizumab. If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab should be omitted until the full-dose anticoagulation period is over.  
If the planned duration of full-dose anticoagulation is ≥2 weeks, bevacizumab may be resumed during full-dose anticoagulation **IF** ALL of the criteria below are met:  
− The subject must not have pathological conditions that carry high risk of bleeding (e.g., tumor involving major vessels or other conditions).  
− The subject must not have had hemorrhagic events while on study.  
− The subject must be on stable dose of heparin or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab.  
If thromboembolic worsen/recur upon resumption of study therapy, discontinue bevacizumab. Continue with fluoropyrimidine (and oxaliplatin). |
|                                | Grade 4 (symptomatic) |       | Discontinue bevacizumab. Continue with fluoropyrimidine (and oxaliplatin). |
| Peripheral ischemia\(^3\) Any grade | | | Discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring. |
| Visceral arterial ischemia\(^3\) Any grade | | | Discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring. |
| All other non-hematologic adverse events\(^4\) | ≥Grade 3 | Bevacizumab 5-FU (or capecitabine) Oxaliplatin | Hold all protocol treatment and monitor toxicity at least weekly. If toxicity resolves to ≤grade 1 within 4 weeks, treatment may be resumed, with 5-FU (or capecitabine) and oxaliplatin at one lower dose level. Otherwise discontinue all study agents and patient goes to Observation (for 28-42 days), then to Event Monitoring. |

\(^1\) The dose of leucovorin will not be adjusted due to adverse event. It should remain at 400 mg/m\(^2\) for all courses. Leucovorin will be given immediately prior to each 5-fluorouracil dose; thus, if 5-fluorouracil is delayed, leucovorin will be delayed.

\(^2\) Recommended evaluation of suspected HUS: Evaluation should include CBC differential, platelets, PT, PTT, fibrinogen, FDP (Fibrin degradation products), Anti thrombin III, Von Willebrand factor, anti-nuclear antibody, rheumatoid factor, Compliment Cascade C3, C4, and CH\(_{50}\), anti-platelet antibodies, platelet-associated IgG, and circulating immune complexes. Renal evaluation should include creatinine, BUN, and urinalysis with microscopic examination. Other laboratory and hematological evaluations as appropriate should also be obtained, including peripheral blood smear and free hemoglobin.

\(^3\) Arterial thromboembolic events include myocardial infarction, stroke, transient ischemic attack, peripheral ischemia and visceral arterial ischemia.

\(^4\) Exceptions: alopecia, fatigue, anorexia, nausea/vomiting if can be controlled by antiemetics, viral infections.

Table 8.3 Adverse Events at Time of Retreatment

Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified

<table>
<thead>
<tr>
<th>CTCAE System/Organ/Class (SOC)</th>
<th>ADVERSE EVENT</th>
<th>AGENT(^1)</th>
<th>DOSAGE CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td>Blood and lymphatic system disorders – Other hematologic adverse events ≥ Grade 3</td>
<td>5-FU</td>
<td>Dose modifications for other hematologic adverse events at the time of retreatment are also based on CTEP Version 4.0 of the NCI CTCAE and are the same as recommended for neutrophils above.</td>
</tr>
<tr>
<td>Febrile neutropenia ≥ Grade 3</td>
<td></td>
<td></td>
<td>If ANC&lt;1500 at start of cycle, delay retreatment and check at least weekly until recovery to ≥1500, then retreat based on interval adverse event. If ANC not recovered to ≥1500 after 14 days, discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring.</td>
</tr>
<tr>
<td>Hemolytic uremic syndrome ≥ Grade 3</td>
<td>Bevacizumab Oxaliplatin</td>
<td>Hold bevacizumab until resolution. Discontinue oxaliplatin.</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td>Left ventricular systolic dysfunction ≥ Grade 3</td>
<td>Bevacizumab</td>
<td>Discontinue bevacizumab. Continue fluoropyrimidine (and oxaliplatin).</td>
</tr>
<tr>
<td>Myocardial infarction Any grade</td>
<td></td>
<td></td>
<td>Discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring.</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Diarrhea ≥ Grade 2</td>
<td>5-FU (or capecitabine) Oxaliplatin</td>
<td>If ≥ Grade 2 at start of cycle, delay and check weekly then treat based on interval adverse event. If ≥ Grade 2 after 14 days, discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring.</td>
</tr>
</tbody>
</table>
| Epistaxis, esophageal, gastric, lower gastrointestinal, intra-abdominal, and retroperitoneal hemorrhage Grade 3 | Bevacizumab | • Patients who are also receiving full-dose anticoagulation will discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring.  
• For patients not on full-dose anticoagulation, omit bevacizumab until all of the following criteria are met then resume at same dose:  
  − The bleeding has resolved and hemoglobin is stable.  
  − There is no bleeding diathesis that would increase the risk of therapy  
  − There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.  
• Patients who experience a repeat Grade 3 hemorrhagic event will discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring. |
| Epistaxis, esophageal, gastric, lower gastrointestinal, intra-abdominal, and retroperitoneal hemorrhage (continued) Grade 4 | | Discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring. |
### Table 8.3 Adverse Events at Time of Retreatment

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<table>
<thead>
<tr>
<th>CTCAE System/Organ/Class (SOC)</th>
<th>Adverse Event</th>
<th>Agent</th>
<th>Dosage Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders (continued)</td>
<td>Esophageal, gastric, colonic, and small intestinal obstruction Grade 2</td>
<td>Bevacizumab</td>
<td>Hold until resolution of obstruction. Then resume treatment.</td>
</tr>
<tr>
<td></td>
<td>≥ Grade 3</td>
<td></td>
<td>Hold until resolution. If surgery is necessary, patient may restart bevacizumab ≥28 days but ≤56 days following surgery and at investigator’s discretion.</td>
</tr>
<tr>
<td></td>
<td>Esophageal, gastric, colonic, and small intestinal perforation Any grade</td>
<td></td>
<td>Discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring.</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal fistula Any grade</td>
<td></td>
<td>Discontinue bevacizumab. Continue fluoropyrimidine (and oxaliplatin).</td>
</tr>
<tr>
<td></td>
<td>Mucositis oral ≥ Grade 2</td>
<td>5-FU (or capecitabine) Oxaliplatin</td>
<td>If ≥ Grade 2 at start of cycle, delay and check weekly then treat based on interval adverse event. If ≥ Grade 2 after 14 days, discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring.</td>
</tr>
<tr>
<td></td>
<td>Vomiting ≥ Grade 2</td>
<td></td>
<td>If ≥ Grade 2 at start of cycle, delay and check weekly then treat based on interval adverse event. If ≥ Grade 2 after 14 days, discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring.</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Allergic reaction Grade 2-4</td>
<td>Oxaliplatin</td>
<td>Discontinue oxaliplatin, continue fluoropyrimidine and bevacizumab treatment.</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Biliary, esophageal, gastric, large intestinal, small intestinal anastomotic leak Grade 1</td>
<td>Bevacizumab</td>
<td>Hold bevacizumab until healing.</td>
</tr>
<tr>
<td></td>
<td>≥ Grade 2</td>
<td></td>
<td>Discontinue bevacizumab. Continue fluoropyrimidine (and oxaliplatin).</td>
</tr>
<tr>
<td></td>
<td>Wound complication ≤ Grade 2</td>
<td></td>
<td>Hold bevacizumab until healing.</td>
</tr>
<tr>
<td></td>
<td>≥ Grade 3</td>
<td></td>
<td>Discontinue bevacizumab. Continue fluoropyrimidine (and oxaliplatin).</td>
</tr>
<tr>
<td></td>
<td>Wound dehiscence ≤ Grade 2</td>
<td></td>
<td>Hold bevacizumab until healing.</td>
</tr>
<tr>
<td></td>
<td>≥ Grade 3</td>
<td></td>
<td>Discontinue bevacizumab. Continue fluoropyrimidine (and oxaliplatin).</td>
</tr>
<tr>
<td>Investigations</td>
<td>Alanine aminotransferase increased ≥ Grade 3 (&gt; 5.0 x ULN; &gt; 5 x ULN for &gt; 2 weeks)</td>
<td>5-FU</td>
<td>Delay retreatment until recovery to &lt; Grade 2 and decrease 5-FU by one dose level. If &gt; Grade 2 after 14 days, discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring.</td>
</tr>
</tbody>
</table>
### Table 8.3 Adverse Events at Time of Retreatment

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<table>
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<tr>
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<th>ADVERSE EVENT</th>
<th>AGENT</th>
<th>DOSAGE CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigations (continued)</strong></td>
<td>Alkaline phosphatase increased ≥ Grade 3 (&gt;5.0 x ULN)</td>
<td>5-FU</td>
<td>Delay retreatment until recovery to &lt; Grade 2 and decrease 5-FU by one dose level. If &gt; Grade 2 after 14 days, discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring. For patients with liver metastases whose starting ALK PHOS was Grade 2, delay until recovery to &lt; Grade 3. If &gt; Grade 3 after 14 days, discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring.</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td>Aspartate aminotransferase increased ≥ Grade 3 (&gt;5.0 x ULN; &gt;5 x ULN for &gt;2 weeks)</td>
<td>5-FU (or capecitabine) Oxaliplatin</td>
<td>Delay retreatment until recovery to &lt; Grade 2 and decrease 5-FU by one dose level. If &gt; Grade 2 after 14 days, discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring. For patients with liver metastases whose starting AST was Grade 2, delay until recovery to &lt; Grade 3. If &gt; Grade 3 after 14 days, discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring.</td>
</tr>
<tr>
<td></td>
<td>Blood bilirubin increased ≥ Grade 3 (&gt;3.0 x ULN)</td>
<td>5-FU</td>
<td>Delay therapy for up to 14 days until resolved to ≤ Grade 2. Decrease 5-FU one dose level at retreatment. If not resolved to ≤ Grade 2 after 14 days, patient goes to Observation (for 28-42 days), then to Event Monitoring.</td>
</tr>
<tr>
<td></td>
<td>Neutrophil count decreased ≥ Grade 2 (&lt;1500; &lt;1.5 x 10^9/L) OR Platelet count decreased ≥ Grade 3 (&lt;50,000; &lt;50.0 x 10^9/L)</td>
<td>Oxaliplatin</td>
<td>Hold all treatment. Resume treatment when ANC ≥1500 and platelets ≥50,000 and decrease all drugs by one dose level. If no recovery after a 3-week delay, despite institution of all clinically appropriate symptomatic treatment, discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring. Dose may not be re-escalated after reduction for adverse event.</td>
</tr>
<tr>
<td></td>
<td>Hypomagnesemia ≥ Grade 2</td>
<td>5-FU Oxaliplatin</td>
<td>Dose reduction is not required unless symptoms are present. If Grade ≥ 2 after 4 weeks, discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring.</td>
</tr>
</tbody>
</table>
**Table 8.3 Adverse Events at Time of Retreatment**

*Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified.

<table>
<thead>
<tr>
<th>CTCAE System/Organ/Class (SOC)</th>
<th>ADVERSE EVENT</th>
<th>AGENT</th>
<th>DOSAGE CHANGE</th>
</tr>
</thead>
</table>
| Nervous system disorders       | Intracranial hemorrhage Grade 1 | Bevacizumab | • Patients who are also receiving full-dose anticoagulation will discontinue all study agents. Patient goes to Observation (for 28–42 days), then to Event Monitoring.  
  • All patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met then resume at same dose:  
    - The bleeding has resolved and hemoglobin is stable.  
    - There is no bleeding diathesis that would increase the risk of therapy  
    - There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. |
| Nervous system disorders (continued) | ≥Grade 2 | Bevacizumab | Discontinue all study agents. Patient goes to Observation (for 28–42 days), then to Event Monitoring. |
|                                 | Ischemia cerebrovascular Any grade |         | Discontinue bevacizumab. Continue fluoropyrimidine (and oxaliplatin). |
|                                 | Reversible posterior leukoencephalopathy syndrome Any grade |         | Discontinue bevacizumab. Continue fluoropyrimidine (and oxaliplatin). |
|                                 | Stroke³ Any grade |         | Discontinue all study agents. Patient goes to Observation (for 28–42 days), then to Event Monitoring. |
|                                 | Transient ischemic attack³ Any grade | Bevacizumab | Discontinue bevacizumab. Continue fluoropyrimidine (and oxaliplatin). |
| Renal and urinary disorders     | Proteinuria ≥Grade 3 (≥3.5 g/24 hr) | Bevacizumab | Omit until proteinuria improves to ≤Grade 2. If no recovery after 14 days, discontinue bevacizumab. Continue fluoropyrimidine (and oxaliplatin). |
| Respiratory, thoracic and mediastinal disorders | Bronchopulmonary hemorrhage Grade 1 | Bevacizumab | • Patients who are also receiving full-dose anticoagulation will discontinue all study agents. Patient goes to Observation (for 28–42 days), then to Event Monitoring.  
  • For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met:  
    - the bleeding has resolved and hemoglobin is stable  
    - there is no bleeding diathesis that would increase the risk of therapy  
    - there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence |
|                                 | ≥ Grade 2 |         | Discontinue bevacizumab. Continue fluoropyrimidine (and oxaliplatin). |
|                                 | Cough ≥Grade 3 | Oxaliplatin | Hold oxaliplatin until interstitial lung disease is ruled out. If interstitial lung disease, discontinue oxaliplatin. Continue fluoropyrimidine and bevacizumab treatment. |
**Table 8.3 Adverse Events at Time of Retreatment**

Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified.

<table>
<thead>
<tr>
<th>CTCAE System/Organ/Class (SOC)</th>
<th>ADVERSE EVENT</th>
<th>AGENT(^1)</th>
<th>DOSAGE CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders (continued)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥Grade 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypoxia</td>
<td></td>
<td>Hold bevacizumab until resolution. Hold oxaliplatin until interstitial lung disease is ruled out. If interstitial lung disease, discontinue oxaliplatin. Continue fluoropyrimidine treatment.</td>
</tr>
<tr>
<td></td>
<td>≥Grade 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥Grade 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td>Hypertension</td>
<td>Bevacizumab</td>
<td>See Section 8.5 for management.</td>
</tr>
<tr>
<td></td>
<td>Any grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vascular disorders (continued)</strong></td>
<td>Thromboembolic event(^1) (Venous)</td>
<td>Bevacizumab</td>
<td>• Omit bevacizumab. If the planned duration of full-dose anticoagulation is &lt;2 weeks, bevacizumab should be omitted until the full-dose anticoagulation period is over.</td>
</tr>
<tr>
<td></td>
<td>≥Grade 3 (asymptomatic thrombosis)</td>
<td></td>
<td>• If the planned duration of full-dose anticoagulation is ≥2 weeks, bevacizumab may be resumed if all of the criteria below are met:</td>
</tr>
<tr>
<td></td>
<td>≥Grade 3 (symptomatic)</td>
<td></td>
<td>• The subject must not have pathological conditions that carry high risk of bleeding (e.g., tumor involving major vessels or other conditions).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• The subject must not have had hemorrhagic events while on study.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• The subject must be on a stable dose of warfarin or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• If thromboembolic worsen/recur upon resumption of study therapy, discontinue bevacizumab. Continue with fluoropyrimidine (and oxaliplatin).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Discontinue bevacizumab. Continue with fluoropyrimidine (and oxaliplatin).</td>
</tr>
<tr>
<td></td>
<td>Peripheral ischemia(^3)</td>
<td></td>
<td>Discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring.</td>
</tr>
<tr>
<td></td>
<td>Any grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Visceral arterial ischemia(^3)</td>
<td></td>
<td>Discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring.</td>
</tr>
<tr>
<td></td>
<td>Any grade</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 8.3 Adverse Events at Time of Retreatment

*Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified

<table>
<thead>
<tr>
<th>CTCAE System/Organ/Class (SOC)</th>
<th>ADVERSE EVENT</th>
<th>AGENT¹</th>
<th>DOSAGE CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AT TIME OF RETREATMENT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All other non-hematologic adverse events⁴</td>
<td>≥Grade 3</td>
<td>5-FU (or capecitabine)</td>
<td>Dose modification for other non-hematologic adverse events at time of retreatment are also based on NCI CTCAE Version 4.0. Treatment should be delayed until all adverse events have resolved to ≤Grade 2 up to 14 days, otherwise patient goes to Observation (for 28-42 days), then to Event Monitoring. Then, doses of all drugs should be decreased by one level unless otherwise specified above.</td>
</tr>
<tr>
<td>Grade 2-4 (excludes nausea/vomiting that has not been pre-medicated)</td>
<td>Bevacizumab</td>
<td>Hold responsible agent/agents until resolved to grade 0-1 adverse event, then decrease by one dose level. If no recovery after a 21-day delay, despite institution of all clinically appropriate symptomatic treatment, discontinue bevacizumab and patient goes to Observation (for 28-42 days), then to Event Monitoring. If bevacizumab is discontinued, continue with fluoropyrimidine (and oxaliplatin).</td>
<td></td>
</tr>
</tbody>
</table>


¹ The dose of leucovorin will not be adjusted due to adverse event. It should remain at 400 mg/m² for all courses. Leucovorin will be given immediately prior to each 5-fluorouracil dose; thus, if 5-fluorouracil is delayed, leucovorin will be delayed.

² Recommended evaluation of suspected HUS: Evaluation should include CBC differential, platelets, PT, PTT, fibrinogen, FDP (Fibrin degradation products), Anti thrombin III, Von Willebrand factor, anti-nuclear antibody, rheumatoid factor, Compliment Cascade C3, C4, and CH₅₀, anti-platelet antibodies, platelet-associated IgG, and circulating immune complexes. Renal evaluation should include creatinine, BUN, and urinalysis with microscopic examination. Other laboratory and hematological evaluations as appropriate should also be obtained, including peripheral blood smear and free hemoglobin.

³ Arterial thromboembolic events include myocardial infarction, stroke, transient ischemic attack, peripheral ischemia and visceral arterial ischemia.

⁴ Exceptions: alopecia, fatigue, anorexia, nausea/vomiting if can be controlled by antiemetics, viral infections.
### Table 8.4 Oxaliplatin Dose Modifications for Non-CTCAE Neurologic Adverse Events – Arm B

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Duration of Adverse Event</th>
<th>Persistent Between Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 - 7 Days</td>
<td>&gt;7 Days</td>
</tr>
<tr>
<td><strong>Paresthesias/Dysesthesias</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paresthesias/dysesthesias(^1) of short duration that resolve and do not interfere with function (Grade 1)</td>
<td>no change</td>
<td>no change</td>
</tr>
<tr>
<td>Paresthesias/dysesthesias(^2) interfering with function, but not activities of daily living (ADL) (Grade 2)</td>
<td>no change</td>
<td>no change</td>
</tr>
<tr>
<td>Paresthesias/dysesthesias(^2) with pain or with functional impairment that also interfere with ADL (Grade 3)</td>
<td>1(^{st}) time: Decrease oxaliplatin one dose level</td>
<td>1(^{st}) time: Decrease oxaliplatin one dose level</td>
</tr>
<tr>
<td></td>
<td>2(^{nd}) time: Decrease oxaliplatin one dose level</td>
<td>2(^{nd}) time: Decrease oxaliplatin one dose level</td>
</tr>
<tr>
<td>Persistent paresthesias/dysesthesias that are disabling or life-threatening (Grade 4)</td>
<td>Discontinue</td>
<td>Discontinue</td>
</tr>
<tr>
<td><strong>Laryngeal Dysesthesias</strong> (investigator discretion used for grading):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 = mild</td>
<td>No change</td>
<td>Increase duration of infusion to 6 hours</td>
</tr>
<tr>
<td>Grade 2 = moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Also recommended is administration of benzodiazepine and patient education. Management of patient if ≥Grade 2 laryngeal dysesthesias occurs while treatment is being administered.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 = severe</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*If oxaliplatin is discontinued, continue other study agents unless adverse events preclude their continuation.

\(^1\) Not resolved by the beginning of the next cycle.

\(^2\) May be cold-induced.

### 8.5 Management of Hypertension

**Hypertension Grade Definitions from NCI CTCAE Version 4.0:**

- **Grade 1:** Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)
- **Grade 2:** Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 -99 mm Hg); medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated.
- **Grade 3:** Stage 2 hypertension (systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used is indicated.
- **Grade 4:** Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated.
### Table 8.5 Management of Hypertension

<table>
<thead>
<tr>
<th>Grade (see below for definitions)</th>
<th>Antihypertensive Therapy</th>
<th>Blood Pressure Monitoring</th>
<th>Bevacizumab Dose Modification Based on Interval Adverse Event</th>
<th>Bevacizumab Dose Modification at Time of Retreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Initiate anti-hypertensive medication, if appropriate.</td>
<td>Consider increased BP monitoring</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Grade 2 (asymptomatic)</td>
<td>Initiate anti-hypertensive medication (suggest dihydropyridine calcium channel blocker)</td>
<td>Increase frequency and monitor (by health professional) every 2 days until stabilized.</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Grade 2 (symptomatic) OR Grade 3</td>
<td>Initiate or adjust anti-hypertensive medication. (suggest adding one or two of the following agents: calcium channel blocker (if not already used), K+ channel opener, ACE inhibitor, thiazide diuretic, beta-blocker)¹</td>
<td>Increase frequency and monitor (by health professional) every 2 days until stabilized; continue q2d monitoring to stabilization after dosing restarted.</td>
<td>Omit* bevacizumab until symptoms resolve AND BP &lt;160/90 mm/Hg. Resume bevacizumab at same dose. For hypertension that is refractory requiring delay of bevacizumab for &gt; 4 weeks, discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring.</td>
<td>Hold* bevacizumab until symptoms resolve AND BP &lt;160/90 mm/Hg. Resume bevacizumab at same dose. For hypertension that is refractory requiring delay of bevacizumab for &gt; 4 weeks, discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring.</td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
<td></td>
<td>Discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring</td>
<td>Discontinue all study agents. Patient goes to Observation (for 28-42 days), then to Event Monitoring</td>
</tr>
</tbody>
</table>

* If any doses are missed, they will not be made up. Patients requiring a delay of >28 days should go off protocol therapy then go to Observation (for 28-42 days), then to Event Monitoring.

¹ Antihypertensive therapy will be at the discretion of the attending physician and treatment must be recorded on the Evaluation/Treatment Form (see Section 18.0). The recommended, but not mandatory treatment algorithm is: calcium channel blocker → add ACE inhibitor → add hydrochlorothiazide (HCTZ) → add beta-blocker. Use of this algorithm is provider’s choice.

### 9.0 Ancillary Treatment/Supportive Care

**9.1 Hypertension** is a known and potentially serious adverse event associated with bevacizumab treatment. Patients will have their blood pressure monitored and recorded weekly during the first 42 days of therapy and thereafter monitored prior to each new cycle after that, either at the treating location, their local doctor’s office, or using any calibrated electronic device (such as those found at a local drug store or pharmacy) (see Section 4.0). If blood pressure is not taken at the treating location, patients must...
complete a Blood Pressure Diary (Appendix IV). The patient should bring the completed diary with them to each visit at the treating location. An increase in blood pressure of >20 mmHg (systolic) and 10 mmHg (diastolic) should be reported to the treatment physician immediately. (See Section 8.5 for hypertension management and dose reduction guidelines.)

9.2 If patients on treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be omitted for 42-56 days prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin/restart bevacizumab until 28 days after that procedure (in the case of high risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 42 days and bevacizumab no earlier than 56 days after surgery).

9.3 Anti-platelet therapy (e.g., ≤ 325 mg/day aspirin) should be considered for the treatment of patients at high risk of developing an arterial thromboembolic event unless contraindicated and may be continued in patients receiving it at time of entry. Patients developing bleeding on study should be evaluated for possible bevacizumab discontinuation as described in the protocol.

9.4 Antiemetics may be used at the discretion of the attending physician.

9.5 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (Smith et al. 2006).

9.6 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.7 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be hospitalized for intravenous hydration and correction of electrolyte imbalances.

9.8 Patients with indwelling venous catheters may receive prophylaxis anticoagulation against catheter thrombosis in accordance with the local standard of care.
9.9 Patients who experience infusion-associated temperature elevations to ≥ 38.5°C (101.3°F) or other infusion-associated symptoms may be treated symptomatically with acetaminophen, diphenhydramine, meperidine, or other medications as clinically indicated.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Event Characteristics

**CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/forms/default.htm).

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE v4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether an adverse event should be reported as an expedited report (see Section 10.4). **Important:** Expedited adverse event reporting requires submission of an Adverse Event Expedited Reporting System (AdEERS) report(s). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Section 10.4 and 10.5. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.4 and 18.0).

10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). Grade is an essential element of the Guidelines and, in general, relates to severity for the purposes of regulatory reporting to NCI.

- **NOTE:** A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected

- The determination of whether an AE is expected is based the information provided in Section 15.0 of this protocol.

- Unexpected AEs are those not listed in the information provided in Section 15.0 of this protocol.

**NOTE:** “Unexpected adverse experiences” means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:
Definite - The adverse event is clearly related to the agent(s).
Probable - The adverse event is likely related to the agent(s).
Possible - The adverse event may be related to the agent(s).
Unlikely - The adverse event is doubtfully related to the agent(s).
Unrelated - The adverse event is clearly NOT related to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.31 Special Situations for Expedited Reporting

10.311 An expedited report is not required for a specific protocol where an AE is listed as expected. These events must still be reported via routine reporting as specified in Section 10.5. The protocol-specific guidelines supersede the NCI Adverse Event Reporting Guidelines (See Section 10.4) for AE reporting.

10.312 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant disabilities/incapacities, congenital anomalies or birth defects, must be reported via AdEERS if they occur at any time following treatment with an agent under an IND/IDE.

10.313 Death

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24 hours.

**EXCEPTION:** Deaths clearly due to progressive disease should NOT be reported via AdEERS, but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS).

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death (not associated with a CTCAE term)

Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.

Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5

Sudden death NOS: An unexpected cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
10.314 Secondary Malignancy

- A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- CTEP requires all secondary malignancies that occur following treatment with an agent under an IND/IDE be reported via AdEERS. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.315 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS.
10.4 Expedited Reporting Requirements for Studies using Commercial Agent(s) ONLY:

**Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention**

**FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)**

**NOTE:** Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

**ALL SERIOUS** adverse events that meet the above criteria **MUST** be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

<table>
<thead>
<tr>
<th>Hospitalization</th>
<th>Grade 1 Timeframes</th>
<th>Grade 2 Timeframes</th>
<th>Grade 3 Timeframes</th>
<th>Grade 4 &amp; 5 Timeframes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resulting in Hospitalization ≥ 24 hrs</td>
<td></td>
<td>10 Calendar Days</td>
<td></td>
<td>24-Hour 5 Calendar Days</td>
</tr>
<tr>
<td>Not resulting in Hospitalization ≥ 24 hrs</td>
<td>Not required</td>
<td>10 Calendar Days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### NOTE

Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

**Expedited AE reporting timelines are defined as:**

- **"24-Hour; 5 Calendar Days"** - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- **"10 Calendar Days"** - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

---

1Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

- **Expedited 24-hour notification followed by complete report within 5 calendar days for:**
  - All Grade 4, and Grade 5 AEs

- **Expedited 10 calendar day reports for:**
  - Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
  - Grade 3 adverse events

2 For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.

Effective Date: May 5, 2011

Refer to 10.41 for NCI Contact Information or Technical Help regarding AdEERS reporting.

In the rare event when internet connectivity is disrupted, a 24 hour notification must be made to NCI by telephone. An electronic report must be submitted immediately upon establishment of internet re-connection.
10.41 - Contact Information for NCI Safety Reporting

<table>
<thead>
<tr>
<th>Website for submitting expedited reports</th>
<th><a href="https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$_startup">https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$_startup</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>AdEERSMD Help Phone (for CTEP)*</td>
<td>301-897-7497 Monday through Friday, 7:00 AM to 7:00 PM (US Eastern Time)</td>
</tr>
<tr>
<td>CIP Help Phone for SAE reporting*</td>
<td>301-897-1704 Monday through Friday, 7:00 AM to 7:00 PM (US Eastern Time)</td>
</tr>
<tr>
<td>Fax for expedited report supporting Medical Documentation for CTEP trials</td>
<td>301-230-0159 (back-up FAX: 301-897-7404)</td>
</tr>
<tr>
<td>Fax for expedited report supporting Medical Documentation for CIP trials</td>
<td>301-897-7402</td>
</tr>
<tr>
<td>AdEERSMD Help Email: <a href="mailto:adeersmd@tech-res.com">adeersmd@tech-res.com</a></td>
<td></td>
</tr>
<tr>
<td>CIP SAE Reporting Email: <a href="mailto:CIPSAEReporting@tech-res.com">CIPSAEReporting@tech-res.com</a></td>
<td></td>
</tr>
<tr>
<td>Technical (e.g., IT or computer issues ONLY) Help Phone*</td>
<td>1-888-283-7457 or 301-840-8202</td>
</tr>
<tr>
<td>AdEERS Technical Help Email</td>
<td><a href="mailto:ncitctephelp@ctep.nci.nih.gov">ncitctephelp@ctep.nci.nih.gov</a>.</td>
</tr>
<tr>
<td>CTCAE v4 Help/Questions Email</td>
<td><a href="mailto:ncitctcaehelp@mail.nih.gov">ncitctcaehelp@mail.nih.gov</a></td>
</tr>
<tr>
<td>AdEERS FAQs link</td>
<td><a href="https://webapps.ctep.nci.nih.gov/ctep-html/adr_faq.htm">https://webapps.ctep.nci.nih.gov/ctep-html/adr_faq.htm</a></td>
</tr>
<tr>
<td>AdEERS Computer Based Training link</td>
<td><a href="http://ctep.cancer.gov/reporting/AdEERS_CBT_v3/start.html">http://ctep.cancer.gov/reporting/AdEERS_CBT_v3/start.html</a></td>
</tr>
</tbody>
</table>

*Office phone and fax are accessible 24 hrs per day 7 days a week (The AdEERSMD phone line is staffed from Monday through Friday, 7:00 AM to 7:00 PM ET. Any phone call after these hours will go to voicemail. Please leave contact information and the phone call will be returned the following business day.

10.5 Other Required Expedited Reporting

<table>
<thead>
<tr>
<th>EVENT TYPE</th>
<th>REPORTING PROCEDURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report</td>
<td><strong>NCCTG Institutions Only:</strong> Complete a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form electronically via the NCCTG Remote Data Entry System within 5 working days of the date the clinical research associate (CRA) is aware of the event(s) necessitating the form. If an AdEERS report has been submitted, this form does not need to be submitted.</td>
</tr>
</tbody>
</table>
10.51 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per CTCAE v4.0 grading unless otherwise stated in the table below:

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Adverse event/Symptoms</th>
<th>Baseline</th>
<th>Each evaluation</th>
<th>Grading scale (if not CTCAE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Febrile neutropenia</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Acute coronary syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td># stools per day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Esophagitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mucositis oral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fever</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Abdominal infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bladder infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Catheter related infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lung infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Wound dehiscence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight loss</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dysesthesia</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paresthesia</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral Sensory Neuropathy&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Proteinuria</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Pharyngeal mucositis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thromboembolic event</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

1.Standardized questions have been developed to assist in classifying patient-reported symptoms to determine peripheral sensory neuropathy grade (see Appendix III).

10.511 Submit via appropriate North Central Cancer Treatment Group (NCCTG) Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section...
10.511 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.512 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.513 Grade 5 AEs (Deaths)

10.5131 Any death within 30 days of the patient’s last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5132 Any death more than 30 days after the patient’s last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.52 Submit via appropriate North Central Cancer Treatment Group (NCCTG) Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.4:

10.521 Grade 1 and 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.522 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.523 Grade 5 AEs (Deaths)

10.5231 Any death within 30 days of the patient’s last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5232 Any death more than 30 days after the patient’s last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.53 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.54 Additional Instructions or Exceptions

Add 1

The NCCTG SAE Coordinator will forward a copy of all AdEERS reports to: Genentech Drug Safety at Fax #: (650) 225-4682 or (650) 225-5288.
11.0 Treatment Evaluation Using RECIST Guideline

NOTE: This study uses protocol RECIST v1.1 template dated 2/16/2011. See the footnote for the table regarding measureable disease in Section 11.44, as it pertains to data collection and analysis.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) (Eisenhauer et al. 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations: For the purposes of this study, patients should be re-evaluated every 6 weeks.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.213 A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Tumor lesions in a previously irradiated area are not considered measurable disease.

11.22 Non-Measurable Disease

11.221 All other lesions (or sites of disease), are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.
11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.

- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.

- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

- Chest X-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scans are preferable.

- Physical Examination: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A ‘positive’ FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered ‘negative.’ New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
   i. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
   ii. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.
   iii. If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

11.33 Measurement at Follow-up Evaluation:
- A subsequent scan must be obtained 6 weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR).
- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks (see Section 11.44).
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect
11.41 Target Lesions & Target Lymph Nodes
- Measurable lesions (as defined in Section 11.21) up to a maximum of 3 lesions, representative of all involved organs, should be identified as “Target Lesions” and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in 11.21), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

Note: If fewer than 3 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.
- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
• Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

• The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non-target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

11.431 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 Evaluation of Target Lesions

• Complete Response (CR): All of the following must be true:
  a. Disappearance of all target lesions.
  b. Each target lymph node must have reduction in short axis to <1.0 cm.

• Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (see Section 11.41).

• Progression (PD): At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and has increased to ≥1.0 cm short axis during follow-up.
  b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph
nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the MSD.

11.433 Evaluation of Non-Target Lesions & Non-Target Lymph Nodes

- **Complete Response (CR):** All of the following must be true:
  a. Disappearance of all non-target lesions.
  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

- **Non-CR/Non-PD:** Persistence of one or more non-target lesions or non-target lymph nodes.

- **Progression (PD):** At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
  b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)
  c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.
11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient’s status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

### For Patients with Measurable Disease

<table>
<thead>
<tr>
<th>Target Lesions &amp; Target Lymph Nodes</th>
<th>Non-Target Lesions &amp; Non-Target Lymph Nodes</th>
<th>New Sites of Disease</th>
<th>Overall Objective Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>Non-CR/Non-PD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>Non-CR/Non-PD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>CR/PR</td>
<td>Not All Evaluated*</td>
<td>No</td>
<td>PR**</td>
</tr>
<tr>
<td>SD</td>
<td>CR</td>
<td>No</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td>Non-CR/Non-PD</td>
<td>No</td>
<td>Not Evaluated (NE)</td>
</tr>
<tr>
<td>Not all Evaluated</td>
<td>CR</td>
<td>No</td>
<td>Not Evaluated (NE)</td>
</tr>
<tr>
<td></td>
<td>Non-CR/Non-PD</td>
<td>No</td>
<td>Not Evaluated (NE)</td>
</tr>
<tr>
<td>PD</td>
<td>Unequivocal PD</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td></td>
<td>CR</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td></td>
<td>Non-CR/Non-PD</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>CR/PR/SD/PD/Not All Evaluated</td>
<td>Unequivocal PD</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>CR/PR/SD/PD/Not All Evaluated</td>
<td>CR</td>
<td>Yes</td>
<td>PD</td>
</tr>
<tr>
<td></td>
<td>Non-CR/Non-PD</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

*See Section 11.431

**NOTE:** This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the NCCTG protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

### For Patients with Non-Measurable Disease Only

<table>
<thead>
<tr>
<th>Non-Target Lesions &amp; Non-Target Lymph Nodes</th>
<th>New Sites of Disease</th>
<th>Overall Objective Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>Non-CR/Non-PD</td>
<td>No</td>
<td>Non-CR/Non-PD</td>
</tr>
<tr>
<td>Not All Evaluated*</td>
<td>No</td>
<td>Not Evaluated (NE)</td>
</tr>
<tr>
<td>Unequivocal PD</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

*See Section 11.431

11.45 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A patient is classified as having PD due to “symptomatic deterioration” if any of the following occur that are not either related to study treatment or other medical conditions:
• Weight loss >10% of body weight.
• Worsening of tumor-related symptoms.
• Decline in performance status of >1 level on ECOG scale.

12.0 Descriptive Factors

12.1 Disease status: Recurrent without previous adjuvant therapy vs. recurrence with prior adjuvant therapy (chemotherapy with/without radiation) vs. Initial presentation with metastatic disease

12.2 Primary tumor intact (Y/N)

13.0 Treatment/Follow-up Decision at Evaluation of Patient

13.1 Patients who are CR, PR, or SD will continue treatment per protocol.

13.2 Patients who develop PD while receiving therapy will be observed one time at 28-42 days after termination of treatment, then go to the event-monitoring phase and be followed for up to a total of 5 years from randomization per Section 18.0.

13.3 Patients who go off protocol treatment for reasons other than PD will be observed one time at 28-42 days after termination of treatment, then go to the event-monitoring phase per Section 18.0.

13.4 Patients who experience intolerable adverse events or who refuse further treatment will be observed one time at 28-42 days after termination of treatment, then go to Event Monitoring and will be followed for up to a total of 5 years from randomization per Section 18.0.

13.5 Patients who have an ongoing bevacizumab-related Grade 4 or serious adverse event at the time of discontinuation from study treatment will continue to be followed until resolution of the event or until the event is considered irreversible (see Section 8.0).

13.6 A patient is deemed ineligible if after randomization, it is determined that at the time of randomization, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

• If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

• If the patient never received treatment, only on-study material must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

13.7 A patient is deemed a major violation, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary endpoint is questionable. The patient may continue treatment off-protocol at the discretion of the
physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.8 A patient is deemed a cancel if he/she is removed from the study for any reason before any study treatment is given. On-study material and end of Active Treatment/Cancel Notification Form must be submitted. The patient will go directly to the event-monitoring phase of the study. Event monitoring will be required per Section 18.0 of the protocol.

14.0 Body Fluid Biospecimens

14.1 Body Fluid Biospecimen Submission

14.11 Summary Table of Body Fluid Biospecimens for This Protocol

<table>
<thead>
<tr>
<th>Type of biospecimen to submit</th>
<th>Mandatory or optional</th>
<th>When to submit</th>
<th>Reason for submission (background/methodology section)</th>
<th>Where to find specific details for specimen submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood/blood products (EDTA whole blood)</td>
<td>Mandatory</td>
<td>Baseline prior to study treatment</td>
<td>Pharmacogenetic studies (Section 14.41)</td>
<td>Section 14.2</td>
</tr>
<tr>
<td>Blood/blood products (EDTA plasma and WBC)</td>
<td>Mandatory</td>
<td>Multiple draws (see Section 14.24 for schedule)</td>
<td>Circulating marker analyses and optional future banking (Section 14.41)</td>
<td>Section 14.2</td>
</tr>
<tr>
<td>Blood/blood products (No additive serum)</td>
<td>Mandatory</td>
<td>Multiple draws (see Section 14.24 for schedule)</td>
<td>Circulating marker analyses and optional future banking (Section 14.41)</td>
<td>Section 14.2</td>
</tr>
</tbody>
</table>

14.2 Blood/Blood Products Handling

14.21 Kits are required for this study. (Mayo Clinic Rochester will use Special Study Cards in place of kits.)

14.211 The kit contains supplies and instructions for collecting, processing, and shipping specimens.

14.212 Participating institutions may obtain kits by completing and faxing the Supply Order Form (found in the Forms Packet) to the number listed on the form. Fill out the site address to where the kits will be shipped on the Fax Supply form. Because we are now being charged for all outgoing kits, a small, but sufficient supply of the specimen collection kits should be ordered prior to patient entry. Do not send the unused kits back to Biospecimen Accessioning and Processing (BAP) Receiving or the BAP Shared Resource, Mayo Clinic Rochester.
14.213 Kits will be sent via FedEx® Group at no additional cost to the participating institutions. **Allow at least two weeks to receive the kits.** Kits will arrive inside the shipping boxes.

14.214 Kits will not be sent via rush delivery service unless the participating institution provides their own FedEx® account number or alternate billing number for express service. **NCCTG will not cover the cost for rush delivery of kits.**

14.22 All samples must be collected **Monday-Thursdays ONLY.**

14.23 Label specimen tube(s) with protocol number, NCCTG patient ID number, and time and data blood is drawn.

14.24 Collect and process all blood/blood products according to specific kit instructions and table below.
## 14.241 Summary Table of Research Blood/Blood Products to Be Collected for This Protocol

<table>
<thead>
<tr>
<th>Indicate if specimen is mandatory or optional</th>
<th>Collection tube description and/or additive (color of tube top)</th>
<th>Volume to collect per tube (number of tubes to be collected)</th>
<th>Blood product being processed and submitted by participating site</th>
<th>Baseline, prior to treatment</th>
<th>After 6 weeks of treatment</th>
<th>At time patient discontinues treatment</th>
<th>Additional processing required at site after blood draw?</th>
<th>Storage /shipping conditions¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandatory</td>
<td>No additive (red)</td>
<td>10 ml (1)</td>
<td>Serum</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Yes</td>
<td>Freeze/dry ice</td>
</tr>
<tr>
<td>Mandatory</td>
<td>EDTA (purple)</td>
<td>10 ml (1)</td>
<td>Plasma, WBCs²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Yes</td>
<td>Freeze/dry ice</td>
</tr>
<tr>
<td>Mandatory</td>
<td>EDTA (purple)</td>
<td>10 ml (1)</td>
<td>Whole blood</td>
<td></td>
<td></td>
<td>X</td>
<td>No</td>
<td>Refrigerate/cold pack DO NOT FREEZE</td>
</tr>
</tbody>
</table>

1. After all samples have been processed according to kit instructions, ship all specimens according to shipping instructions (see Section 14.25 for detailed shipping instructions.)
2. WBCs, white blood cells

### 14.25 Shipping

#### 14.251 Verify ALL sections of the Research Blood Submission Form (see Forms Packet), BAP Requisition Form (provided in kit), and specimen collection labels are completed and filled in correctly. **NCCTG sites** enter information from the Research Blood Submission Form into the remote data entry system ≤7 days after specimen collection (see Forms Packet). **Non-NCTG sites** submit the Research Blood Submission Form to NCCTG ≤7 days after specimen collection for data entry (see Forms Packet).

#### 14.252 Specimens must be shipped the same day they are drawn.

#### 14.253 **Baseline specimens only:** Specimens will be shipped in a dual-temperature shipping container. Place the refrigerated EDTA tube with a properly prepared cold pack in one compartment. See kit instructions for specific details for cold pack preparation (i.e., frozen or refrigerated) and proper packing of blood and cold pack to avoid freezing of specimen. Place the frozen serum and plasma samples with dry ice in the other compartment of the dual temperature shipping container.
14.254 **Follow-up specimens:** All serum, plasma, and WBC specimens will be packed and shipped on dry ice. See kit instructions for specific details.

14.255 All visits: Ship specimens via Priority Overnight service, **Monday-Thursday ONLY,** to BAP Receiving according to kit instructions. **Do not send samples on weekends or just prior to federal holidays.**

14.256 The BAP kits will include a smart shipper label (3x5 white bar-coded label) affixed to the shipping boxes. The smart shipper label is a pre-addressed return label, which replaces the need for an airbill. Shipping costs will be covered by NCCTG if the shipping box is used for shipping specimens to BAP Receiving.


14.258 BAP Shared Resource will process specimens according to Appendix XIII instructions.

### 14.3 Other Body Fluids Handling (None)

### 14.4 Study Methodology and Storage Information

14.41 Blood/blood product samples will be collected for the following research:

14.411 DNA will be extracted by the BAP Shared Resource, Mayo Clinic Rochester and stored for pharmacogenetic assays (e.g., for genetic polymorphisms) that may correlate with efficacy and tolerability of study treatment, using standard laboratory protocols in the Genotyping Shared Resource (GSR), Mayo Clinic Rochester (See Section 1.5 for additional details). An aliquot of DNA from each specimen will be transferred to the CALGB Pathology Coordinating Office (PCO) for the planned genome-wide pharmacogenomic analyses. Residual DNA will be stored frozen at −80°C by the BAP Shared Resource, according to patient consent information (see Sections 6.34-6.36) until specific analyses are identified. As protocols are developed, they will be presented for NCCTG and IRB review and approval. (This collection is part of a general strategy of investigation for the majority of NCCTG studies.)

14.412 As part of ongoing NCCTG research, we will collect serum and plasma for circulating marker analyses. The circulating markers to be assayed will be determined at the conclusion of the study and based on the current state of the science. Residual blood products (i.e., serum, plasma, and WBCs) will be stored for future research studies, according to patient consent information (see Sections 6.34-6.36), on molecular determinants of efficacy and tolerability. Samples will be stored frozen at −80°C by the BAP Shared Resource until specific analyses are identified. As protocols are developed, they will be presented for NCCTG and IRB review and approval.
14.5 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Drug Information

15.1 Fluorouracil (Adrucil, Efudex, [5FU])

- Commercial Supply - Please refer to the package insert for further information on 5-fluorouracil.

15.11 Background: Antineoplastic Agent, Antimetabolite (Pyrimidine Analog). Fluorouracil is a fluorinated Pyrimidine Antimetabolite that inhibits thymidylate synthetase, blocking the methylation of deoxyuridylic acid to thymidylic acid, interfering with DNA, and to a lesser degree, RNA synthesis. Fluorouracil appears to be phase specific for the G1 and S phases of the cell cycle.

15.12 Formulation: Commercially available for injection 50 mg/mL (10 mL, 20 mL, 50 mL, and 100 mL).

15.13 Preparation, storage, and stability: Store intact vials at room temperature and protect from light. A slight discoloration may occur with storage but usually does not denote decomposition. Dilute in 50 – 1000 mL of 0.9% NaCl or D5W. If exposed to cold, a precipitate may form; gentle heating to 60°C will dissolve the precipitate without impairing the potency. Solutions in 50 – 1000 mL 0.9% NaCl or D5W or undiluted solutions in syringes are stable for 72 hours at room temperature. Fluorouracil should not be coadministered with either diazepam, doxorubicin, daunorubicin, idarubicin, cisplatin, or cytarabine. However, fluorouracil and leucovorin are compatible for 14 days at room temperature. Fluorouracil is compatible with vincristine, methotrexate, and cyclophosphamide.

15.14 Administration: Fluorouracil may be given IV infusion. Refer to section 7.0 (treatment) administration instructions specific to the protocol.

15.15 Pharmacokinetic information:
Distribution: \( V_d \approx 22\% \) of total body water; penetrates extracellular fluid, CSF, and third space fluids (e.g., pleural effusions and ascitic fluid)
Metabolism: Hepatic (90%); via a dehydrogenase enzyme; Fluorouracil must be metabolized to be active.
**Half-life elimination**: Biphasic: Initial: 6-20 minutes; two metabolites, FdUMP and FUTP, have prolonged half-lives depending on the type of tissue.

**Excretion**: Lung (large amounts as CO₂); urine (5% as unchanged drug) in 6 hours.

15.16 **Potential Drug Interactions**: Fluorouracil may increase effects of warfarin. Avoid ethanol (due to GI irritation). Avoid black cohosh.

15.17 **Known potential adverse events**: Consult the package insert for the most current and complete information.

**Common known potential toxicities, > 10%**:  
Dermatologic: Dermatitis, pruritic maculopapular rash, alopecia.  
Gastrointestinal (route and schedule dependent): Heartburn, nausea, vomiting, anorexia, stomatitis, esophagitis, anorexia, diarrhea. GI toxicity (anorexia, nausea, and vomiting) is generally more severe with continuous-infusion schedules.  
Emetic potential: <1000 mg: Moderately low (10% to 30%) ≥ 1000 mg: Moderate (30% to 60%)  
Hematologic: Leukopenia; Myelosuppressive (tends to be more pronounced in patients receiving bolus dosing of FU). Decreased white blood cell count with increased risk of infection; decreased platelet count with increased risk of bleeding.  
Local: Irritant chemotherapy.

**Less common known potential toxicities, 1% - 10%**:  
Dermatologic: Dry skin  
Gastrointestinal: GI ulceration

**Rare known potential toxicities, <1% (Limited to important or life-threatening)**:  
Cardiac enzyme abnormalities, chest pain, coagulopathy, dyspnea, ECG changes similar to ischemic changes, hepatotoxicity; hyperpigmentation of nail beds, face, hands, and veins used in infusion; hypotension, palmar-plantar syndrome (hand-foot syndrome), photosensitization. Cerebellar ataxia, headache, somnolence, ataxia are seen primarily in intracarotid arterial infusions for head and neck tumors.

15.18 **Drug procurement**: Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.19 **Nursing Guidelines**:

15.191 Monitor complete blood count and platelet count. Instruct patient to report signs and symptoms of infection, unusual bruising or bleeding to the physician.

15.192 Administer antiemetics as indicated.
15.193  Diarrhea may be dose–limiting; encourage fluids and treat symptomatically.

15.194  Assess for stomatitis; oral care measures as indicated. May try vitamin E oil dabbed on sore, six times daily.

15.195  Monitor for neurologic symptoms (headache, ataxia).

15.196  Inform patient of potential alopecia.

15.197  Those patients on continuous infusion may need instruction regarding central intravenous catheters and portable intravenous or IA infusion devices.

15.198  5FU–induced conjunctivitis is a common problem. Advise patient to report any eye soreness or redness to the healthcare team.

15.199  Photosensitivity may occur. Instruct patients to wear sun block when outdoors.

15.2  Leucovorin Calcium (CF)

- Commercial Supply - Please refer to the package insert for further information on leucovorin calcium.

15.21  **Background**: A reduced form of folic acid, leucovorin supplies the necessary cofactor blocked by methotrexate, enters the cells via the same active transport system as methotrexate. Stabilizes the binding of 5-dUMP and thymidylate synthetase, enhancing the activity of fluorouracil.

15.22  **Formulation**: Commercially available as:
Injection, powder for reconstitution: 50 mg, 100 mg, 200 mg, 350 mg
Injection, solution: 10 mg/mL (50 mL)

15.23  **Preparation, storage, and stability**:
Powder for injection: Store at room temperature, protect from light. Reconstitute with sterile water for injection or bacteriostatic water for injection; dilute in 100-1000 mL 0.9% NaCl or D5W. When doses > 10 mg/m² are required, reconstitute using sterile water for injection, not a solution containing benzyl alcohol. Solutions reconstituted with bacteriostatic water for injection must be used within 7 days. Solutions reconstituted with sterile water for injection must be used immediately. Parenteral admixture is stable for 24 hours stored at room temperature and for 4 days when stored under refrigeration. Solution for injection: Prior to dilution, store vials under refrigeration, protect from light.

15.24  **Administration**: Due to calcium content, do not administer I.V. solutions at a rate > 160 mg/minute. Refer to individual protocols for specific administration instructions.
Leucovorin should be administered I.V. infusion (15 minutes to 2 hours).

**In combination with fluorouracil:** The fluorouracil is usually given after the leucovorin infusion. Leucovorin is usually administered by I.V. bolus injection or short (10-120 minutes) I.V. infusion. Other administration schedules have been used; refer to the treatment section (Section 7.0) of the protocol for specific directions.

**In combination with oxaliplatin:** Leucovorin is compatible with oxaliplatin and may be administered concurrently via Y-connector at normal doses. Oxaliplatin is incompatible with 0.9% NaCl. Leucovorin must be diluted in D$_5$W when administered with oxaliplatin.

**15.25 Pharmacokinetic information:**

**Metabolism:** Intestinal mucosa and hepatically to 5-methyl-tetrahydrofolate (5MTHF; active)

**Half-life elimination:** ~4-8 hours

**Time to peak:** I.V.: Total folates: 10 minutes; 5MTHF: ~1 hour

**Excretion:** Urine (primarily); feces

**15.26 Potential Drug Interactions:**

**Decreased Effect:** May decrease efficacy of trimethoprim/sulfamethoxazole against *Pneumocystis carinii* pneumonia.

**15.27 Known potential adverse events:** Consult the package insert for the most current and complete information.

**Common known potential toxicities, > 10%:**

None

**Less common known potential toxicities, 1% - 10%:**

Dermatologic: Rash, pruritus, erythema, urticaria

Gastrointestinal: Nausea, vomiting

**Rare known potential toxicities, <1% (Limited to important or life-threatening):**

Allergic reactions, anaphylactoid reactions, dyspnea, thrombocytosis

**15.28 Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

**15.29 Nursing Guidelines:**

15.291 Headache may occur. Advise patient that analgesics such as Tylenol may help. Instruct patient to report any headache that is unrelieved.

15.292 Observe for sensitization reaction (rash, hives, pruritis, facial flushing, and wheezing).

15.293 May potentiate the toxic effects of fluoropyrimidine (5-FU) therapy, resulting in increased hematologic and gastrointestinal (diarrhea, stomatitis) adverse effects. Monitor closely.
15.294 May cause mild nausea or upset stomach. Administer antiemetics if necessary and evaluate for their effectiveness.

15.3 **Capecitabine (Xeloda®)**

- Commercial Supply - Please refer to the package insert for further information on capecitabine.

15.31 **Background**: Capecitabine is classified as an antineoplastic agent, Antimetabolite (Pyrimidine Analog). Capecitabine is a prodrug of fluorouracil. It undergoes hydrolysis in the liver and tissues to form fluorouracil which is the active moiety. Fluorouracil is a fluorinated Pyrimidine Antimetabolite that inhibits thymidylate synthetase, blocking the methylation of deoxyuridylic acid to thymidylic acid, interfering with DNA, and to a lesser degree, RNA synthesis. Fluorouracil appears to be phase specific for the G1 and S phases of the cell cycle.

15.32 **Formulation**: Commercially available in 150 mg and 500 mg tablets for oral administration.

15.33 **Preparation, storage, and stability**: Store at room temperature of 25°C, with excursions between 15°C and 30°C permitted.

15.34 **Administration**: Usually administered in 2 divided doses taken 12 hours apart. Doses should be taken with water within 30 minutes after a meal (Because current safety and efficacy data are based upon administration with food, it is recommended that capecitabine be administered with food. In all clinical trials, patients are instructed to take with water within 30 minutes after a meal).

15.35 **Pharmacokinetic information**:

**Absorption**: Rapid and extensive

**Protein Binding**: <60%; ~35% to albumin

**Metabolism**:

- Hepatic: Inactive metabolites
- Tissue, Active metabolite, Fluorouracil

**Distribution**: Vd: 46 mL/kg

**Half-life elimination**: 0.5-1 hour

**Time to peak**: 1.5 hours; Fluorouracil, 2 hours

**Excretion**: Urine (96%), Feces (<3%)

15.36 **Potential Drug Interactions**:

**Increased Effect/Toxicity**: Phenytoin and warfarin levels or effects may be increased. [U.S. Boxed Warning] Capecitabine may increase the anticoagulant effects of warfarin; monitor closely.

**Nutrition Interactions**: Food reduced the rate and extent of absorption of capecitabine.

15.37 **Known potential adverse events**: Consult the package insert for the most
current and complete information. Frequency listed derived from Monotherapy trials.

**Common known potential toxicities, > 10%:**
- Cardiovascular: Edema
- Central nervous system: Fatigue, fever, pain
- Dermatologic: Palmar-plantar erythrodysesthesia (hand-and-foot syndrome), dermatitis.
- Gastrointestinal: Diarrhea may be dose limiting, nausea, vomiting, abdominal pain, stomatitis, appetite decreased, anorexia, constipation.
- Hematologic: Lymphopenia, anemia, neutropenia, thrombocytopenia.
- Hepatic: Bilirubin increased.
- Neuromuscular & skeletal: Paresthesia.
- Ocular: Eye irritation.
- Respiratory: Dyspnea.

**Less common known potential toxicities, 5% - 10%:**
- Cardiovascular: Venous thrombosis, chest pain.
- Central Nervous System: Headache, lethargy, dizziness, insomnia, mood alteration, depression.
- Dermatologic: Nail disorder, rash, skin discoloration, alopecia, erythema.
- Endocrine & metabolic: Dehydration.
- Gastrointestinal: Motility disorder, oral discomfort, dyspepsia, upper GI inflammatory disorders, hemorrhage, ileus, taste perversion.
- Neuromuscular & skeletal: Back pain, weakness, neuropathy, myalgia, arthralgia, limb pain
- Ocular: Abnormal vision, conjunctivitis.
- Respiratory: Cough.
- Miscellaneous: Viral infection.

**Rare known potential toxicities, <5% (Limited to important or life-threatening):**
- Angina, ascites, asthma, atrial fibrillation, bradycardia, bronchitis, bronchopneumonia, bronchospasm, cachexia, cardiac arrest, cardiac failure, cardiomyopathy, cerebral vascular accident, cholestasis, coagulation disorder, colitis, deep vein thrombosis, diaphoresis, duodenitis, dysphagia, dysrhythmia, ECG changes, encéphalopathy, epistaxis, fungal infection, gastric ulcer, gastroenteritis, hematemesis, hemoptysis, hepatic failure, hepatic fibrosis, hepatitis, hypokalemia, hypomagnesemia, hyper-/hypotension, hypersensitivity, hypertriglyceridemia, idiopathic thrombocytopenia purpura, ileus, infection, intestinal obstruction, keratoconjunctivitis, lacrimal duct stenosis, leukopenia, loss of consciousness, lymphedema, MI, multifocal leukoencephalopathy, myocardial ischemia, myocarditis, necrotizing enterocolitis (typhlitis), oral candidiasis, pericardial effusion, thrombocytopenic purpura, pancytopenia, photosensitivity reaction, pneumonia, pruritus, pulmonary embolism, radiation recall syndrome, renal impairment, respiratory distress, sedation, sepsis, skin ulceration, tachycardia, thrombophlebitis, toxic megacolon, tremor, ventricular extrasystoles.

15.38 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain
supplies from normal commercial supply chain or wholesaler.

15.39 **Nursing Guidelines:**

15.391 Instruct patients to take the tablets within 30 minutes of a meal (breakfast and dinner). Tablets should be swallowed with 6-8 oz. of water.

15.392 Instruct patient to avoid taking a missed dose, to never double up on a dose, and to notify the health care team if a dose has been missed.

15.393 Diarrhea can be severe and dose-limiting. Instruct patient to contact the health care team immediately if they experience >4 BMs/day and/or nocturnal diarrhea above baseline. Monitor carefully for dehydration and need for fluid and electrolyte replacement. Standard antidiarrheal treatment, e.g., loperamide is recommended.

15.394 Nausea and vomiting can be severe and dose-limiting. Instruct patient to report nausea and vomiting to the health care team if they experience >2 episodes of emesis in a 24-hour period. Initiate symptomatic treatment.

15.395 Hand and Foot Syndrome is common and dose-limiting (redness, swelling, pain, numbness, tingling, blistering, and moist desquamation). Instruct patient to notify health care team immediately if symptoms appear. Chemotherapy may have to be discontinued until symptoms subside with future dose reduction initiated. The syndrome may recur with a rechallenge.

- Advise patient to apply cool compress for comfort.
- Advise patient to avoid harsh soaps and to use alcohol-free emollients.
- Administer analgesics as prescribed.
- Administer systemic steroids and pyridoxine as prescribed.

15.396 Treat stomatitis symptomatically -- may try dabbing vitamin E oil on lesions. Do not swallow oil. Advise frequent and careful oral hygiene.

15.397 Assess for warfarin use. Patients taking coumadin-derivative anticoagulants concomitantly with capecitabine should be monitored regularly for alterations in their coagulation parameters (PT or INR).

15.398 Carefully assess patient’s understanding and need of instruction in adequate birth control measures. Discuss importance of avoiding pregnancy. Periodically re-assess.

15.399a Renal impairment: Check creatinine values and calculate creatinine clearance weekly for signs of renal impairment at beginning of each treatment cycle. Follow dose modifications.

15.399b The use of Sorivudine or its analogue, Birivudine, is contraindicated for this study due to a possible, even fatal, drug reaction. Assess patient’s drug use. Impress on patients the importance of avoiding these drugs
while on study.

15.399c Cardiotoxicity (including MI, angina, dysrhythmias, and cardiac arrest) has been seen with capecitabine. Observe patients closely for signs of cardiac dysfunction. Instruct patient to report any chest pain or palpitations to the health care team immediately or seek emergency medical attention.

15.399d Monitor patient closely who are taking concomitant phenytoin therapy. There have been reports of increased levels of phenytoin in patients who are also taking capecitabine. These patients may require more frequent monitoring of their phenytoin levels and dose adjustments as necessary.

15.399e Cimetidine may alter the clearance of capecitabine and cause toxic levels. Cimetidine should be avoided while taking capecitabine.

15.4 Bevacizumab (Avastin)

- Commercial Supply - Please refer to the package insert for further information on bevacizumab.

15.41 Background: Bevacizumab is classified as an Anti-VEGF Monoclonal Antibody and a Vascular Endothelial Growth Factor (VEGF) Inhibitor. Bevacizumab is a recombinant, humanized monoclonal antibody which binds to, and neutralizes, vascular endothelial growth factor (VEGF), preventing its association with endothelial receptors, Flt-1 and KDR. VEGF binding initiates angiogenesis (endothelial proliferation and the formation of new blood vessels). The inhibition of microvascular growth is believed to retard the growth of all tissues (including metastatic tissue).

15.42 Formulation: Commercially available for injection 25 mg/mL (4 mL, 16 mL).

15.43 Preparation, storage, and stability: Refer to package insert for complete preparation and dispensing instructions. Store intact vials at refrigeration temperature, protect from light, do not freeze or shake. Prior to infusion, dilute prescribed dose of bevacizumab in 100 mL 0.9% NaCl. Do not mix with dextrose-containing solutions. Diluted solutions are stable for up to 8 hours under refrigeration.

15.44 Administration: IV infusion, usually after the other antineoplastic agents. Refer to treatment section for specific order of administration. Infuse the initial dose over 90 minutes. Infusion may be shortened to 60 minutes if the initial infusion is well tolerated. The third and subsequent infusions may be shortened to 30 minutes if the 60-minute infusion is well tolerated. Monitor closely during the infusion for signs/symptoms of an infusion reaction. Some institutions use a 10-minute infusion (0.5 mg/kg/minute) for bevacizumab dosed at 5 mg/kg (Reidy et al., 2007).

15.45 Pharmacokinetic information:
Distribution: $V_d = 46 \text{ mL/kg}$
Half-life elimination: ~20 days (range: 11-50 days)
Clearance: 2.75-5 mL/kg/day

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

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with **bold** and *italicized* text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via AdEERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' [http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf) for further clarification.

**NOTE:** Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERS, use the lower of the grades to determine if expedited reporting is required.
<table>
<thead>
<tr>
<th>Likely (&gt;20%)</th>
<th>Less Likely (&lt;=20%)</th>
<th>Rare but Serious (&lt;3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLOOD AND LYMPHATIC SYSTEM DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>Anemia (Gr. 3)</td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)</td>
<td>Febrile neutropenia (Gr. 3)</td>
</tr>
<tr>
<td><strong>CARDIAC DISORDERS</strong></td>
<td></td>
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</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>Supraventricular tachycardia (Gr. 3)</td>
<td></td>
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<tr>
<td>Heart failure</td>
<td>Ventricular arrhythmia</td>
<td></td>
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<tr>
<td>Left ventricular systolic dysfunction</td>
<td>Ventricular fibrillation</td>
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<tr>
<td>Myocardial infarction</td>
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<tr>
<td>Supraventricular tachycardia</td>
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<tr>
<td><strong>EAR AND LABYRINTH DISORDERS</strong></td>
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<tr>
<td>Vertigo</td>
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<tr>
<td><strong>GASTROINTESTINAL DISORDERS</strong></td>
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<td>Abdominal pain</td>
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<td>Colitis</td>
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<tr>
<td>Diarrhea</td>
<td>Diarrhea (Gr. 3)</td>
<td>Dyspepsia (Gr. 2)</td>
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<td>Dyspepsia</td>
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<tr>
<td>Gastrointestinal fistula*</td>
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<tr>
<td>Gastrointestinal hemorrhage*</td>
<td>Gastrointestinal hemorrhage* (Gr. 2)</td>
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<tr>
<td>Gastrointestinal obstruction*</td>
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<td>Gastrointestinal perforation*</td>
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<tr>
<td>Ileus</td>
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<td>Ileus</td>
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</tr>
<tr>
<td>Mucositis oral</td>
<td>Mucositis oral (Gr. 3)</td>
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</tr>
<tr>
<td>Nausea</td>
<td>Nausea (Gr. 3)</td>
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</tr>
<tr>
<td>Vomiting</td>
<td>Vomiting (Gr. 3)</td>
<td></td>
</tr>
<tr>
<td><strong>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</strong></td>
<td></td>
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<tr>
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<td>Fatigue (Gr. 3)</td>
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<tr>
<td>Infusion related reaction</td>
<td>Infusion related reaction (Gr. 2)</td>
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<tr>
<td>Non-cardiac chest pain</td>
<td>Non-cardiac chest pain (Gr. 3)</td>
<td>Pain (Gr. 3)</td>
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<tr>
<td><strong>IMMUNE SYSTEM DISORDERS</strong></td>
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<td><strong>INFECTIONS AND INFESTATIONS</strong></td>
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<td>Infection7</td>
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<td>Category</td>
<td>Diagnosis</td>
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<td>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</td>
<td>Gastrointestinal anastomotic leak</td>
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<tr>
<td>Wound dehiscence</td>
<td>Wound dehiscence (Gr. 2)</td>
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<tr>
<td>INVESTIGATIONS</td>
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<td>Alanine aminotransferase increased</td>
<td>Alanine aminotransferase increased (Gr. 3)</td>
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<td>Alkaline phosphatase increased</td>
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<td>Aspartate aminotransferase increased</td>
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<td>Blood bilirubin increased</td>
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<td>Cardiac troponin I increased</td>
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<td>Neutrophil count decreased</td>
<td>Neutrophil count decreased (Gr. 3)</td>
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<td>Weight loss</td>
<td>Weight loss (Gr. 3)</td>
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<td>White blood cell decreased</td>
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<td>METABOLISM AND NUTRITION DISORDERS</td>
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<td>Anorexia</td>
<td>Anorexia (Gr. 3)</td>
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<td>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</td>
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<tr>
<td>Arthralgia</td>
<td>Arthralgia (Gr. 3)</td>
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<td>Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)</td>
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<td>Myalgia</td>
<td>Myalgia (Gr. 3)</td>
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<td>Osteonecrosis of jaw</td>
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<td>NERVOUS SYSTEM DISORDERS</td>
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<td>Dizziness</td>
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<td>Headache</td>
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<td>Intracranial hemorrhage</td>
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<td>Peripheral sensory neuropathy</td>
<td>Ischemia cerebrovascular</td>
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<td>Syncope</td>
<td>Reversible posterior leukoencephalopathy syndrome</td>
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<td>RENAL AND URINARY DISORDERS</td>
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<td>Hematuria</td>
<td>Hematuria (Gr. 3)</td>
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<td>Proteinuria</td>
<td>Proteinuria (Gr. 2)</td>
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<td>Acute kidney injury</td>
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<td>Renal and urinary disorders - Other (Nephrotic Syndrome)</td>
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<td>Urinary fistula</td>
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<tr>
<td>REPRODUCTIVE SYSTEM AND BREAST DISORDERS</td>
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<td></td>
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<tr>
<td>Reproductive system and breast disorders - Other (ovarian failure)</td>
<td></td>
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<tr>
<td>Vaginal hemorrhage</td>
<td>Vaginal hemorrhage (Gr. 3)</td>
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<tr>
<td>REPRODUCTIVE SYSTEM AND BREAST DISORDERS</td>
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</tr>
<tr>
<td>Allergic rhinitis</td>
<td>Allergic rhinitis (Gr. 3)</td>
<td></td>
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<tr>
<td>Bronchopleural fistula</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Biliary obstruction | Bronchopulmonary hemorrhage | Cough (Gr. 3) 
|---------------------|-----------------------------|-------------------
| Cough               | Epistaxis (Gr. 3)           | Dyspnea (Gr. 2) 
| Dyspnea             | Hoarseness (Gr. 3)          | Epistaxis (Gr. 3) 
| Epistaxis           | Hoarseness (Gr. 3)          | Hoarseness (Gr. 3) 
| Hoarseness          | Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation) 
|                     | Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula) 

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS**

| Pruritus            | Pruritus (Gr. 2) 
|---------------------|-------------------
| Rash maculo-papular | Rash maculo-papular (Gr. 2) 
| Urticaria           | Urticaria (Gr. 2) 

**VASCULAR DISORDERS**

| Hypertension        | Hypertension (Gr. 3) 
|---------------------|-------------------
| Thromboembolic event| Thromboembolic event (Gr. 3) 

Vascular disorders - Other (arterial thromboembolic event)\(^2\)

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

\(^2\)Gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

\(^3\)Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

\(^4\)Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

\(^5\)Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, Small intestinal perforation, and other sites under the GASTROINTESTINAL DISORDERS SOC.

\(^6\)Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.

\(^7\)Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

\(^8\)Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.

\(^9\)Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.
Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.

Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation ($\geq$30 mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level $<$30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.

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

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

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

**CARDIAC DISORDERS** - Pericardial effusion

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

**HEPATOBILIARY DISORDERS** - Hepatic failure

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

**INVESTIGATIONS** - Platelet count decreased

**METABOLISM AND NUTRITION DISORDERS** - Hyponatremia

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

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

**PSYCHIATRIC DISORDERS** - Confusion

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

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Palmar-plantar erythrodysesthesia syndrome; Skin ulceration

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

15.47 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.48 **Nursing Guidelines:**

15.481 Monitor patients closely for infusion type reactions, including fever, chills, myalgias, rigors, or other allergic reactions. While this is less likely given that bevacizumab is a humanized antibody, there still exists the potential for severe allergic reactions. If these signs or symptoms occur stop the infusion immediately and contact physician. Have emergency equipment nearby and be prepared to administer emergency treatment as ordered by physician.

15.482 Monitor urine dipstick or UPC as required by the test schedule.
15.483 Evaluate IV site regularly for signs of infiltration.

15.484 Bleeding in the absence of thrombocytopenia is a dose limiting toxicity. Monitor patient closely for hemorrhagic events, including CNS hemorrhage, epistaxis, hematemesis and hemoptysis. Most cases of bleeding have occurred at the tumor site. Advise patient about the potential for bleeding or thrombosis.

15.485 In patients receiving treatment for lung cancer, hemoptysis and pulmonary hemorrhage occurred in up to 10% of patients in one study. Monitor these patients especially closely.

15.486 Patient may experience Grade 1-2 nausea, however vomiting is uncommon. Medicate as ordered and monitor for effectiveness.

15.487 Monitor for skin rash, instruct patient to report to physician.

15.488 Monitor blood pressure. Administer antihypertensives as ordered by physician.

15.489a Monitor for signs and symptoms of deep vein thrombosis (DVT) or pulmonary embolism (PE), or myocardial infarction (MI) including new or worsening angina. These have been reported with therapy. Instruct patient to report any calf pain, chest pain or shortness of breath to physician immediately.

15.489b Asthenia and headache were reported commonly during therapy (in up to 70% and 50% of patients respectively). Administer acetaminophen as needed. Monitor for its effectiveness. Avoid the use of aspirin, or ibuprofen as this may interfere with the coagulation cascade and further add to the risk of bleeding.

15.489c Monitor CBC, including platelets. Instruct patient to report signs and symptoms of infection, unusual bruising or bleeding to the physician.

15.489d Patients receiving warfarin therapy for thrombosis should have their PT or INR monitored weekly until two stable therapeutic levels are attained. For patients on warfarin for venous access prophylaxis, routine monitoring is satisfactory.

15.489e A rare but serious complication of bevacizumab is wound dehiscence. Patients who have had recent surgery or have other open wounds should be monitored carefully.

15.489f Gastrointestinal perforation with or without abdominal abscess is rare but possible. This may present itself as vague abdominal pain associated with constipation and vomiting. Instruct patient to report abdominal pain to the physician.

15.489g Reversible Posterior Leukoencephalopathy Syndrome (RPLS) is a rare
(<1%) but serious condition. Presenting symptoms may include changes in mental status, visual disturbance, seizure, or other CNS changes. Patients with this syndrome generally had HTN as well, therefore BP monitoring is important. Instruct patient to report any mental status changes, visual changes, seizures, or other CNS changes to the physician immediately. These may be a sign of RPLS or more serious condition, such as hemorrhagic event in the CNS.

15.5 Oxaliplatin (Eloxatin®, OXAL)

- Commercial Supply - Please refer to the package insert for further information on oxaliplatin.

15.51 Background: Oxaliplatin, a platinum derivative, is an alkylating agent. Following intracellular hydrolysis, the platinum compound binds to DNA forming cross-links which inhibit DNA replication and transcription, resulting in cell death. Cytotoxicity is cell-cycle nonspecific.

15.52 Formulation: Commercially available for injection as:
Solution [preservative free]: 5 mg/mL (10 mL, 20 mL, 40 mL)

15.53 Preparation, storage, and stability: Refer to package insert for complete preparation and dispensing instructions. Store intact vials in original outer carton at room temperature and; do not freeze. According to the manufacturer, solutions diluted for infusion are stable up to 6 hours at room temperature or up to 24 hours under refrigeration. Oxaliplatin solution diluted with D5W to a final concentration of 0.7 mg/mL (polyolefin container) has been shown to retain >90% of it’s original concentration for up to 30 days when stored at room temperature or refrigerated; artificial light did not affect the concentration (Andre, 2007). As this study did not examine sterility, refrigeration would be preferred to limit microbial growth. Do not prepare using a chloride-containing solution (e.g., NaCl). Dilution with D5W (250 or 500 mL) is required prior to administration. Infusion solutions do not require protection from light.

15.54 Administration: Refer to the treatment section (Section 7.0) for specific administration instructions. Administer as I.V. infusion over 2 hours. Flush infusion line with D5W prior to administration of any concomitant medication. Patients should receive an antiemetic premedication regimen. Cold temperature may exacerbate acute neuropathy. Avoid mucositis prophylaxis with ice chips during Oxaliplatin infusion.

15.55 Pharmacokinetic information:
Distribution: Vd: 440 L
Protein binding: >90% primarily albumin and gamma globulin (irreversible binding to platinum)
Metabolism: Nonenzymatic (rapid and extensive), forms active and inactive derivatives
Half-life elimination: Terminal: 391 hours; Distribution: Alpha phase: 0.4 hours, Beta phase: 16.8 hours
Excretion: Primarily urine (~54%); feces (~2%)
15.56 **Potential Drug Interactions:**

**Increased Effect/Toxicity:** Nephrotoxic agents may increase Oxaliplatin toxicity. When administered as sequential infusions, observational studies indicate a potential for increased toxicity when platinum derivatives (carboplatin, cisplatin, oxaliplatin) are administered before taxane derivatives (docetaxel, paclitaxel).

**Decreased Effect:** Oxaliplatin may decrease plasma levels of digoxin.

15.57 **Comprehensive Adverse Events and Potential Risks list (CAEPR) for Oxaliplatin (NSC 266046)**

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with *bold* and *italicized* text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' [http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_aeers](http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_aeers) for further clarification. Frequency is provided based on 1141 patients. Below is the CAEPR for oxaliplatin.

<table>
<thead>
<tr>
<th>Adverse Events with Possible Relationship to Oxaliplatin (CTCAE 4.0 Term) [n= 1141]</th>
<th>EXPECTED AEs FOR ADEERS REPORTING Agent Specific Adverse Event List (ASAEL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely (&gt;20%)</td>
<td>Less Likely (&lt;=20%)</td>
</tr>
<tr>
<td><strong>BLOOD AND LYMPHATIC SYSTEM DISORDERS</strong></td>
<td></td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura</td>
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<td></td>
<td>Disseminated intravascular coagulation</td>
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<tr>
<td></td>
<td>Febrile neutropenia</td>
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<td></td>
<td>Hemolysis</td>
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<td><strong>CARDIAC DISORDERS</strong></td>
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<tr>
<td></td>
<td>Atrial flutter</td>
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<td></td>
<td>Paroxysmal atrial tachycardia</td>
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<td></td>
<td>Sinus bradycardia</td>
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<td></td>
<td>Sinus tachycardia</td>
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<td></td>
<td>Supraventricular tachycardia</td>
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<td></td>
<td>Ventricular arrhythmia</td>
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<td></td>
<td>Ventricular fibrillation</td>
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<td></td>
<td>Ventricular tachycardia</td>
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Version 2.2, March 11, 2010
### Adverse Events with Possible Relationship to Oxaliplatin (CTCAE 4.0 Term)

[n= 1141]

<table>
<thead>
<tr>
<th>Likely (&gt;20%)</th>
<th>Less Likely (&lt;=20%)</th>
<th>Rare but Serious (&lt;3%)</th>
<th>Expected</th>
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</thead>
<tbody>
<tr>
<td><strong>EAR AND LABYRINTH DISORDERS</strong></td>
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<tr>
<td>Hearing impaired</td>
<td>Middle ear inflammation</td>
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<td><strong>EYE DISORDERS</strong></td>
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<tr>
<td>Conjunctivitis</td>
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<tr>
<td>Dry eye</td>
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<tr>
<td>Eye disorders - Other (amaurosis fugax)</td>
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<td>Eye disorders - Other (amaurosis fugax)</td>
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<tr>
<td>Eye disorders - Other (cold-induced transient visual abnormalities)</td>
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<td>Eye disorders - Other (cold-induced transient visual abnormalities)</td>
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<tr>
<td>Eyelid function disorder</td>
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<td>Eyelid function disorder</td>
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<tr>
<td>Papilledema</td>
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<tr>
<td><strong>GASTROINTESTINAL DISORDERS</strong></td>
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<td>Abdominal pain</td>
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<tr>
<td>Colitis</td>
<td>Constipation</td>
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<td><strong>Diarrhea</strong></td>
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<td>Dry mouth</td>
<td>Dyspepsia</td>
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<td>Dysphagia</td>
<td>Enterocolitis</td>
<td>Esophagitis</td>
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<td>Gastritis</td>
<td>Gastrointestinal disorders – Other (pneumatosis intestinalis)</td>
<td>Flatulence</td>
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<td>Gastrointestinal hemorrhage²</td>
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<td>Gastrointestinal hemorrhage²</td>
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<td>Gastrointestinal necrosis³</td>
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<td>Gastrointestinal ulcer⁴</td>
<td>Ileus</td>
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<td>Gastrointestinal ulcer⁴</td>
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<tr>
<td>Mucositis oral</td>
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<td><strong>Nausea</strong></td>
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<tr>
<td>Pancreatitis</td>
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<tr>
<td>Small intestinal obstruction</td>
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<td>Small intestinal obstruction</td>
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<tr>
<td><strong>Vomiting</strong></td>
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<td>Vomiting</td>
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<tr>
<td><strong>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</strong></td>
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<td></td>
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<tr>
<td>Chills</td>
<td>Edema face</td>
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<td>Chills</td>
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<tr>
<td>Edema limbs</td>
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<td>Edema limbs</td>
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<tr>
<td>Fatigue</td>
<td>Fever</td>
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<td>Fatigue</td>
</tr>
<tr>
<td>Gait disturbance</td>
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<td>Gait disturbance</td>
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<tr>
<td>Likely (&gt;20%)</td>
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<td>Expected</td>
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</tr>
<tr>
<td>General disorders and administration site conditions - Other (Hepato-renal syndrome)</td>
<td>Injection site reaction</td>
<td>Non-cardiac chest pain</td>
<td>General disorders and administration site conditions - Other (Hepato-renal syndrome) Injection site reaction</td>
</tr>
</tbody>
</table>

**HEPATOBILIARY DISORDERS**

- Hepatic failure
- Hepatobiliary disorders - Other (hepatic enlargement)
- Hepatobiliary disorders - Other (veno-occlusive liver disease)

**IMMUNE SYSTEM DISORDERS**

- Allergic reaction

**INFECTIONS AND INFESTATIONS**

<table>
<thead>
<tr>
<th>Infection³</th>
</tr>
</thead>
</table>

**INVESTIGATIONS**

- Activated partial thromboplastin time prolonged
- Alanine aminotransferase increased
- Alkaline phosphatase increased
- Aspartate aminotransferase increased
- Blood bilirubin increased
- Creatinine increased
- GGT increased
- INR increased
- Lymphocyte count decreased
- Neutrophil count decreased
- Platelet count decreased
- Weight gain
- Weight loss
- White blood cell decreased

**METABOLISM AND NUTRITION DISORDERS**

- Acidosis
- Anorexia
- Dehydration
- Hyperglycemia
- Hyperuricemia
- Hypoalbuminemia
- Hypocalcemia
- Hypoglycemia
- Hypokalemia
<table>
<thead>
<tr>
<th>Likely (&gt;20%)</th>
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<th>Rare but Serious (&lt;3%)</th>
<th>Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypomagnesemia</td>
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<td>Hypomagnesemia</td>
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<tr>
<td>Hyponatremia</td>
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<td>Hyponatremia</td>
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<tr>
<td>Hypophosphatemia</td>
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<td>Hypophosphatemia</td>
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<tr>
<td><strong>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</strong></td>
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<td>Arthralgia</td>
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<td>Arthralgia</td>
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<td>Back pain</td>
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<tr>
<td>Bone pain</td>
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<tr>
<td>Myalgia</td>
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<td>Myalgia</td>
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<tr>
<td>Trismus</td>
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<td>Trismus</td>
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<tr>
<td><strong>NERVOUS SYSTEM DISORDERS</strong></td>
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<tr>
<td>Ataxia</td>
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<td>Ataxia</td>
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<tr>
<td>Depressed level of consciousness</td>
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<td>Dizziness</td>
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<tr>
<td>Dyseusia</td>
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<tr>
<td>Dysphasia</td>
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<tr>
<td>Extrapyramidal disorder</td>
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<tr>
<td>Intracranial hemorrhage</td>
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<td>Intracranial hemorrhage</td>
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<tr>
<td>Ischemia cerebrovascular</td>
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<td>Ischemia cerebrovascular</td>
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<tr>
<td>Nerve disorder</td>
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<td>Nerve disorder</td>
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<tr>
<td>Nervous system disorders - Other</td>
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<td></td>
<td>Nervous system disorders - Other</td>
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<tr>
<td>(multiple cranial nerve palsies)</td>
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<td>(multiple cranial nerve palsies)</td>
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<tr>
<td>Peripheral motor neuropathy</td>
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<td>Peripheral motor neuropathy</td>
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<td>Peripheral sensory neuropathy</td>
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<tr>
<td>Seizure</td>
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<tr>
<td><strong>PSYCHIATRIC DISORDERS</strong></td>
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<tr>
<td>Anxiety</td>
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<td>Anxiety</td>
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<tr>
<td>Confusion</td>
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<td>Confusion</td>
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<td>Depression</td>
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<tr>
<td>Insomnia</td>
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<tr>
<td><strong>RENOV AND URINARY DISORDERS</strong></td>
<td></td>
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<tr>
<td>Acute kidney injury</td>
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<td>Acute kidney injury</td>
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<tr>
<td>Hematuria</td>
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<td>Renal hemorrhage</td>
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<td>Renal hemorrhage</td>
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<td>Urinary frequency</td>
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<td>Urinary frequency</td>
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<tr>
<td>Urinary retention</td>
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<td>Urinary retention</td>
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<tr>
<td><strong>REPRODUCTIVE SYSTEM AND BREAST DISORDERS</strong></td>
<td></td>
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<tr>
<td>Hematosalpinx</td>
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<td>Hematosalpinx</td>
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<tr>
<td>Ovarian hemorrhage</td>
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<td>Prostatic hemorrhage</td>
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<td>Prostatic hemorrhage</td>
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<td>Spermatic cord hemorrhage</td>
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<td>Spermatic cord hemorrhage</td>
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<td>Testicular hemorrhage</td>
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<td>Testicular hemorrhage</td>
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<tr>
<td>Uterine hemorrhage</td>
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<td>Uterine hemorrhage</td>
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<tr>
<td>Vaginal hemorrhage</td>
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<td></td>
<td>Vaginal hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Likely (&gt;20%)</td>
<td>Less Likely (&lt;=20%)</td>
<td>Rare but Serious (&lt;3%)</td>
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<tr>
<td>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</td>
<td>Adult respiratory distress syndrome</td>
<td>Allergic rhinitis</td>
<td>Bronchopulmonary hemorrhage</td>
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<tr>
<td></td>
<td></td>
<td>Bronchospasm</td>
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<td></td>
<td></td>
<td>Cough</td>
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<td></td>
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<td>Dyspnea</td>
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<td>Hiccups</td>
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<td></td>
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<td>Pneumonitis</td>
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<td>Pulmonary fibrosis</td>
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<td></td>
<td></td>
<td>Sinus disorder</td>
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<td></td>
<td></td>
<td>Voice alteration</td>
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<tr>
<td>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</td>
<td>Alopecia</td>
<td>Hyperhidrosis</td>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
</tr>
<tr>
<td></td>
<td>Dry skin</td>
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<td></td>
<td></td>
<td>Pruritus</td>
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<td></td>
<td></td>
<td>Rash maculo-papular</td>
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<tr>
<td></td>
<td></td>
<td>Urticaria</td>
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<tr>
<td>VASCULAR DISORDERS</td>
<td>Flushing</td>
<td>Hot flashes</td>
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<td></td>
<td></td>
<td>Hypertension</td>
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<td></td>
<td></td>
<td>Hypotension</td>
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<td></td>
<td></td>
<td>Phlebitis</td>
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<td></td>
<td></td>
<td>Thromboembolic event</td>
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<tr>
<td></td>
<td></td>
<td>Vascular disorders - Other (hemorrhage with thrombocytopenia)</td>
<td></td>
</tr>
</tbody>
</table>

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

2 Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.
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3Gastrointestinal necrosis includes Anal necrosis, Esophageal necrosis, Gastric necrosis, Pancreatic necrosis, Peritoneal necrosis, and Rectal necrosis under the GASTROINTESTINAL DISORDERS SOC.

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

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

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

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

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

CARDIAC DISORDERS - Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Pericardial effusion
EYE DISORDERS - Eye pain
GASTROINTESTINAL DISORDERS – Gastrointestinal perforation
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Injury to superior vena cava; Vascular access complication
INVESTIGATIONS - Cardiac troponin I increased; Lipase increased; Serum amylase increased
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness
NERVOUS SYSTEM DISORDERS - Syncope
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Hypoxia
VASCULAR DISORDERS - Visceral arterial ischemia

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

15.58 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.59 **Nursing Guidelines:**

15.591 GI toxicity similar to cisplatin occurs with doses above 30 mg/m². It can be almost constant and frequently severe, but not always dose-limiting. Monitor for nausea and vomiting and treat accordingly.

15.592 Dose-limiting side effect can be paresthesias of hands, fingers, toes, pharynx, and occasionally cramps which develops with a dose-related frequency (>90 mg/m²). Duration of symptoms tend to be brief (less than a week) with the first course, but longer with subsequent courses. Phase I patients have reported exacerbation of paresthesias by touching
cold surfaces or exposure to cold. Advise patient of these possibilities and instruct patient to report these symptoms to the health care team. Also advise patient to refrain from operating dangerous machinery that requires fine sensory-motor coordination, if symptoms appear.

15.593 These sensory neuropathies developed after subsequent courses with increasing intensity (Grade 3 toxicity after the fourth course) and with increasing duration. In 63% of the patients tested in phase I at high doses (135-200 mg/m²), neuropathies became long-term with slow reversal over several months. Disabling walking and handwriting difficulties, as well as mouth and throat dyesthesias and laryngospasms were seen. Instruct patient to report any swallowing difficulties or gait changes.

15.594 Oxaliplatin is incompatible with NS. Flush lines with D5W prior to and following oxaliplatin infusion.

15.595 Low back pain is a common side effect, perhaps a form of hypersensitivity reaction. Instruct patient in good body mechanics, advise light massage, heat, etc.

15.596 Laryngopharyngeal dysesthesia (LPD) occurs in about 15% of patients and is acute, sporadic, and self-limited. It usually occurs within hours of infusion, is induced or exacerbated by exposure to cold, and presents with dyspnea and dysphagia. The incidence and severity appear to be reduced by prolonging infusion time. Instruct patient to avoid ice and cold drinks the day of infusion. If ≥Grade 2 laryngopharyngeal dysesthesia occurs during the administration of oxaliplatin, do the following:

- Stop oxaliplatin infusion
- Administer benzodiazepine and give patient reassurance
- Test oxygen saturation via a pulse oximeter
- At the discretion of the investigator, the infusion can be restarted at 1/3 the original rate of infusion.
- Rapid resolution is typical within minutes to a few hours. Can recur with retreatment.

<table>
<thead>
<tr>
<th>Clinical Symptoms</th>
<th>Laryngopharyngeal Dysesthesias</th>
<th>Platinum Hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>present</td>
<td>present</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>Laryngospasm</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>Anxiety</td>
<td>present</td>
<td>present</td>
</tr>
<tr>
<td>O₂ saturation</td>
<td>normal</td>
<td>decreased</td>
</tr>
<tr>
<td>Difficulty swallowing</td>
<td>present (loss of sensation)</td>
<td>absent</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Absent</td>
<td>present</td>
</tr>
</tbody>
</table>

Comparison of the Symptoms and Treatment of Laryngopharyngeal Dysesthesias and Platinum Hypersensitivity Reactions
### Comparison of the Symptoms and Treatment of Laryngopharyngeal Dysesthesias and Platinum Hypersensitivity Reactions

<table>
<thead>
<tr>
<th>Clinical Symptoms</th>
<th>Laryngopharyngeal Dysesthesias</th>
<th>Platinum Hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>urticaria/rash</td>
<td>Absent</td>
<td>present</td>
</tr>
<tr>
<td>cold-induced symptoms</td>
<td>Yes</td>
<td>no</td>
</tr>
<tr>
<td>BP</td>
<td>normal or increased</td>
<td>normal or decreased</td>
</tr>
</tbody>
</table>

| Treatment                  | anxiolytics, observation in a controlled clinical setting until symptoms abate or at the physicians’ discretion | oxygen, steroids, epinephrine, bronchodilators; fluids and vasopressors, if appropriate |

15.597 Alopecia is rare with oxaliplatin alone, but is seen with fluorouracil-oxaliplatin combination. Advise patient.

15.598 Mild-moderate diarrhea has been seen -- usually of short duration. Treat accordingly. See Section 9.7 for ancillary treatment.

15.599a Respiratory problems (i.e., pulmonary fibrosis, cough, dyspnea, rales, pulmonary infiltrates, hypoxia, air hunger and tachypnea) have been observed in patients administered oxaliplatin. In rare cases, death has occurred due to pulmonary fibrosis. Please monitor and instruct the patient to report any respiratory difficulties and hold oxaliplatin until interstitial lung disease is ruled out for cases of Grade ≥3. If patient is experiencing shortness of breath, a chest x-ray and assessment of oxygenation via either finger oximetry or arterial blood gas evaluation are required to confirm the absence or presence of pulmonary infiltrates and/or hypoxia (treat accordingly: no intervention, steroids, diuretics, oxygen, or assisted ventilation).

15.599b Veno-occlusive disease (VOD) is a rare but serious complication that has been reported in patients receiving oxaliplatin in combination with 5-FU. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Instruct patients to report any jaundice, ascites, or hematemesis to the physician immediately as these could be a sign of VOD or other serious condition.

15.599c Acute vein irritation can occur with infusion. Apply heat to arm of infusion if you are using a peripheral line. However, extravasation of drug can cause severe pain, redness, soreness, and exfoliation of the skin in the affected area with loss of affected vein for a long period. If a patient has a problem with pain or sclerosis when chemotherapy is given by a peripheral line, then placement of a central line should be considered.

15.599d Hemolytic Uremic Syndrome (HUS) may result in kidney damage. Oxaliplatin is to be discontinued in cases where hematocrit is <25%, thrombocytopenia <100,000, and creatinine ≥1.6 mg/dL.

15.599e Patients may experience sleep disturbances, specifically insomnia.
Encourage good sleep hygiene, and instruct patient to report any problems with sleep to the physician, to assess for the potential use of sleeping aids.

15.599f Cold-induced transient visual abnormalities can be experienced by patients while receiving oxaliplatin, although the relationship to oxaliplatin has not been completely determined. Instruct patient to report any problems with vision to the physician.

15.599g Extrapyramidal side effects and/or involuntary limb movement has been seen with oxaliplatin administration. Patients may also experience restlessness. Instruct patient to report any of these side effects to the physician.

16.0 Statistical Considerations and Methodology

This is a two-arm randomized phase III trial with a primary endpoint of progression free survival, testing for the superiority of mFOLFOX7 or XELOX + bevacizumab (experimental Arm B) versus fluoropyrimidine-based therapy (i.e., 5-FU/LV or capecitabine) + bevacizumab (control Arm A). Following randomization, patients will be treated with a physician directed fluoropyrimidine-based therapy (i.e., 5-FU/LV or capecitabine) on each of these two arms based on a direct assignment to 1 of 4 treatments (i.e., Arms C-F). Thus, there are a total of 6 arms for this study:

- Arm A (control arm) consists of Arm C (5-FU/LV plus bevacizumab) and Arm D (capecitabine + bevacizumab).
- Arm B (experimental arm) consists of Arm E (mFOLFOX7 + bevacizumab) and Arm F (XELOX + bevacizumab).

Other unique features of this phase III trial include:

- The study will be available for patients aged 70 and older, up until the number of patients aged 70-74 reaches 25% of the planned total accrual. Thereafter, patient enrollment will be restricted to patients aged 75 and older.
- The CALBG will be performing the analysis of geriatric assessments, as well as jointly performing the analysis for quality of life (Qol) assessments and pharmacogenetics.
- Data from this study will be later combined and analyzed with data from an identical trial conducted by the Japanese Clinical Oncology Group (JCOG).
- This study has built in a contingency plan in the case of accrual lagging below a pre-specified rate and relative to the primary endpoint, as discussed in Section 16.2.

16.1 Endpoints

16.11 Primary Endpoint

The primary endpoint for this trial will be progression-free survival (PFS). Progression free survival is defined as the time (in days) from the date of randomization to the date of documented disease progression or death, whichever occurs first. Patients will be followed until progression (and progression will be
declared) regardless of whether the patient is on the first line treatment or not. Patients who progress following a missed scan will have their date of progression back-dated to the date of missing scan. Patients without a progression who are still alive at the time of analysis will be censored at the date of last follow-up. All randomized patients will be included in the primary endpoint analysis in an intention to treat analysis.

16.12 Secondary Endpoints

16.121 Overall survival. Overall survival will be defined as the time (in days) from randomization to death.

16.122 Response rate. Response rate will be defined as the proportion of patients in each arm who have an objective status of CR or PR, confirmed by a second assessment measured at least 6 weeks from the initial assessment.

16.123 Adverse Events as per the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grading.

16.13 Correlative Endpoints

16.131 Geriatric/frailty and QoL assessment endpoints (see Section 16.5)

16.132 Pharmacogenetic markers and their ability to predict response and toxicity (see Section 16.6)

16.2 Accrual. The study will be available for patients aged 70 and older, up until the number of patients aged 70-74 reached 25% of the planned total accrual. Thereafter, patient enrollment will be restricted to patients aged 75 and older. Although we have not done studies in this specific population, the anticipated accrual rate at steady state is approximately 12 patients per month based on the intergroup trials NCCTG N9741 and CALGB C80405. As such we expect an accrual period of 30 months to accrue the required 380 patients. The accrual to this study will be conducted jointly through the NCCTG, CALGB and the US Intergroup.

Contingency plans in case of slow accrual. This protocol will yield valuable data for secondary endpoints even if the accrual is less than projected, or if the concurrent JCOG trial lags substantially in accrual. Specifically, the sample size requirements for the secondary endpoints related to the geriatric assessments require fewer than 380 patients (see below). Thus, if after 2 years from date of study opening the accrual rate is less than 100 patients/year, or if at trial completion the total accrual is less than 200 patients, the primary endpoint of progression free survival will become a secondary endpoint and the secondary endpoint of the geriatric assessment will become the primary endpoint.

16.3 Analysis plans and power. We assume a median PFS of 9 months in the control group (Kabbinavar et al. 2005b), and base our sample size calculations on obtaining a sufficient number events to achieve 80% power to detect a hazard ratio of 0.75 (an increase in median PFS to 12 months in the experimental arm). Assuming an accrual rate of 12 patients a month, an accrual period of 2.5 years, exponential survival distributions, and
one year minimum follow-up, 380 total patients will provide 304 events to provide 80% power using a one-sided log-rank test at level 0.05. The use of a one-sided test is appropriate in this setting as this is clearly a one-sided testing situation, with oxaliplatin adding toxicity to the fluoropyrimidine + bevacizumab regimen and there being no interest in proving that the addition of oxaliplatin to fluoropyrimidine + bevacizumab results in inferior PFS.

To address the secondary endpoint of overall survival, a virtually identical trial is being planned by the Japanese Clinical Oncology Group (JCOG). The study will also intend to accrue 380 patients. The data will be pooled between these two concurrent protocols at the NCCTG statistical office for final analysis, which will be stratified by the source of the patient (US vs. JCOG). Data will also be made available to the CALGB for analysis regarding geriatric assessment endpoints and the pharmacogenomics and QoL correlative studies where the CALGB will lead the analyses.

For the secondary endpoint of overall survival, which will only be formally tested in a closed testing procedure if success is achieved on the primary endpoint of PFS, we assume a median survival of 17 months in the control group (Kabbinavar et al. 2005b), and base our sample size calculations on obtaining enough events to achieve 80% power to detect a hazard ratio of 0.81 (an increase in median survival to 21.2 months in the experimental arm). Assuming an accrual rate of 25 patients a month for the joint trials, an accrual period of 2.5 years, and two years minimum follow-up, 760 total patients will provide 567 events to provide 80% power using a one-sided log-rank test at level 0.05. The use of a one-sided test is again appropriate in this setting as this is clearly a one-sided testing situation, with oxaliplatin adding toxicity to the fluoropyrimidine + bevacizumab regimen and there being no interest in proving that the addition of oxaliplatin to fluoropyrimidine + bevacizumab results in inferior survival.

Response rates and adverse events will be tabulated by arm and compared using two-sided chi-squared tests at level 0.05.

16.31 Interim analyses.

16.311 Futility analysis. One interim analyses will be conducted for futility for the primary endpoint of PFS, after 50% of the planned number of events, using the rule of Wieand, Schroeder, and O’Fallon (Wieand et al. 1994) (if the HR for comparing the oxaliplatin arm to the no oxaliplatin arm at this time point is > 1.0, the trial will be terminated for futility).

16.312 Efficacy analyses. Interim analyses for efficacy on the primary endpoint will not be conducted, specifically as there may be an improvement in PFS without any OS advantage, and this is critical information to determine through the joint analysis with the JCOG study. Efficacy interim analyses will be conducted on the secondary endpoint of OS. Because the study is powered for OS only in the joint analysis with the JCOG trial, and we anticipate that this trial will observe 567/2 = 283 OS events at the time of final OS analysis, efficacy analyses will be conducted after 25%, 50%, and 75% of this number of events using a fixed cut-off of a one-sided p-value less than 0.001 (Lan and DeMets 1983).
16.4 Subgroup analyses. Subgroup analyses based on the status on each of the stratification factors are planned and will be conducted, in addition to the gender and minority analyses described in Section 16.7 below.

16.5 Statistical Design for Geriatric/Frailty and QoL Assessment Study: Prognostic Ability and Between-arm Comparison

As the NCCTG QoL tool is being used, those measures will be analyzed by the NCCTG. As the CALGB CSGA tool is being used, those measures will be analyzed by the CALGB. The comparative work of assessing the various methods for frailty and other QoL measurements will be done collaboratively.

16.5.1 CSGA

To evaluate the ability of baseline CSGA to predict the overall incidence of ≥ grade 3 toxicity in elderly patients with metastatic colorectal cancer receiving fluoropyrimidine-based therapy plus bevacizumab, with or without oxaliplatin, a composite score will be computed from the following risk factors, as detailed in Section 1.411:

- Hemoglobin (male: <11, female: <10), creatinine clearance (Jelliffe –ideal wt <34), falls in last 6 months (≥1), hearing impairment (fair or worse), physical limitation in walking 1 block, assistance required in medication intake, and decreased social activity.

A logistic regression model will be used to determine the odd ratios for the occurrence of grade 3+ toxicity with a 95% confidence interval, and the overall association will be assessed by a likelihood ratio test with a two-sided alpha level of 0.05. As a secondary analysis, a multivariate logistic model will be applied including covariates for treatment arm and the stratification factors: age, PS and metastatic sites. Based on the ongoing CALGB Breast Cancer correlative study, we anticipate that at least 90% of patients will complete CSGA at baseline. Assuming an overall rate of ≥ grade 3 toxicity of 21% (Saltz et al. 2008), NCCTG/US Intergroup/CALGB cohort of 380 patients will provide 90% power to detect an odds ratio of 1.6 between a one standard deviation change in the composite score. This equates to the 84-th percentile having a 29% probability of toxicity, and the 16-th percentile would have a 14% probability of toxicity.

To characterize general associations of CSGA with clinical outcomes of ≥ grade 3 toxicity to chemotherapy, hospitalization, dose modification (delay or reduction), and discontinuation of chemotherapy due to toxicity, morbidity, and mortality in elderly patients with cancer, logistic regression models will evaluate the odd ratio for the following CSGA subscales [MOS Physical Functioning, Karnofsky Performance Status Rated Healthcare Professional, Timed Up and Go, OARS Physical Health Section] and OARS MFAQ (IADL). For changes in QoL from baseline to post-treatment in overall score and EQ-5D, Wilcoxon signed rank tests will be used to evaluate difference scores across CSGA subgroups.

For the comparison of the prognostic ability of baseline CSGA, the primary
analysis will pool over the two treatment arms and test for an association of baseline scores on each of the 6 subdomains of functional status (Section 1.4.14: IADL, ADL, KPS, KSPS, TUG, number of falls) with PFS and OS using a two-sided log-rank test at level 0.05. The NCCTG/US Intergroup/CALGB cohort of 380 patients will provide 90% power to detect a hazard ratio of 1.45 for PFS and a hazard ratio of 1.50 for OS based upon a median split of each CSGA subscale. All tests will be conducted using two-sided alpha levels of 0.05.

16.52 QoL

For the comparison of the prognostic ability of baseline QoL, the primary analysis will pool over the two treatment arms and test for an association of baseline QoL (as measured by the Fatigue/Uniscale, LASA, and EQ-5D items in Appendix VI) and PFS and OS using a two-sided log-rank test at level 0.05. A cut-point of 5 or lower on the overall QoL question will be defined to be the primary cut-off for analysis as that has been demonstrated to represent clinically deficient QoL. We anticipate approximately 20% of patients will have clinically deficient QoL (higher than the previous NCCTG experience of approximately 15%, based on the characteristics of our proposed population). Tan et al. (Tan et al. 2008) reported a hazard ratio of 1.56 for clinically deficient vs. non-clinically deficient QoL in a multivariate pooled analysis of over 3400 patients from NCCTG trials. The sample size of 300 patients will provide > 90% power to detect a clinically meaningful hazard ratio of 2.0 for this comparison.

Analysis of the Completion Questions will involve two processes. First, descriptive analysis pooling over treatment arms will be conducted with the goal of assessing overall satisfaction with the clinical trials process and this trial in particular. If considerable dissatisfaction is documented, it would suggest multiple aspects of the process need to be reassessed. Secondly, we will compare patient satisfaction between treatment arms, using each question individually. With 300 patients per arm for the primary comparison of the completion questionnaires, each test will have 80% power to detect a difference of 12% in the proportion of “yes” responses between study arms. This calculation allows a 15% no-completion rate for the completion questionnaire.

16.53 Frailty

For the comparison of the prognostic ability of baseline geriatric/frailty measures (Rockwood Frailty Index physician and patient-reported items as well as the NCCTG frailty measure; see Appendices VI-VII, X-XI), the primary analysis will pool over the two treatment arms and test for an association of baseline scores on each of the measures of frailty with PFS and OS using a two-sided log-rank test at level 0.05. The various measures of geriatric/frailty (CGSA, Rockwood, and NCCTG measures) will be compared head to head using Bland-Altman methods to assess the differences between clinician and patient reported frailty and the relative information obtained from the various assessments. This will be the first head to head comparison of its type to assess geriatric/frailty measures.

16.54 Patient Satisfaction
The Was It Worth It (WIWI) questionnaire items will be summarized descriptively to identify the number of patients who were satisfied with each treatment and indications for improvements therein. The proportion of patients reporting satisfaction via the three items of the WIWI questionnaire (Appendix X) will be compared between treatments by a Fisher’s exact test. The impact of the clinical trial on patient QOL will be summarized via means and standard deviations and compared between treatment arms via a Wilcoxon rank sum test.

16.55 PRO-CTCAE

The PRO-CTCAE items will be summarized descriptively to identify the number of patients who report adverse events and compared to the proportion of patients for whom clinicians identify an adverse event on the same symptoms. At each time point, Kendall’s coefficient of concordance (tau) between each CTCAE and PRO-CTCAE item will be calculated. PRO-CTCAE and the relationship with averages of the QOL scales will be compared via Kruskal-Wallis testing after dichotomization. The impact of PRO-CTAE on the primary treatment comparison will be undertaken via the modeling specified in the primary analysis using PRO-CTCAE data as covariates.

16.6 Statistical Design for Assessment of Pharmacogenetic Markers to Predict Tumor Response and Toxicity

The primary clinical endpoint for this pharmacogenomic companion is bevacizumab induced hypertension. The primary objective is to identify prognostic SNPs for grade 3+ hypertension. Other clinical endpoints of interest include tumor response, progression-free survival and overall survival.

For the GWAS data analysis, initial quality studies will be conducted to identify SNPs that have generated sufficiently poor quality genotype data and should be removed from analyses. Call rate, patterns of missing data, and departures from Hardy-Weinberg equilibrium (HWE) assessed using an exact test will all be scrutinized to identify markers that will not be used in analysis. In general, SNPs with call rates <95% and those with highly significant departures from HWE (p<10^-7) will not be included in analyses. Non-random patterns of missing data are sometimes encountered in data generated on high-throughput genotyping platforms; the most common non-random missing data problem is that heterozygous genotypes are more likely to be assigned as missing than either homozygous genotype. We will perform analyses using blind duplicates as well as analyses assessing the relationship between heterozygous call rates and missing data to identify any SNPs in which data are clearly not missing at random. Depending on the number and degree of difficulty observed, we will either remove problematic SNPs from analysis, or assign quality scores to reflect the extent of the non-random missing data.

Additional preliminary quality control analyses will be conducted to ensure that the sample does not include duplicated samples or closely related individuals. These analyses can be rapidly conducted using PLINK (Purcell et al. 2007). Duplicated samples (or unrecognized identical twins) will be reduced to a single sample for further analyses. Although we do not expect to have closely related individuals included in this sample, only one member of any set of first-degree relatives will be included in subsequent
Population structure that is not appropriately recognized and accommodated can lead to both false positive and false negative results in association studies. We will conduct studies using structure (Falush et al. 2003) to estimate ancestry proportions using 10,000 SNPs chosen for having no pairwise LD with unrelated individuals from the HapMap CEU, YRI and CHB+JPT samples used to model the ancestral populations. Substantial previous research has shown this to be a rapid and effective approach to defining historical geographic ancestry. Although self-identified race/ethnicity is usually highly correlated with estimated historical geographic ancestry, there are often a few individuals who appear to be misclassified with self-defined labels, and it is the genetically defined ancestry that is critical to correctly accommodate to ensure robust results from association studies. Each individual will then have estimates of European, African and Asian ancestry. For individuals with high ancestry proportion for a single group (>98%), we will conduct further analyses with eigenstrat (Price et al. 2006) using all SNPs to determine whether there are additional important sources of variation among individuals leading to detectable stratification by allele frequencies (reflecting, for example, differences in ethnic make-up within individuals of European descent from different U.S. cities from which subjects for the trial were obtained). Primary analyses, described below, will be conducted within groups defined by historical geographic ancestry. Secondary analyses will be conducted using logistic regression with ancestry proportions (and any additional stratification identified using eigenstrat) as covariates.

The association between the genotype call (say AA, AB or BB) for each autosomal SNP and the outcome will be powered for the additive model will be investigated within the framework of 2 by 3 contingency table stratified by ancestry. The Cochran-Armitage test (Agresti 2002) will be used for carrying out inference on these tables. A feature (SNP) will be considered significant if the corresponding nominal unadjusted two-sided P-value is less than 0.05/K, where K is number of features which pass the pre-processing step. Needless to say, this approach may be conservative. It does however guarantee strict type I error control.

For the sake of discussion, let B denote the risk allele with an assumed relative allelic frequency of 4q. Under the Hardy-Weinberg equilibrium assumption, the genotypes AA, AB or BB will have relative genotypic frequencies of (1-q)^2, 2q(1-q) and q^2, respectively. Let D denote the binary clinical outcome (D=1 if patient responds or =0 otherwise) and define the probability of a response given the copies of the risk allele on the genotype, to be denoted by G, as p_g=P[D=1|G=g], for g=0,1 or 2. The relationship between the event probability p=P[D=1] in the general population is then expressible as the following mixture p=(1-q)^2p_0+2q(1-q)p_1+q^2p_2. The effect size in the context of genome-wide association studies is typically quantified using the genotype relative risk (GRR) whose definition depends on the disease model. Under the recessive disease model, p_0=p_1 and p_2=GRRp_0 while under the dominant disease model p_1=p_2=GRRp_0. Finally, under the log-additive model, GRR=p_1/p_0=p_2/p_1. Under these disease models, the event probability in the population, p, can then be reformulated as the mixture p=(1-q)^2p_0w_0+2q(1-q)p_1w_1+q^2p_2w_2, where w=(w_0,w_1,w_2)=(1,1,GRR), for the recessive model, =1,GRR,GRR) for the dominant model and =(1,GRR,GRR^2) for the additive model.

A total of 380 patients will be randomized to the clinical study. It will be assumed that 85% of these patients will be classified as genetic Europeans. This expected set of 323
patients will serve as the target population for these analyses. The probability of an event (grade 3+ hypertension) is expected to be 0.2. The Illumina Huma610-Quad chip, which types about 620,000 SNPs, is expected to be used for this analysis. For a given q, the GRR detectable with a power of 0.8, at the two sided 0.05/600,000 level (i.e., assume K=600,000 autosomal SNP markers pass through the pre-processing step), is illustrated in Figure 1.

![Figure 1](image-url)

**Figure 1.** Power illustration: The minimum Genotype Relative Risk (GRR) detectable with a power of 0.8, at the two-sided level of 0.05/600,000 for a range of relative allele frequencies (q) assuming the probability of an event is P[D=1]=0.2, under recessive, dominant and additive models assuming HWE. The sample size used in the illustration is based on N=323 patients.

Logistic regression models and conditional inference trees (or more generally conditional random forests) will be used to construct multi-variable models based on the SNPs identified as interesting. These models also allow for inclusion of other potentially relevant clinical and demographic variables.

As an example, the Illumina Human610 Quad chip contains 184,064 SNPs in regions with common copy number variants (CNVs). Given the complex structure of CNVs, it is not always clear how to define the genotype of a CNV. Instead of categorizing copy numbers into genotypes, we will estimate relative genomic abundance probe intensities.
This approach allows for the consideration of other CNVs beyond deletions, including duplications and combinations of both. For notational brevity, we shall refer to these as CNV markers.

For each objective, the association between each CNV marker and the clinical AE endpoint, will be assessed using the Wilcoxon two-sample test. The family-wise error rate will be controlled at the 0.05 level using permutation resampling (based on B=100,000 replicates). Regression methods, as in the case of the SNP markers, will be employed to construct multivariable models based on the CNV markers.

Secondary relevant clinical endpoints include other adverse events, progression-free and overall survival. For censored time-to-event outcomes, the stratified Cox score test will be primarily used for assessment of significance.

A risk analysis will be carried out by comparing the genotypic distributions of the SNPs from the data from NCCTG N0949 to those from controls (thought to not to have cancer). The SNP data from the controls will be obtained from public databases.

In addition to conducting analyses on all features directly assessed on the high-throughput platform used in these studies, we will also interrogate all additional HapMap SNPs that are not in strong pairwise LD with any genotyped SNP but for which there is sufficient multi-locus LD to SNPs on the high-throughput platform. TUNA (Testing UNtyped Alleles) is a robust approach for conducting such analyses that provides inexpensive in silico follow up to the initial analysis and allows us to more efficiently design any follow up genotyping studies (Nicolae 2006; Nicolae 2006). For example, use of Illumina HumanHap300 enables direct testing of 270K-450K SNPs, and indirect testing of 750K-1.5M additional SNPs (i.e., these SNPs are so highly correlated with SNPs that are directly tested for association that testing them would provide little additional information). The ranges given above bracket the expectations for different human populations, with European populations at the high end of the range and populations of recent African descent at the lower end. Use of TUNA enables interrogation of an additional 100K-250K SNPs that are neither on the platform nor highly correlated with any individual SNP on the platform. Note that use of TUNA will facilitate comparisons to genome-wide association studies on potentially related phenotypes (e.g. clinical trials of the same or related drugs) conducted using other high-throughput platforms or candidate gene studies utilizing SNPs not directly genotyped on the high-throughput platform chosen for our studies.

The R statistical environment (Team 2006) and Bioconductor (Gentleman et al. 2004) packages will be used for all of the primary statistical analyses relating features to phenotypes. Specialized statistical genetics software, including PLINK (Purcell et al. 2007), structure (Falush et al. 2003), eigenstrat (Price et al. 2006), and TUNA (Nicolae 2006; Nicolae 2006) will be used for some of the quality or secondary analyses, and R will be used for logistic regression analyses allowing for ancestry covariates.

While the primary analyses will focus on the genetic European population, we plan to genotype all samples. We may test any signal observed based on the primary analyses in these other populations. We may also use these data to conduct meta analyses using data from other GWAS in colorectal cancer.

As genotyping technology is a fast moving field, we may use a chip other than the 610 Quad chip. These analyses may be followed up by additional candidate genotyping as
well as more extensive typing including gene, exome or whole-genome sequencing. The data may also be used to serve as a validation set for existing GWAS in colorectal cancer.

16.7 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.71 There is no information currently available regarding differential effects of oxaliplatin, 5-fluorouracil or bevacizumab in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for ethnic subset analyses.

16.72 To predict characteristics of patients likely to enroll in this trial, we reviewed the total accrual into the NCCTG led GI Intergroup advanced disease colon trial N9741 gender, and race. This demonstrated that 6% (24/380) of patients could be classified as minorities by race and that 38% (143/380) of patients were women.

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Sex/Gender</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
<td>Total</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>3</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>140</td>
<td>225</td>
<td>365</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of all subjects</strong></td>
<td>143</td>
<td>237</td>
<td>380</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Category</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Black or African American</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>138</td>
<td>218</td>
</tr>
<tr>
<td><strong>Racial Category: Total of all subjects</strong></td>
<td>143</td>
<td>237</td>
</tr>
</tbody>
</table>
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. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”

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. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”

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.

16.8 This study will be reported to CTEP using the Clinical Data Update System (CDUS). Cumulative data for CDUS “abbreviated” reporting purposes will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

16.9 In accordance with the NCI’s current DMC policy, the NCCTG External Data Monitoring Committee will meet every 6 months in conjunction with the NCCTG semi-annual group meetings to review the progress of this protocol.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Tissue Biospecimen Submission

17.11 Summary Table of Tissue Biospecimens for This Protocol

<table>
<thead>
<tr>
<th>Type of tissue biospecimen to submit</th>
<th>Mandatory or optional</th>
<th>When to submit</th>
<th>Reason for submission (background/methodology section)</th>
<th>Where to find specific details for biospecimen submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formalin-fixed paraffin-embedded (FFPE) tissue blocks (OR unstained slides with corresponding H&amp;E)*</td>
<td>Optional</td>
<td>≤30 days after randomization</td>
<td>Correlative studies and future banking (Section 17.5)</td>
<td>Section 17.3</td>
</tr>
</tbody>
</table>

*If an institution is not able to provide the optional tissue, it does not cause the patient to be ineligible; however, the collection of these tissues is strongly recommended.

17.2 Diagnostic Slides (None)
17.3 Paraffin Embedded Tissue Blocks/Slides

17.31 Submit one formalin fixed paraffin-embedded (FFPE) tumor tissue block with largest amount of invasive tumor (at least 1 cm of tumor for cases of surgical resection) from original surgery. If tissue is not available from the original surgery, metastatic tissue is acceptable. **A corresponding H&E slide for each submitted block must be provided** to permit quality assessment of each tissue block.

17.32 The FFPE tissue block is preferred; however, if an institution is unable to provide a tissue block, sequentially cut 21 five-micron sections and mount on charged slides (for correlative studies), then cut 10 ten-micron sections and mount on uncharged slides (for DNA extraction). **Label the slides with NCCTG patient ID number, accession number, order of cut sections (i.e., 1-21 for the five-micron slides and 22-31 for the ten-micron slides), and micron thickness of section (either five- or ten-microns). H&E stain the five-micron slides labeled 1, 11, and 21 for tissue block quality assessment. Ideally, each slide must have a minimum of 75% tumor tissue on the slide to be deemed adequate for study. Do not bake or place covers slips on the slides.**

17.33 If the patient has consented to provide research tissue, the following materials below are required for shipment (unless indicated otherwise):
- Paraffin embedded tissue blocks with corresponding H&E slide (OR 18 five-micron and 10 ten-micron unstained slides with 3 five-micron corresponding H&Es).
- Baseline Research Tissue Submission Form
- Surgical Pathology Report
- Operative Report (optional)

**Note: Please include the NCCTG patient ID number on all materials listed above.**

17.34 The block/slides must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, NCCTG patient ID number, and patient initials.

17.35 Tissue specimens must be shipped ≤30 days after randomization.

17.36 Verify that the appropriate sections of the Baseline Research Tissue Submission Form are completed and filled in correctly. **NCCTG sites** enter information from the Baseline Research Tissue Submission Form into the remote data entry system ≤30 days after randomization, preferably on the same day the specimen is submitted (see Forms Packet). **Non-NCCTG submit** the Baseline Research Tissue Submission Form to NCCTG ≤30 days after randomization for data entry (see Forms Packet). Include a copy of this form with tissue submission (see Section 17.33).
17.37 Ship all block/slide tissue specimens and accompanying materials to the NCCTG Research Base:

NCCTG Operations Office  
Attn: PC Office (Study N0949)  
RO_FF_03_24-CC/NW Clinic  
200 First Street SW  
Rochester, MN 55905

17.38 If a corresponding H&E wasn’t submitted with the block/slides, the NCCTG Operations Office will request a slide to be processed (i.e., cut and H&E stained) from the tumor tissue block and forwarded to Dr. Thomas C. Smyrk to be reviewed under the research base’s protocol for assessing tissue quality for the proposed correlative studies, unless the tumor size is too small. If the tumor tissue is too small, assessment of tissue quality will occur at the time the correlative studies are performed.

17.39a After the pathologist assesses the tissue quality, the block and appropriate paperwork will be returned to the NCCTG Operations Office.

17.39b When an appropriate request is submitted, the NCCTG Operations Office will forward the block/slides to the NCCTG Research Base TACMA Shared Resource, Stabile 13-10B, Mayo Clinic Rochester (Attn: TACMA Supervisor) for processing as outlined in Section 17.5.

17.4 Frozen Tumor Tissue (None)

17.5 Study Methodology and Storage Information

Submitted tissue samples will be analyzed as follows:

17.51 DNA will be extracted by the BAP Shared Resource, Mayo Clinic Rochester, from tumor tissue for pharmacogenetic assays (e.g., single nucleotide polymorphism [SNP] analyses) to determine correlations with efficacy and tolerability of fluoropyrimidine-based plus bevacizumab with or without oxaliplatin. Pharmacogenetic research of molecular targets to be analyzed includes, but is not limited to, KRAS and BRAF status (if results are not provided by the submitting institution) and will be performed in the Genotyping Shared Resource, Mayo Clinic Rochester.

17.52 At the completion of the study, any unused/remaining material will be stored in the NCCTG Central Operations Office (attn: Pathology Coordinator) for future research according to the patient consent permission (see Sections 6.34-6.36). Potential future research may include immunohistochemistry (IHC) analyses and/or tissue microarray (TMA) construction to analyze predictive biomarkers, changes in expression pattern with therapy, and correlation with response and/or adverse events. For TMAs, the donor block remains intact except for 6 small (0.6mm) holes where the cores were taken. This process has minimal impact on the utility of the block for future clinical diagnostic needs. When a protocol is developed, it will be presented for IRB review and approval.
17.53 The institutional pathologist will be notified by the NCCTG Operations Office (Pathology Coordinator) if the block may be depleted.

17.54 Blocks requested to accommodate individual patient management will be returned promptly upon request.

17.6 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

<table>
<thead>
<tr>
<th>Initial Material(s)</th>
<th>Active-Monitoring Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRF</strong></td>
<td>(Compliance with Test Schedule Section 4.0)</td>
</tr>
<tr>
<td>Physician Fluoropyrimidine Treatment Decision Form</td>
<td>≤7 days after randomization¹</td>
</tr>
<tr>
<td>On-Study Form</td>
<td></td>
</tr>
<tr>
<td>Baseline Adverse Event Form</td>
<td></td>
</tr>
<tr>
<td>Pretreatment RECIST Measurement Form</td>
<td></td>
</tr>
<tr>
<td>Research Blood Submission Form (see Section 14.0)</td>
<td>≤3 weeks after randomization</td>
</tr>
<tr>
<td>Concomitant Medication Form (Baseline)</td>
<td></td>
</tr>
<tr>
<td>Research Tissue Submission Form (Baseline) (see Section 17.0)</td>
<td>≤30 days after randomization</td>
</tr>
<tr>
<td>OP and Path Reports (see Section 17.0)</td>
<td></td>
</tr>
<tr>
<td>End of Active Treatment/Cancel Notification Form</td>
<td>Submit ≤3 weeks after randomization if withdrawal/refusal occurs prior to beginning protocol therapy</td>
</tr>
<tr>
<td>Patient Questionnaire Booklet – Baseline (Appendix VI)</td>
<td>≤3 weeks after randomization²</td>
</tr>
<tr>
<td>Patient Questionnaire Booklet Compliance Form</td>
<td>≤3 weeks after randomization. This form must be completed only if the Patient Questionnaire Booklet – Baseline contains absolutely NO patient provided assessment information.</td>
</tr>
<tr>
<td>Research Team Questionnaire Booklet – Baseline (Appendix VII)</td>
<td>≤3 weeks after randomization²</td>
</tr>
<tr>
<td>Research Team Questionnaire Booklet Compliance Form</td>
<td>≤3 weeks after randomization</td>
</tr>
</tbody>
</table>

¹ The mention of ‘randomization’ in this context is included to emphasize the importance of timeliness in the submission of documents.

² The requirement to complete forms only if certain conditions are met highlights the need for careful monitoring and follow-up in clinical trials.
1. The Physician Fluoropyrimidine Treatment Decision Form must be faxed to the NCCTG Registration Office at (507) 284-0885 ≤ 7 days after randomization (see Section 6.39g). NCCTG sites will NOT submit this form via NCCTG Remote Data Entry System.

2. Patient Questionnaire Booklets and Research Team Questionnaire Booklets must be used; copies are not acceptable for this submission. Submit booklets to the NCCTG Operations Office, NW Clinic 3-24, 200 First Street SW, Rochester MN 55905 Attention: QAS for N0949.

**Test Schedule Material(s)**

<table>
<thead>
<tr>
<th>CRF</th>
<th>Active-Monitoring Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Compliance with Test Schedule Section 4.0)</td>
</tr>
<tr>
<td></td>
<td>At each evaluation during treatment</td>
</tr>
<tr>
<td>Evaluation/Treatment Form</td>
<td>X¹</td>
</tr>
<tr>
<td>Evaluation/Observation Form</td>
<td>X³</td>
</tr>
<tr>
<td>Adverse Event Form</td>
<td></td>
</tr>
<tr>
<td>Active Monitoring RECIST Measurement Form</td>
<td>X⁴</td>
</tr>
<tr>
<td>Research Blood Submission Form</td>
<td>X (see Section 14.0)</td>
</tr>
<tr>
<td>Patient Questionnaire Booklet – Active Treatment, Current Cycle (Appendix VIII)</td>
<td>X⁵</td>
</tr>
<tr>
<td>Patient Questionnaire Booklet – Active Treatment, Every 3 Months (Appendix IX)</td>
<td>X⁵</td>
</tr>
<tr>
<td>Patient Questionnaire Booklet – Observation Phase (Appendix X)</td>
<td></td>
</tr>
<tr>
<td>Patient Questionnaire Booklet Compliance Form</td>
<td>X⁶</td>
</tr>
<tr>
<td>Research Team Questionnaire Booklet – Observation Phase (Appendix XI)</td>
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</tr>
<tr>
<td>Research Team Questionnaire Booklet Compliance Form</td>
<td></td>
</tr>
<tr>
<td>End of Active Treatment/Cancel Notification Form</td>
<td></td>
</tr>
<tr>
<td>Notification Form – Grade 4 or 5 Non-AER Reportable Events/Hospitalization</td>
<td>At each occurrence (see Section 10.0)⁸</td>
</tr>
<tr>
<td>ADR/AER</td>
<td>At each occurrence (see Section 10.0)</td>
</tr>
</tbody>
</table>

1. Complete at each evaluation during Active Treatment (see Section 4.0).
2. Complete at each evaluation during Observation (see Section 4.0).
3. Toxicity check 28-42 days after treatment discontinuation: Because of the long half-life of bevacizumab, all patients (including those who have left the study because of progressive disease, unacceptable toxicity, patient refusal, investigator’s decision to remove patient, etc) must have a toxicity check at this time point.
4. Submit copy of documentation of response or progression to the NCCTG Operations Office, NW Clinic 3-24, 200 First Street SW, Rochester MN 55905 Attention: QAS for N0949.
5. Patient Questionnaire Booklets and Research Team Questionnaire Booklets must be used; copies are not acceptable for this submission. Submit booklets to the NCCTG Operations Office, NW Clinic 3-24, 200 First Street SW, Rochester MN 55905 Attention: QAS for N0949.
6. This form must be completed only if the Patient Questionnaire Booklet (Appendices VIII, IX, X) contains absolutely NO patient provided assessment information.
7. Submit this form only if withdrawal/refusal prior to beginning protocol therapy occurs.
8. NCCTG Institutions Only
Follow-up Material(s)

<table>
<thead>
<tr>
<th>CRF</th>
<th>Event Monitoring Phase¹</th>
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<tr>
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<td>q. 3 months until PD</td>
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<tr>
<td>Event Monitoring Form</td>
<td>X²</td>
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</tbody>
</table>

1. If a patient is still alive 5 years after randomization, no further follow-up is required.
2. Submit copy of documentation of response or progression to the NCCTG Operations Office, Attention: QAS for N0949.

18.2 Additional submission instructions

18.21 NCCTG sites

18.211 Submit all forms (except Physician Fluoropyrimidine Treatment Decision Form, see Section 6.39g) via NCCTG Remote Data Entry System.

18.212 After entering into the NCCTG Remote Data Entry System, mail all Patient and Research Team Questionnaire Booklets to: NCCTG Operations Office, NW Clinic 3-24, 200 First Street SW, Rochester MN 55905 Attention: QAS for N0949.

18.22 Non-NCCTG intergroup sites

18.221 Non-NCCTG sites will fax forms (except Physician Fluoropyrimidine Treatment Decision Form, see Section 6.39g and Patient and Research Team Questionnaire Booklets, see Section 18.222) to NCCTG Operations Office, Attention: N0949 QAS at 507-266-7240.

18.222 Non-NCCTG sites will mail all Patient and Research Team Questionnaire Booklets to: NCCTG Operations Office, NW Clinic 3-24, 200 First Street SW, Rochester MN 55905 Attention: QAS for N0949.

18.223 Each site will be responsible for insuring that all materials contain the patient’s initials, NCCTG registration number, and NCCTG protocol number. Patient’s name must be removed.

18.224 Any materials deemed incomplete by the NCCTG Operations Office will be considered “not received” and will not be edited or otherwise processed until the missing information is received. A list of the missing documents will be made available to the institution responsible for the patient.

18.225 Overdue lists: A list of overdue materials and forms for study patients will be generated monthly. The listings will be sorted by location and will include the patient study registration number. NCCTG will contact the patients’ institutions in order to obtain the overdue material.

18.226 Correction forms: If a correction is made by NCCTG, a correction form will be sent to the institution to make the correction on the institution’s form. In cases of disagreement with a given correction, a query letter may be written.
19.0 Budget

19.1 Costs charged to patient: Routine clinical care costs will be the responsibility of the patient and/or the patient’s insurance company. This includes cost of the study drugs and costs associated with the administration of those study drugs. All study drugs are commercially available.

19.2 Tests to be research funded: Correlative studies and specimen kits for research blood collections.

20.0 References


Kozloff, M. F., M. M. Sugrue, et al. (2008b). "Safety and effectiveness of bevacizumab (BV) and chemotherapy (CT) in elderly patients (pts) with metastatic colorectal cancer (mCRC): Results from the BRiTE observational cohort study." J Clin Oncol (Meeting Abstracts) 26(15_suppl): 4026-. Medline ID: NA.


Medline ID: NA.


NCI Informed Consent Template for Cancer Treatment Trials
(English Language)

*NOTES FOR LOCAL INVESTIGATORS: [NOTE: Retain this section and asterisk item below for NCCTG model consents]

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/

- A blank line, __________, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.

- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "Taking Part in Cancer Treatment Research Studies". This pamphlet may be ordered on the NCI Web site at https://cissecure.nci.nih.gov/ncipubs/ or call 1-800-4-CANCER (1-800-422-6237) to request a free copy.

- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for (authors and) investigators are instructional and should not be included in the informed consent form given to the prospective research participant.
Randomized Phase III Trial of mFOLFOX7 or XELOX Plus Bevacizumab Versus 5-Fluorouracil/Leucovorin or Capecitabine Plus Bevacizumab as First-line Treatment in Elderly Patients with Metastatic Colorectal Cancer

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

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

You are being asked to take part in this research study because you have metastatic colorectal cancer.

Why is this research study being done?
In general, clinical trials usually enroll significantly more younger patients (<70 years old) than older patients (≥70 years old), so it’s not clear if the current day therapies for metastatic colorectal cancer need to include oxaliplatin in the treatment of older patients. This is of particular importance since oxaliplatin can affect the nerve system with loss of sensation in hands and feet which can affect activities of daily living, in particular, in elderly patients. The purpose of this research study is to compare the length of time during and after treatment that metastatic colorectal cancer does not get worse in older patients treated with bevacizumab plus either 5-fluorouracil/leucovorin or capecitabine without oxaliplatin or in patients treated with bevacizumab plus 5-fluorouracil/leucovorin or capecitabine with oxaliplatin.

How many people will take part in the research study?
About 380 people will take part in this 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 or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- A physical history and exam, including your height, weight, pulse, temperature, and tests to rate how well you perform activities of daily living.
- Blood pressure.
- Routine blood tests. About 2 teaspoons of blood will be drawn.
• You will have tests to see if you have any problems with your blood clotting.
• Tests to check for protein in your urine to find out how well your kidneys are functioning.
• Measurement of your tumor by either CT scan or MRI (scans that take pictures of your body’s organs).
• Chest x-ray. This will not be needed if a CT scan of your chest is performed to measure your tumor.
• If you have any type of neurological symptoms, you must have a CT scan or MRI of your head.
• An electrocardiogram to find out how well your heart is functioning.
• Before start of treatment, you will have an evaluation to see if any of the possible side effects are already present before treatment.
• You will also be asked to give blood and tissue samples for additional research studies. The blood samples are required and about 6 teaspoons will be drawn. The tissue samples are not required, but we strongly encourage you to provide them for these studies. More information about these research studies is given starting on page 18 of this consent form.
• Before you start treatment, you will be required to fill out a Patient Questionnaire Booklet that contains seven sets of questions (about 92 questions total). This booklet will take about 35 minutes to complete.

During the study…

A cycle of treatment will be either 2 or 3 weeks long. If your doctor chooses 5-fluorouracil/leucovorin as part of your treatment, your cycle of treatment will be 2 weeks. If your doctor chooses capecitabine as part of your treatment, your cycle of treatment will be 3 weeks.

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

Weekly:
• Blood pressure (weekly for first 6 weeks then before each treatment cycle after that, either every 2 or 3 weeks). You may have your blood pressure taken in your local doctor’s office or take it yourself on a blood pressure machine in, for example, a local drug store.
• If you take your blood pressure yourself, you will have to record your blood pressure in a Blood Pressure Diary.

Before each new cycle (either every 2 or 3 weeks):
• A physical history and exam, including your weight, pulse, temperature, and tests to rate how well you perform activities of daily living.
• Blood pressure. You may have your blood pressure taken in your local doctor’s office or take it yourself on a blood pressure machine in, for example, a local drug store.
• If you take your blood pressure yourself, you will have to record your blood pressure in a Blood Pressure Diary.
• Routine blood tests. About 2 teaspoons of blood will be drawn.
• Evaluation of any side effects you are having.
• If you are taking capecitabine instead of 5-fluorouracil/leucovorin, you will have to record the date and times you take your pills in your Capecitabine Medication Diary.
• You will be required to fill out a Patient Questionnaire Booklet that contains two sets of questions (17 questions total). This booklet will take about 6-7 minutes to complete.

Other procedures during the study:
• Before cycle 3 treatment (or more often if your doctor tells you to), you will have tests to see if you have any problems with your blood clotting.
• Before every other cycle (every 4 weeks), tests to check for protein in your urine will be done to find out how well your kidneys are functioning.
• Every 6 weeks, measurement of your tumor by either CT scan or MRI will be done (scans that take pictures of your body’s organs).
• After 6 weeks of treatment, you will also be asked to give blood samples for additional research studies. The blood samples are required and about 4 teaspoons will be drawn. More information about these research studies is given starting on page 18 of this consent form.
• Every three months, you will be required to fill out a Patient Questionnaire Booklet that contains two sets of questions (12 questions total). This booklet will take about 5 minutes to complete.
• If your blood pressure gets too high, you may have to have your blood pressure checked by a health professional every 2 days until your blood pressure gets better.

After you are finished receiving the study treatment:
• A physical history and exam, including your weight, pulse, temperature, and tests to rate how well you perform activities of daily living.
• Blood pressure.
• Routine blood tests. About 2 teaspoons of blood will be drawn.
• Evaluation of any side effects you are having.
• Measurement of your tumor by either CT scan or MRI (scans that take pictures of your body’s organs).
• You will also be asked to give blood samples for additional research studies. The blood samples are required and about 4 teaspoons will be drawn. More information about these research studies is given starting on page 18 of this consent form.
• You will be required to fill out a Patient Questionnaire Booklet that contains eight sets of questions (about 99 questions total). This booklet will take about 35 minutes to complete.
Treatment

You will be "randomized" into one of the two study groups described below. Randomization means that you are put into a group by chance (as in the flip of a coin). 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 group. All of the study drugs used in either group have been FDA-approved for the treatment of metastatic colorectal cancer.

If you are in Group 1 (control arm), your doctor will first decide whether you will receive 5-fluorouracil/leucovorin or capecitabine.

- If your doctor chooses 5-fluorouracil/leucovorin, you will be given leucovorin through a vein in your arm for 2 hours on day 1 and given 5-fluorouracil through a vein in your arm via a small portable pump for 46-48 hours. You will also be given bevacizumab through a vein in your arm for 10-90 minutes on Day 1 of each cycle. You will be retreated with 5-fluorouracil/leucovorin and bevacizumab every two weeks.

- If your doctor chooses capecitabine, you will take capecitabine by mouth, two times each day for 14 days (“Days 1-14”). The next 7 days (“Days 15-21”) you will not take capecitabine. You should swallow the tablets whole with 6-8 ounces (about one cup) of water. Capecitabine should be taken within 30 minutes after your morning and evening meals (12 hours apart). Do NOT take a missed dose, never double up on a dose, and tell your health care team if you miss a dose. You will need to bring your capecitabine bottles and Patient Medication Diary with you to every clinic visit. You will also be given bevacizumab through a vein in your arm for 30-90 minutes on Day 1 of each cycle. You will be retreated with capecitabine and bevacizumab every three weeks.

If you are in Group 2 (experimental arm), your doctor will first decide whether you will receive 5-fluorouracil/leucovorin or capecitabine.

- If your doctor chooses 5-fluorouracil/leucovorin, you will be given leucovorin through a vein in your arm for 2 hours on day 1 and given 5-fluorouracil through a vein in your arm via a small portable pump for 46-48 hours. You will also be given oxaliplatin through a vein in your arm for 2 hours on Day 1 and bevacizumab through a vein in your arm for 10-90 minutes on Day 1 of each cycle. You will be retreated with 5-fluorouracil/leucovorin, oxaliplatin, and bevacizumab every two weeks.

- If your doctor chooses capecitabine, you will take capecitabine by mouth, two times each day for 14 days (“Days 1-14”). The next 7 days (“Days 15-21”) you will not take capecitabine. You should swallow the tablets whole with 6-8 ounces (about one cup) of water. Capecitabine should be taken within 30 minutes after your morning and evening meals (12 hours apart). Do NOT take a missed dose, never double up on a dose, and tell your health care team if you miss a dose. You
will need to bring your capecitabine bottles and Patient Medication Diary with you to every clinic visit. You will also be given oxaliplatin through a vein in your arm for 2 hours and bevacizumab through a vein in your arm for 30-90 minutes on Day 1 of each cycle. You will be retreated with capecitabine, oxaliplatin, and bevacizumab every three weeks.

**If your cancer gets worse**, you will stop treatment. If at any time while you are on the study you or your doctor feel that the side effects of the drugs are too bad, you will stop treatment and go off the study.

**When I am finished taking the study treatment…**

If your cancer gets worse, if you have unacceptable side effects, or if you decide you no longer want to take part in this study, you will stop taking the study drugs. When you are finished taking the study treatment, we will follow you up to 5 years after the date you registered, but you will no longer take the study treatment or follow the study treatment schedule. Your doctor will talk to you about other treatment options.

**How long will I be in the research study?**

You will be asked to take the study treatment until your cancer gets worse, you have bad side effects, or you and/or your doctor think you should stop. At that time, you will stop taking treatment. Once you stop taking treatment, you will not need to return for regularly scheduled visits; but, we will continue to keep track of your medical condition for up to 5 years after the date you were randomized on the study. If you stop taking treatment because of bad side effects or you and/or your doctor think you should stop, we will contact you by phone about every 3 months to keep track of your medical condition. If your cancer gets worse, we will contact you by phone about every 6 months to keep track of your medical condition.

**Can I stop being in the research 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.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.
What side effects or risks can I expect from being in the research study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don’t know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. As with any medication, allergic reactions are a possibility. Many side effects go away soon after you stop taking bevacizumab and 5-fluorouracil/leucovorin or capecitabine with or without oxaliplatin. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

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

### Risks and side effects related to 5-fluorouracil include those which are:

**Likely risks of 5-fluorouracil** *(events that occur more than 20% of the time)*
- Decrease white blood cell count with increased risk of infection
- Decreased platelet count with increased risk of bleeding
- Darkening of skin and nail beds, dry, flaky skin
- Nausea
- Vomiting
- Sores in mouth or on lips
- Thinning hair
- Diarrhea
- Brittle nails
- Increased sensitivity to sun

**Less Likely risks of 5-fluorouracil** *(events that occur 5 to 20% of the time)*
- Darkening and stiffening of vein used for giving the drug
- Decreased appetite
- Headache
- Weakness
- Muscle aches

**Rare but serious risks of 5-fluorouracil** *(events that occur less than 5% of the time)*
- Difficulty walking
- Irritation of eyes
- Increased tearing of eyes
- Blurred vision

While you are being treated with 5-fluorouracil, and after you stop treatment, do not have any immunizations (vaccinations) without your doctor's okay. Try to avoid contact with people who have recently taken the oral polio vaccine. Check with your doctor about this.

### Risks and side effects related to leucovorin include those which are:

Side effects that you may experience with this drug are uncommon. These, however, include an allergic reaction, varying from an itchy rash to breathing difficulties. Measures are available to help you if these should occur.

Leucovorin may interfere with the effects of anti-seizure medications such as phenobarbital, phenytoin, and primidone. When leucovorin is given together with a drug called 5-fluorouracil, it may increase the side-effects of this drug.
Risks and side effects related to capecitabine include those which are:

Likely risks of capecitabine *(events that occur more than 20% of the time)*
- Loose stools (Diarrhea)
- Inflammation and/or sores in the mouth that may make swallowing difficult and are painful (Mucositis)
- Feeling sick to your stomach (Nausea)
- Redness or sores of the palms of the hands or soles of the feet (Palmar-plantar erythrodysesthesia—“hand-foot syndrome”)
- Dry skin (Xerosis)
- Itching sensation (Pruritis)

Less Likely risks of capecitabine *(events that occur 5 to 20% of the time)*
- Decrease in red blood cells, which are the oxygen carrying cells, which could make you feel tired (Anemia)
- Decreased white blood cells, which are the infection fighting cells, which could put you at risk for infection (Leukopenia)
- Decreased number of blood cells (platelets) that help to clot the blood (which could put you at increased risk of bleeding) (Thrombocytopenia)
- Throwing up (Vomiting)
- Stomach or abdominal pain
- Loss of appetite, not feeling hungry (Anorexia)
- Difficulty passing stools (Constipation)
- Heart burn (Dyspepsia)
- Feeling tired (Fatigue)
- Generalized weakness and loss of strength (Asthenia)
- Hair loss (Alopecia)
- Rash
- Red, sore eyes
- Fever (Pyrexia)
- Sensation of lightheadedness or vertigo—spinning sensation (Dizziness)
- Headache
- Pain, including joint (arthralgia), muscle (myalgia), or bone.
- Infection

Rare but serious risks of capecitabine *(events that occur less than 5% of the time)*
- Blood clots and/or bleeding
- Excessive or abnormal loss of body fluids (Dehydration)
- Abnormal Liver function tests which may indicate that your liver is not functioning properly
- Lack of oxygen to the heart muscle which can cause damage to the heart (Heart attack)
- Abnormal heartbeat (Arrhythmia)

Risks and side effects related to bevacizumab include those which are:

Likely risks of bevacizumab *(events that occur more than 20% of the time)*
- High blood pressure

Less Likely risks of bevacizumab *(events that occur 5 to 20% of the time)*
- Lack of enough red blood cells (anemia)
- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- Fast heartbeat usually originating in an area located above the ventricles
- Feeling of spinning or whirling
- Belly pain
- Inflammation (swelling and redness) of the large bowel (colon)
- Constipation
- Diarrhea
- Heartburn
- Bleeding in some organ(s) of the digestive tract
- Blockage in an organ(s)/part(s) of the digestive tract
- Partial or complete blockage of the small and/or large bowel. Ileus is a functional rather than actual blockage of the bowel.
- Irritation or sores in the lining of the mouth
- Nausea or the urge to vomit
- Vomiting
- Fatigue or tiredness
- Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.
- Chest pain not heart-related
- Pain
- Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.
- Infection
- Infection (collection of pus) around the rectum
- Premature opening of a wound along surgical stitches after surgery
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Increased blood level of a liver enzyme (AST/SGOT)
- Increased blood level of a liver pigment (bilirubin) often a sign of liver problems
- Increased blood level of a heart muscle protein (troponin I) indicating damage to the heart muscle
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Weight loss
- Decrease in the total number of white blood cells (leukocytes)
- Loss of appetite
- Joint pain
- Muscle pain
- Destruction or death of jawbone
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- Headache or head pain
- Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning
- Fainting
- Blood in the urine
- More protein leaking into the urine than usual, often a sign of kidney disease
- Bleeding in the vagina
- Cough
- Shortness of breath
- Nose bleed
- Hoarseness
- Stuffy or runny nose, sneezing
- Itching
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
- Hives
- Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung
Rare but serious risks of bevacizumab (events that occur less than 5% of the time)

- Damage of or clots in small blood vessels in the kidney that can cause complications, some of which are serious including abnormal destruction of red blood cells (hemolysis) or platelets (that help to clot blood) and kidney failure
- Collection of signs and symptoms that indicate sudden heart disease in which the heart does not get enough oxygen. Sudden symptoms such as chest pain, shortness of breath, or fainting could indicate heart disease and should be reported right away. Signs such as abnormal EKG and blood tests can confirm damage to the heart.
- Heart failure: inability of the heart to adequately pump blood to supply oxygen to the body
- Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)
- Heart attack caused by a blockage or decreased blood supply to the heart
- Irregular heartbeat resulting from an abnormality in the one of the lower chambers of the heart (ventricle)
- Ventricular fibrillation: irregular heartbeat that involves the lower chambers of the heart (ventricles) that results in uncoordinated contraction of the heart; life threatening and potentially fatal, needing immediate attention
- Gastrointestinal fistula: Abnormal hole between an organ of the digestive tract and another organ or tissue
- Gastrointestinal perforation: A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair
- Sore (ulcer) somewhere in the digestive tract
- Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.
- Leakage from stomach due to breakdown of an anastomosis (surgical connection of two separate body structures)
- Bleeding in the brain
- Stroke caused by decreased blood flow to the brain
- Abnormal changes in the brain that can cause a collection of symptoms including headache, confusion, seizures, and vision loss associated with MRI imaging findings Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
- Sudden decrease of kidney function
- A condition in which the kidneys leak a large amount of protein into the urine that can cause complications including swelling and kidney failure
- Abnormal hole between part of the urinary system and another organ or tissue
- Abnormal hole between the vagina and another organ or tissue
- Abnormal hole between the lower breathing tube and the body cavity that surrounds the lungs
- Bleeding from the lungs
- Hole in the wall that separates the nostrils of the nose
- Abnormal hole between the breathing tube (windpipe) and the tube that goes from mouth to stomach through which food passes (esophagus). This is life-threatening and potentially fatal.
- Blockage or narrowing of a blood vessel (artery) that can cause damage or loss of function including a heart attack or stroke

Intravenous Injection Side Effects: If the drug leaks from the vein where the infusion is given, it may cause sores on the skin or severe local redness, pain, and/or swelling.
**Risks and side effects related to oxaliplatin include those which are:**

**Likely risks of oxaliplatin** *(events that occur more than 20% of the time)*
- Lack of enough red blood cells (anemia)
- Diarrhea
- Nausea or the urge to vomit
- Vomiting
- Fatigue or tiredness
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver enzyme (AST/SGOT)
- Decreased number of a type of blood cell that help to clot blood (platelet)
- Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning

**Less Likely risks of oxaliplatin** *(events that occur 5 to 20% of the time)*
- Abnormal blood clotting and/or bleeding
- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- Destruction of red blood cells
- Abnormal heartbeat that could include slow, fast, regular or irregular rhythm. **May be life-threatening, needs immediate attention**
- Hearing loss
- Inflammation (swelling and redness) to the middle ear
- Inflammation (swelling and redness) of the conjunctiva (the outermost layer of the eye and the inner surface of the eyelids). Commonly called "pink eye".
- Dry eye
- A situation in which one has temporary blindness of one eye, due to a blockage (or decreased blood flow) in the blood vessels leading to that eye
- Temporary vision problems caused by the cold
- Problem with eyelid
- Swelling around the nerve responsible for sight
- Belly pain
- Fluid collection in the abdomen
- Constipation
- Dry mouth
- Heartburn
- Difficulty swallowing
- Inflammation (swelling and redness) of the small and large bowel
- Inflammation (swelling and redness) of the esophagus (gullet or the tube that goes from mouth to stomach through which food passes)
- Excess passing of gas
- Inflammation (swelling and redness) of the stomach lining
- Bleeding in some organ(s) of the digestive tract
- Death of tissue somewhere in the digestive tract
- Sore (ulcer) somewhere in the digestive tract
- Partial or complete blockage of the small and/or large bowel. Ileus is a functional rather than actual blockage of the bowel.
- Irritation or sores in the lining of the mouth
- Inflammation (swelling and redness) of the pancreas
- Chills
- Swelling of the face
- Swelling of the extremities (arms and/or legs)
- Fever
- Limp or difficulty walking
- A condition in which both the liver and kidneys fail
• Inflammation (swelling and redness) or damage to the tissue surrounding where a drug was injected
• Pain: joint, back, bone, muscle, or chest pain (not heart-related)
• Liver failure
• Increase in size of the liver
• A condition in which there is blockage of the veins of the liver; leads to liver damage
• Abnormal reaction of the body to substances, called allergens, that are contacted through the skin, inhaled into the lungs, swallowed, or injected (allergic reaction)
• Infection
• Test that shows a problem in blood clotting
• Increased blood level of a liver or bone enzyme (alkaline phosphatase)
• Increased blood level of a liver pigment (bilirubin) often a sign of liver problems
• Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)
• Increased blood level of a liver enzyme (GGT)
• Increased INR (measure of the ability of the blood to clot properly) which increases the risk of bleeding
• Decreased number of a type of white blood cell (lymphocyte, neutrophil/granulocyte,) or total number of white blood cells (leukocytes)
• Weight gain or loss
• More acid than normal in the blood
• Loss of appetite
• Dehydration (when your body does not have as much water and fluid as it should)
• Increased blood sugar level
• Increased blood level of uric acid, a waste material from food digestion
• Decreased levels of a blood protein called albumin
• Decreased blood level of calcium
• Decreased blood sugar level
• Changes in blood tests measuring body salts (potassium, magnesium, sodium, or phosphate)
• Difficulty or limitation in ability to open mouth
• Loss of muscle coordination; awkward, uncoordinated walking; unsteadiness when walking
• Sleepiness
• Dizziness (or sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking)
• Taste changes
• Speech problems
• Restless, repetitive, or involuntary movements and rapid speech
• Headache or head pain
• Bleeding in the brain
• Decreased blood flow to the brain which may lead to stroke
• A malfunction of the nerves within the head and neck
• Paralysis of facial muscles due to problems with the nerves that supply them
• Weakness or paralysis (loss of muscle function) caused by damage to peripheral nerves (those nerves outside of brain and spinal cord)
• Convulsion or seizure
• Anxiety, feelings of dread or danger
• Confusion
• Feelings of sadness, worthlessness, thoughts of suicide or death (depression)
• Difficulty sleeping or falling asleep
• Blood in the urine
• Bleeding in the kidney
• Need to urinate often
• Difficulty emptying the bladder
• Bleeding from somewhere in the reproductive organs (e.g., vagina, testes)
• Bleeding in the prostate
• Stuffy or runny nose, sneezing
• Bleeding in the respiratory tract
• Sudden constriction of the muscles in the walls of the bronchioles (small airways of the lung)
• Cough
• Shortness of breath
• Hiccups
• Inflammation (swelling and redness) of the lungs
• Scarring of the lungs that can cause shortness of breath and interfere with breathing
• Changes in the blood vessels in the liver
• Voice change
• Hair loss
• Dry skin
• Excess sweating
• Itching
• Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
• Hives
• Sudden reddening of the face and/or neck
• Hot flashes
• High blood pressure
• Low blood pressure
• Inflammation (swelling and irritation) of a vein; blood clot
• Formation of a blood clot that breaks loose and is carried by the blood stream to plug another blood vessel
• Bleeding with a decreased number of blood cells that help to clot blood (platelets)

**Rare but serious risks of oxaliplatin (events that occur less than 5% of the time)**

• Formation of blood clots in small blood vessels around the body that leads to a low platelet (a type of blood cell that helps to clot blood) count
• Gas in the intestinal (bowel) wall
• Inflammation (swelling and redness) of the gallbladder possibly associated with gall stones
• Sudden or traumatic injury to the kidney
• Severe potentially life-threatening damage to the lungs which can lead to fluid in the lungs
• Swelling and redness of the skin on the palms of the hands and soles of the feet

**Reproductive risks:** Men should not father a baby while on this study because the drugs in this study can affect an unborn baby. It is important you understand that you need to use birth control while on this study and after the end of treatment. Men should use adequate birth control for at least 6 months after the last administration of bevacizumab.

Check with your health care provider about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

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

**Blood draw side effects:** The risks of drawing blood include pain, bruising or rarely infection at the needle site.
Are there benefits to taking part in the research study?

Taking part in this study may or may not make your health better. While doctors hope your fluoropyrimidine (5-fluorouracil or capecitabine) plus bevacizumab treatment with or without oxaliplatin will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about whether oxaliplatin is really needed to improve fluoropyrimidine plus bevacizumab-based therapy in older cancer patients. This information could help future cancer patients 70 years or older.

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

You do not have to be in this study to receive treatment for your cancer. Your other choices may include:

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

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

Will my medical information be kept private?

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

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

- North Central Cancer Treatment Group (NCCTG) and the Cancer & Leukemia Group B (CALGB), co-sponsors of this study
- Local Institutional Review Board (IRB)
- The Cancer Trials Support Unit (CTSU), a service sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials
- The NCI and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

A description of this clinical trial will be available on [http://www.ClinicalTrials.gov](http://www.ClinicalTrials.gov). This Web site will not include information that can identify you. At most, the Web site will include a summary of study results. You can search this Web site at any time.

[Note to Informed Consent Authors: the above paragraph complies with the new FDA regulation]
found at 21 CFR 50.25(c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]

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

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

There is no charge to you for the research tests that will be done using your sample(s).

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

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

What are my rights if I take part in this research 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.

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.
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 research study?**

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

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

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

You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only).

**Additional Research Studies**

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study.

**About Using Biological Samples for Research**

**Blood Samples**

As part of the main study, we will collect blood samples to use in additional research studies. **It is required that you provide these blood samples for these research studies.** All of the research blood samples will be taken at the same time as the blood samples for the main study. About 4-6 teaspoons of blood will be drawn each time for these additional studies.

The blood samples will be sent to Mayo Clinic laboratories associated with NCCTG, where most of the tests will be done. Blood samples will also be sent to laboratories associated with CALGB for additional testing that is being done for this study. These tests will be done in order to understand how your cancer responds to treatment. It is hoped that this will help investigators better understand your type of cancer. New scientific tools will now allow researchers to look at your whole DNA, not just one part or one gene. This kind of research can provide information to researchers about the development of cancer and response to treatment. Because the information gained in these genetic studies can be very useful to the research community, the National Institutes of Health (NIH) has requested that these data be placed in a central database housed at the NIH. The goal is to speed up the process for discovery of new treatments, prevention, and diagnosis of disease. Researchers must get approval from the NIH before they can access the research results and health-related information from your specimen. All information will be
coded with a unique number. Researchers will not have access to your identity; they will only see coded information.

The results of these tests will not be sent to you or your study doctor and will not be used in planning your care. These tests are for research purposes only and you will not have to pay for them.

We would like to keep some of the blood that is left over for future research. If you agree, this blood will be kept and may be used in research to learn more about cancer and other diseases.

**Tissue Samples**

We would like to use leftover tissue samples for additional research studies. **You are not required to let us use this tissue for these research studies in order to take part in the main study, but we strongly encourage you to provide it.** We will use tissue from a biopsy or surgery you have already had done, so you will not need to have an additional biopsy or surgery done. The research that may be done with your tissue is not designed specifically to help you, but the research might help people who have cancer and other diseases in the future. Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. **The tissue samples for additional research studies are not required, but we strongly encourage you to provide them. You are not required to let us use this tissue for additional research in order to take part in the main study.** We will use tissue from a biopsy or surgery that you have already had done, so you will not need an additional biopsy or surgery done.

Please read the “Patient Information Sheet: How is Tissue Used for Research” to learn more about tissue research.

**Please read the following statement and mark your choice:**

I agree to provide tissue sample(s) to NCCTG for research testing planned as part of this study.

☐ Yes    ☐ No    Please initial here: ________ Date: ________

**Things to Think About**

The choice to let us keep the left over sample(s) for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your sample(s) can be kept for research, you can change your mind at any time. You or your physician will need to write to: Quality Assurance Specialist, N0949, North Central Cancer Treatment Group (NCCTG) Operations Office, 200 First Street SW, Rochester, MN 55905. Then any sample(s) that remains will no longer be used for future research.
In the future, people who do research may need to know more about your health. While NCCTG may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes a sample(s) is used for genetic research (about diseases that are passed on in families). Even if your sample(s) is used for this kind of research, the results will not be put in your health records.

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

**Benefits**

The benefits of research using sample(s) include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

**Risks**

The greatest risk to you from the use of your samples is the possible release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

**Making Your Choice**

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

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

1. My blood and tissue samples may be stored for use in future research to learn about, prevent, or treat cancer.
   
   □ Yes □ No Please initial here: _______ Date: _______

2. My blood and tissue samples may be stored for use in future research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

   □ Yes □ No Please initial here: _______ Date: _______

NCCTG has the right to end storage of the samples without telling you.

The samples will be stored at the NCCTG research base at Mayo Clinic in Rochester, MN. Outside researchers may one day ask for a part of your samples for studies now or future studies.
How do outside researchers get the sample?

Researchers from universities, hospitals, and other health organizations do research using blood and tissue. They may call NCCTG and ask for stored samples for their studies. NCCTG looks at the way that these studies will be done, and decides if any of the stored samples can be used. NCCTG sends the samples and some information about you to the researcher. NCCTG will not send your name, address, phone number, social security number, or any other identifying information to the researcher. If you allow your sample(s) to be given to outside researchers, it will be given to them with a code number. If researchers outside NCCTG use the sample(s) for future research, they will decide if you will be contacted and, if so, they would have to contact the researchers at NCCTG. Then NCCTG will contact the clinic where you registered for this study, who will contact you.

Please read the following statements and mark your choice:

1. I permit NCCTG to give my stored sample(s) for use in future research to outside researchers:

   □ Yes    □ No    Please initial here:  Date:

Where can I get more information?

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

   1-800-4-CANCER (1-800-422-6237)

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

   • For NCI’s clinical trials information, go to: http://cancer.gov/clinicaltrials/

   • For NCI’s general information about cancer, go to http://cancer.gov/cancerinfo/

   • For NCI’s general information about cancer in Spanish, go to http://www.cancer.gov/espanol

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

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

Printed Participant Name: ____________________________________________

Participant Signature: _________________________________________________

Date: _____________________________________

Printed name of person obtaining informed consent:

____________________________________________________

Signature of person obtaining informed consent:

____________________________________________________

Date _____________________________________

Local IRB changes to this document are allowed. Sections “What are the risks of the research study” or “What other choices do I have if I don’t take part in this research study?” should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the North Central Cancer Treatment Group Operations Office for approval before a patient may be registered to this study.

Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.
Patient Information Sheet: How is Tissue Used for Research?

Where does tissue come from?
Whenever a biopsy (or surgery) is performed, the tissue that is removed is examined under the microscope by a trained doctor to determine the nature of the disease and assist with the diagnosis. Your tissue will always be used first to help make decisions about your care. After all tests have been done, there is usually some left over tissue. Sometimes, this tissue is not kept because it is not needed for the patient's care. Instead, a patient can choose to have the tissue kept for future research. People who are trained to handle tissue and protect the donor's rights make sure that the highest standards are followed by the North Central Cancer Treatment Group (NCCTG). Your doctor does not work for the NCCTG, but has agreed to help collect tissue from many patients. Many doctors across the country are helping in the same way. If you agree, only left over tissue will be saved for research. Your doctor will only take the tissue needed for your care during surgery.

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

What type of research will be done with my tissue?
Many different kinds of studies use tissue. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs.

Some research looks at diseases that are passed on in families (called genetic research). Research done with your tissue may look for genetic causes and signs of disease.

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

Will I find out the results of the research using my tissue?
No, you will not receive the results of research done with your tissue. This is because research can take a long time and must use tissue samples from many people before results are known. Results from research using your tissue may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.
Though research involves the test results of many different people, your biopsy result involves only you. Your doctor will give you the results of your biopsy when results are known. These test results are ready in a short time and will be used to make decisions about your care.

**Will I benefit from the research using my tissue?**

There will be no direct benefit to you because your tissue may not be used for some time after you donate it and because research can take a long time. However, it is hoped that the results of research on your tissue and tissues from other patients will provide information that will help other patients in the future. Your tissue will be helpful whether you have cancer or not.

**Why do you need information from my health records?**

In order to do research with your tissue, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher includes your age, sex, race, diagnosis, treatments, and possibly some family history. This information is collected by your hospital from your health record and sent to NCCTG but without your name or other identifying information. If more information is needed, NCCTG may send it to the researcher.

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

No. Your name, address, phone number and anything else that could identify you will be removed before they go to the researcher.

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

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

**How am I protected?**

The NCCTG is in charge of making sure that information about you is kept private. The NCCTG will take careful steps to prevent misuse of records. Your name, address, phone number and other identifying information will be taken off anything associated with your tissue before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.
## Standardized Questions to Supplement NCI-CTCAE v4.0 Neurotoxicity Assessment

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<td>CTEP Active Version of the NCI-CTCAE Version 4.0</td>
<td>Asymptomatic; loss of deep tendon reflexes or paresthesia</td>
<td>Moderate symptoms; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
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<th>Questions</th>
<th>Sample answers for each toxicity grade</th>
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<td>Do you have problems tying your shoe laces, buttoning your shirts, fastening buckles, or pulling up zippers?</td>
<td>“No, I might feel some tingling in my hands, but I have no problems tying laces, buttoning shirts, fastening buckles, or pulling up zippers.” “It is a bit harder than before, but I can still tie laces, button shirts, fasten buckles, or pull up zippers.” “I have severe difficulties tying shoe laces, buttoning shirts, fastening buckles, or pulling up zippers” or “I haven’t been able to tie shoe laces, button shirts, fasten buckles, or pull up zippers since my last treatment.” “I cannot tie laces, button shirts, fasten buckles, or pull up zippers anymore.”</td>
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<td>Do you have problems writing?</td>
<td>“No, I might feel some tingling in my hands, but I have no problems writing.” “It is a bit harder than before, but I can still write.” “I have severe difficulties writing” or “I haven’t been able to write since my last treatment.” “I cannot write anymore.”</td>
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<td>Do you have problems putting on your jewelry or your watch?</td>
<td>“No, I might feel some tingling in my hands, but I have no problems putting on my jewelry or my watch.” “It is a bit harder than before, but I can still put on my jewelry or my watch.” “I have severe difficulties putting on my jewelry or my watch” or “I haven’t been able to put on my jewelry or my watch since my last treatment.” “I cannot put on my jewelry or my watch anymore.”</td>
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<td>Do you have problems walking?</td>
<td>“No, I might feel some tingling in my feet, but I have no problems walking.” “It is a bit harder than before, but I can still walk.” “I have severe difficulties walking” or “I haven’t been able to walk since my last treatment.” “I cannot walk anymore.”</td>
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Blood Pressure Diary

Current Cycle Number: ____________
NCCTG Number: _________________  Patient Initials (last, first)_________ Date: ______________

**INSTRUCTIONS TO THE PATIENT:**

1. Your blood pressure readings have two numbers. The first number is the pressure in your blood vessels during a heart beat (systolic), and the second number is the pressure in the vessels when the heart rests in between beats (diastolic). These numbers are usually written with a slash in between them (for example, normal blood pressure is 120/80).

2. Your blood pressure should be taken weekly during the first 6 weeks of treatment. After that your oncologist will tell you how often you should check it or have it checked. Record the date you check it and what your blood pressure was in the chart below. You may have your blood pressure taken at the site where you are getting your cancer treatment or at your local doctor’s office or you can take your own blood pressure on a machine at a drug store or other location.

3. If your systolic pressure (the upper number) is greater than 150 or your diastolic pressure (the lower number) is greater than 90 twice in a row measured several hours apart, **please contact your oncologist for instructions.**

4. Please bring this form to your next clinic visit or appointment.

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Patient’s Signature: _____________________________________  Date: _______________________  

**Physician’s Office will complete this section:**

Date of this clinic visit  
Physician/Nurse/Data Manager’s Signature
Patient Capecitabine Medication Diary

Current Cycle Number: _____________________ Dose: __________________
NCCTG Number: ________________  Patient Initials (LFM) __________________

**INSTRUCTIONS TO PATIENT:**
1. Complete one form for each cycle (3 weeks).
2. Please record the date and times you take your capecitabine pills for this study.
3. You should take these pills by mouth twice a day on Days 1-14 of each 21 day cycle. Take one dose of the pills each morning and one dose of the pills each evening (12 hours apart). Take these pills with about 8 ounces of water each time. It is best to take these pills within 30 minutes after eating food.
4. Bring this medication diary, the pill bottles (even if empty or unopened), and any unused pills with you at the end of each cycle. Make sure that you get a new medication diary at that time.

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Do not take capecitabine pills today

___________________________________                 ______________________________
Patient signature                                                                  Date

**Physician’s office will complete this section:**
1. Date patient started protocol treatment: ____________________
2. Total number of pills taken this cycle: ____________________

Physician/Nurse/Data Manager’s signature

Date ______________________
PATIENT QUESTIONNAIRE BOOKLET
BASELINE

You have been given a booklet to complete for this study. The booklet contains some questions about your quality of life and health status as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel and tolerate treatment.

1. The booklet contains seven sets of questions:
   a. Neurotoxicity Symptom Experience Diary (8 questions)
   b. Patient Reported Outcomes – Adverse Events (9 questions)
   c. Cancer-Specific Geriatric Assessment (56 questions)
   d. NCCTG Brief Frailty Inventory (7 questions)
   e. Fatigue/Uniscale Assessments (2 questions)
   f. Linear Analogue Self Assessment Scale (4 questions)
   g. EQ-5D Assessment (6 questions)

2. Directions on how to complete each set of questions are written on the top of each set.

3. Please complete the booklet during your scheduled clinic visit and return it to your nurse or your physician.

Thank you for taking the time to help us.
Neurotoxicity Symptom Experience Diary

NCCTG Number: ___________________ Patient Initials (last, first)_________ Date: ________________

Directions: Please circle the one number (0-10) for each item below that best describes you.

1. Did you experience sensitivity to touching cold items within the last 24 hours?
   0 1 2 3 4 5 6 7 8 9 10
   Not at all As bad as it can be

2. Did you experience discomfort swallowing cold liquids within the last 24 hours?
   0 1 2 3 4 5 6 7 8 9 10
   Not at all As bad as it can be

3. Did you notice any throat discomfort within the last 24 hours?
   0 1 2 3 4 5 6 7 8 9 10
   Not at all As bad as it can be

4. Did you experience any fever or chills within the last 24 hours?
   0 1 2 3 4 5 6 7 8 9 10
   Not at all As bad as it can be

5. Did you suffer from muscle cramps within the last 24 hours?
   0 1 2 3 4 5 6 7 8 9 10
   Not at all As bad as it can be

6. Did you have difficulties walking within the last 24 hours?
   0 1 2 3 4 5 6 7 8 9 10
   Not at all As bad as it can be

7. Did you have any difficulties buttoning your shirt or tying shoe-laces within the last 24 hours?
   0 1 2 3 4 5 6 7 8 9 10
   Not at all As bad as it can be

8. Did you experience any neurologic side effects that we did not mention?
   _____No _____Yes, please list________________________________________________

Patient Reported Outcomes – Adverse Events
Directions: Please circle your answers to the following questions about your symptoms.

1. In the last 7 days, how OFTEN did you have diarrhea:

   1 2 3 4 5
   Never Rarely Occasionally Frequently Almost constantly

2. In the last 7 days, what was the SEVERITY of your diarrhea at its WORST:

   1 2 3 4 5
   None Mild Moderate Severe Very severe

3. In the last 7 days, what was the SEVERITY of your fatigue, tiredness, or lack of energy at its WORST:

   1 2 3 4 5
   None Mild Moderate Severe Very severe

4. In the last 7 days, how much did fatigue, tiredness, or lack of energy INTERFERE with your usual or daily activities:

   1 2 3 4 5
   Not at all A little bit Somewhat Quite a bit Very much

5. In the last 7 days, what was the SEVERITY of your hand-foot syndrome (a rash of the hands and feet that can cause cracking, peeling, redness, or pain) at its WORST:

   1 2 3 4 5
   None Mild Moderate Severe Very severe

6. In the last 7 days, how OFTEN did you have nausea:

   1 2 3 4 5
   Never Rarely Occasionally Frequently Almost constantly

7. In the last 7 days, what was the SEVERITY of your nausea at its WORST:

   1 2 3 4 5
   None Mild Moderate Severe Very severe

8. In the last 7 days, what was the SEVERITY of your numbness or tingling in your hands or feet at its WORST:

   1 2 3 4 5
   None Mild Moderate Severe Very severe

9. In the last 7 days, how much did numbness or tingling in your hands or feet INTERFERE with your usual or daily activities:

   1 2 3 4 5
   Not at all A little bit Somewhat Quite a bit Very much
Patient Instructions: If you are unable to complete the questionnaire, a member of your health care team will assist you. Please do not have a family member complete the questionnaire for you.

If this questionnaire was not completed at the specified timepoint, specify reason: *(Please mark one)*
- □ Patient refused
- □ Patient withdrew consent
- □ Not done
- □ Other, specify _________________________________________

A. BACKGROUND INFORMATION.

1. What is the highest grade you finished in school? *(Please mark one box only.)*
- □ 1-8 grades
- □ 9-11 grades
- □ High school graduate
- □ Some college
- □ Junior college degree
- □ College degree (B.A. / B.S.)
- □ Some post-college work
- □ Advanced degree

2. What is your marital status? *(Please mark one box only.)*
- □ Single, never married
- □ Married
- □ Separated
- □ Divorced
- □ Widowed

3. With whom do you live? *(Please mark all that apply.)*
- □ Wife / husband / partner
- □ Girlfriend / boyfriend
- □ Children
- □ Parent (s)/ parents (s)-in-law
- □ Live alone
- □ Others

4. What is your current employment status? *(Please mark one box only.)*
- □ Currently working full time
- □ Currently working part-time
- □ Homemaker
- □ Disabled
- □ Unemployed
- □ Retired
- □ Student
B. DAILY ACTIVITIES
(Older Americans Resource Scale for Instrumental Activities of Daily Living (Fillenbaum, G.G., et al., 1981))

PATIENT INSTRUCTIONS: Mark only one box per question.

1. Can you use the telephone…
   □ Without help, including looking up phone numbers and dialing;
   □ With some help (can answer phone or dial operator in an emergency, but need a special phone or help in getting the phone number or dialing); or
   □ Are you completely unable to use the telephone?

2. Can you get to places out of walking distance…
   □ Without help (drive your own car, or travel alone on buses or taxis);
   □ With some help (need someone to help you or go with you when traveling); or
   □ Are you unable to travel unless emergency arrangements are made for a specialized vehicle like an ambulance?

3. Can you go shopping for groceries or clothes (assuming you have transportation) …
   □ Without help (taking care of all shopping needs yourself, assuming you have transportation);
   □ With some help (need someone to go with you on all shopping trips); or
   □ Are you completely unable to do any shopping?

4. Can you prepare your own meals…
   □ Without help (plan and cook full meals yourself);
   □ With some help (can prepare some things but unable to cook full meals yourself); or
   □ Are you completely unable to prepare any meals?

5. Can you do your housework…
   □ Without help (can clean floors, etc);
   □ With some help (can do light housework but need help with heavy work); or
   □ Are you completely unable to do any housework?

6. Can you take your own medicines…
   □ Without help (in the right doses at the right time);
   □ With some help (able to take medicine if someone prepares it for you and/or reminds you to take it); or
   □ Are you completely unable to take your medicines?

7. Can you handle your own money…
   □ Without help (write checks, pay bills, etc.);
   □ With some help (manage day-to-day buying but need help with managing your checkbook and paying your bills); or
   □ Are you completely unable to handle money?
C. PHYSICAL ACTIVITIES

(Medical Outcomes Study, Physical Functioning Scale (Stewart, A.L., et al., 1992))

1. The following items are activities you might do during a typical day. Does your health limit you in these activities?

<table>
<thead>
<tr>
<th>Activities</th>
<th>Limited a lot</th>
<th>Limited a little</th>
<th>Not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Vigorous activities such as: running, lifting heavy objects, participating in strenuous activities</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>b. Moderate activities such as: moving a table, pushing a vacuum cleaner, bowling or playing golf</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>c. Lifting or carrying groceries</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>d. Climbing several flights of stairs</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>e. Climbing one flight of stairs</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>f. Bending, kneeling, or stooping</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>g. Walking more than a mile</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>h. Walking several blocks</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>i. Walking one block</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>j. Bathing or dressing yourself</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>
D. CURRENT HEALTH RATING
(Patient Karnofsky Performance Status (Loprinzi, C.L., et al., 1994))

Which one of the following phrases best describes you at this time? (Please mark one box only.)

- □ Normal, no complaints, no symptoms of disease
- □ Able to carry on normal activity, minor symptoms of disease
- □ Normal activity with effort, some symptoms of disease
- □ Care for self, unable to carry on normal activity or to do active work
- □ Require occasional assistance but able to care for most of personal needs
- □ Require considerable assistance for personal care
- □ Disabled, require special care and assistance
- □ Severely disabled, require continuous nursing care

E. FALLS
How many times have you fallen in the last 6 months? □□□

F. YOUR HEALTH
(Older Americans Resource Scale for Instrumental Activities of Daily Living (Fillenbaum, G.G., et al., 1981))

1. Your General Health
Patient Instructions: Do you have any of the following illnesses at the present time, and if so, how much does it interfere with your activities: Not at all, Somewhat or A Great Deal? (Mark the one box that best reflects your answer.)

<table>
<thead>
<tr>
<th>Illness</th>
<th>No</th>
<th>Yes</th>
<th>Not at All</th>
<th>Somewhat</th>
<th>A Great Deal</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Other cancers or leukemia</td>
<td>□</td>
<td>□</td>
<td>→</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>b. Arthritis, rheumatism or other connective tissue disorders</td>
<td>□</td>
<td>□</td>
<td>→</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>c. Glaucoma</td>
<td>□</td>
<td>□</td>
<td>→</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>d. Emphysema or chronic bronchitis</td>
<td>□</td>
<td>□</td>
<td>→</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>e. High blood pressure</td>
<td>□</td>
<td>□</td>
<td>→</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>f. Heart disease</td>
<td>□</td>
<td>□</td>
<td>→</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>g. Circulation trouble in arms or legs</td>
<td>□</td>
<td>□</td>
<td>→</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>h. Diabetes</td>
<td>□</td>
<td>□</td>
<td>→</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>
i. Stomach or intestinal disorders

j. Osteoporosis

k. Chronic liver or kidney disease

l. Stroke

m. Depression

2. How is your eyesight (with glasses or contacts)? (Mark only one box)

   □ Excellent    □ Good    □ Fair    □ Poor    □ Totally blind

   If fair, poor or totally blind, how much does this interfere with your activities?

   □ Not at all   □ Somewhat   □ A great deal

3. How is your hearing (with a hearing aid, if needed)? (Mark only one box)

   □ Excellent    □ Good    □ Fair    □ Poor    □ Totally deaf

   If fair, poor or totally deaf, how much does this interfere with your activities? (Mark only one box)

   □ Not at all   □ Somewhat   □ A great deal

4. Do you have any other physical problems or illnesses (other than listed in questions 1-3) at the present time that seriously affect your health?

   □ No

   □ Yes, specify: ________________________________________________________________

   If yes, how much does this interfere with your activities?

   □ Not at all   □ Somewhat   □ A great deal
How many medications (either prescribed or over-the-counter), herbs or vitamins do you currently take?

Please list all prescribed or over-the-counter medicines, herbs or vitamins you are currently taking (doses not necessary).

1. _________________________________________________________________
2. _________________________________________________________________
3. _________________________________________________________________
4. _________________________________________________________________
5. _________________________________________________________________
6. _________________________________________________________________
7. _________________________________________________________________
8. _________________________________________________________________
9. _________________________________________________________________
10. __________________________________________________________________
11. __________________________________________________________________
12. __________________________________________________________________
G. HEALTH QUESTIONNAIRE .
(MHI-17 (Stewart and Ware, 1992))

INSTRUCTIONS: These questions are about how you have been feeling within the past two weeks. Please mark the box on each line that best reflects your situation.

<table>
<thead>
<tr>
<th>How much of the time during the past two weeks:</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>A good bit of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Has your daily life been full of things that were interesting to you?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
<tr>
<td>2. Did you feel depressed?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
<tr>
<td>3. Have you felt loved and wanted?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
<tr>
<td>4. Have you been a very nervious person?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
<tr>
<td>5. Have you been in firm control of your behavior, thoughts, emotions, feelings?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
<tr>
<td>6. Have you felt tense or high-strung?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
<tr>
<td>7. Have you felt calm and peaceful?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
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<tr>
<td>8. Have you felt emotionally stable?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
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<tr>
<td>9. Have you felt downhearted and blue?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
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<tr>
<td>10. Have you felt restless, fidgety, or impatient?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
<tr>
<td>11. Have you been moody, or brooded about things?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
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<tr>
<td>12. Have you felt cheerful, lighthearted?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
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<tr>
<td>13. Have you been in low or very low spirits?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
</tbody>
</table>
14. Were you a happy person? □ 1 □ 2 □ 3 □ 4 □ 5 □ 6

15. Did you feel that you had nothing to look forward to? □ 1 □ 2 □ 3 □ 4 □ 5 □ 6

16. Have you felt so down in the dumps that nothing could cheer you up? □ 1 □ 2 □ 3 □ 4 □ 5 □ 6

17. Have you been anxious or worried? □ 1 □ 2 □ 3 □ 4 □ 5 □ 6

1. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc)? (Please mark one box only.)

□ All of the time
□ Most of the time
□ Some of the time
□ A little of the time
□ None of the time

2. Compared to your usual level of social activity, has your social activity during the past 6 months decreased, stayed the same, or increased because of a change in your physical or emotional condition? (Please mark one box only.)

□ Much less socially active than before
□ Somewhat less socially active than before
□ About as socially active as before
□ Somewhat less limited than others
□ Much less limited than others

3. Compared to others your age, are your social activities more or less limited because of your physical health or emotional problems? (Please mark one box only.)

□ Much more limited than others
□ Somewhat more limited than others
□ About the same as others
□ Somewhat less limited than others
□ Much less limited than others

4. During the last 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors or groups? (Please mark one box only.)

□ Not at all
I. SOCIAL SUPPORT.
(Medical Outcomes Study Social Support Survey (Sherbourne, C.D., et al., 1991))

**INSTRUCTIONS:** People sometimes look to others for companionship, assistance or other types of support. How often is each of the following kinds of support available to you now if you need it? (Please mark the box on each line that best reflects your situation.)

<table>
<thead>
<tr>
<th>None of the time</th>
<th>A little of the time</th>
<th>Some of the time</th>
<th>Most of the time</th>
<th>All of the time</th>
</tr>
</thead>
</table>

1. Someone to help you if you were confined to bed
2. Someone you can count on to listen to you when you need to talk
3. Someone to give you good advice about a crisis
4. Someone to take you to the doctor if you needed it
5. Someone to give you information to help you understand a situation
6. Someone to prepare your meals if you were unable to do it yourself
7. Someone whose advice you really want
8. Someone to help you with daily chores if you were sick
9. Someone to share your most private worries and fears with
10. Someone to turn to for suggestions about how to deal with a personal problem.
11. Someone to confide in or talk to about yourself or your problem.
12. Someone who understands your problems
J. QUESTIONS CONCERNING THE QUESTIONNAIRE

1. Were any of these questions difficult to understand?
   □ No
   □ Yes

   If Yes, which questions were they?
   __________________________________________________________
   __________________________________________________________
   __________________________________________________________

2. Was the time it took to answer all the questions too long, just right or too short?
   □ Too short → How long would you have liked the questionnaire to be? □ □ minutes
   □ Just right
   □ Too long → How long would you have liked the questionnaire to be? □ □ minutes

   Which items would you remove?
   __________________________________________________________
   __________________________________________________________
   __________________________________________________________

3. Did you find any of the questions upsetting?
   □ No
   □ Yes

   If Yes, which questions were they?
   __________________________________________________________
   __________________________________________________________
   __________________________________________________________

   Could you tell me why they were upsetting?
   __________________________________________________________
   __________________________________________________________
   __________________________________________________________

4. Do you think the questionnaire left out any questions that were important to ask?
   __________________________________________________________
   __________________________________________________________
   __________________________________________________________

NCCTG Brief Frailty Inventory

NCCTG Number: _______________  Patient Initials (last, first) ___________  Date: _______________
Directions: Please circle the one number (0-10) for each question that describes how much your level of frailty, during the past week, has interfered with your:

1. General activity

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<td>Does not interfere</td>
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<td></td>
<td>Completely interferes</td>
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2. Mood

<table>
<thead>
<tr>
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<th>0</th>
<th>1</th>
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<td></td>
<td></td>
<td>Completely interferes</td>
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3. Walking ability

<table>
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<tr>
<th></th>
<th>0</th>
<th>1</th>
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<td></td>
<td></td>
<td>Completely interferes</td>
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</tbody>
</table>

4. Normal work (includes both work outside the home and daily chores)

<table>
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<tr>
<th></th>
<th>0</th>
<th>1</th>
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<td>Does not interfere</td>
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<td></td>
<td></td>
<td>Completely interferes</td>
</tr>
</tbody>
</table>

5. Relations with other people

<table>
<thead>
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<th>1</th>
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<td>Does not interfere</td>
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<td></td>
<td></td>
<td>Completely interferes</td>
</tr>
</tbody>
</table>

6. Enjoyment of life

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<td>Does not interfere</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Completely interferes</td>
</tr>
</tbody>
</table>

7. Circle the one number that describes your level of frailty over the past week:

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not frail</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>As frail as can be</td>
</tr>
</tbody>
</table>
Fatigue/Uniscale Assessments

NCCTG Number: _________________  Patient Initials (last, first) ________  Date: ______________

Directions: Please circle the one number (0-10) for each item below that best describes you.

How would you describe:

1. your level of fatigue, on the average in the past week including today?
   
   0 1 2 3 4 5 6 7 8 9 10
   No Fatigue                      Fatigue as bad as it can be

2. your overall quality of life in the past week including today?
   
   0 1 2 3 4 5 6 7 8 9 10
   As bad as it can be               As good as it can be
## Linear Analogue Self Assessment (LASA) Scale

**NCCTG Number: ____________________  Patient Initials (last, first)_________ Date: ______________**

Directions: Please circle the number (0-10) best reflecting your response to the following that describes your feelings during the past week, including today.

How would you describe:

1. your overall Quality of Life?

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>As bad as it can be</td>
<td>As good as it can be</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. your overall mental (intellectual) well-being?

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>As bad as it can be</td>
<td>As good as it can be</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. your overall physical well-being?

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>As bad as it can be</td>
<td>As good as it can be</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. your level of fatigue, on the average?

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No fatigue</td>
<td>Constant tiredness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
EQ-5D Assessment

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

**Mobility**
- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

**Self-Care**
- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

**Usual Activities** *(e.g. work, study, housework, family or leisure activities)*
- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

**Pain/Discomfort**
- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

**Anxiety/Depression**
- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.
This booklet is to be completed by the research team (physician, institutional nurse, or CRA) on behalf of the patient prior to completion of the Patient Questionnaire Booklet.

1. The booklet contains the following items:
   a. Cancer-Specific Geriatric Assessment – Research Team Questionnaire (14 questions)
      • Karnofsky Performance Scale (KPS)
      • Timed Up and Go (TUG)
      • Blessed Orientation-Memory-Concentration (BOMC) Test
   b. Canadian Study of Health and Aging Clinical Frailty Scale (CSHA-CFS) – Research Team Questionnaire (1 question)

2. Directions on how to complete each set of questions are written on the top of each set.

3. Please complete this booklet prior to the patient’s completion of the Patient Questionnaire Booklet corresponding to this visit.

Thank you for taking the time to help us.
Cancer Specific Geriatric Assessment – Research Team
Version date June 7, 2011

I. This form completed by: (Please mark all that apply)
□ Physician  □ Nurse  □ CRA

If form was not completed at specified timepoint, specify reason: (mark one)
□ Patient refused  □ Patient withdrew consent  □ Not done
□ Other, specify _________________________________________

II. FUNCTIONAL STATUS

A. KPS (Healthcare professional rated)
(Karnofsky, D.A. et al., 1948)

Directions: Please rate your assessment of patient’s Karnofsky Performance Status as of date this form is completed. (Scale is listed below.)

□□□ %

<table>
<thead>
<tr>
<th>%</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Able to carry on normal activity and able to work. No special care is needed.</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some signs or symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self. Unable to carry on normal activity or do active work</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most of his/her needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospitalization is indicated although death not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospitalization necessary; active supportive treatment necessary</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes progressing rapidly</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>
B. TIMED UP AND GO (TUG)
(Podsiadlo, D., et al., 1991)

INSTRUCTIONS: The timed “Up and Go” measures, in seconds, the time it takes for an individual to stand up from a standard arm chair (approximate seat height of 46 cm [approximately 1.5 ft]), walk a distance of 3 meters (approximately 10 feet), turn, walk back to the chair and sit down again. The subject wears his/her regular footwear and uses their customary walking aid (none, cane, walker, etc.) No physical assistance is given. The subject starts with his/her back against the chair, his/her arm resting on the chair’s arm, and his/her walking aid in hand. She/He is instructed that on the word “go”, she/he is to get up and walk at a comfortable and safe pace to a line on the floor 3 meters (approximately 10 feet) away, turn, and return to the chair and sit down again. The subject walks through the test once before being timed in order to become familiar with the test. Either a wrist watch with a second hand or a stopwatch can be used to time the performance.

Time required to complete the Timed Up and Go: □□□ seconds

III. COGNITION

BLESSED ORIENTATION-MEMORY-CONCENTRATION (BOMC) TEST
(Kawas, C., et al., 1991)

<table>
<thead>
<tr>
<th>1. What year is it now (without looking at a calendar)?</th>
<th>Patient's Response</th>
<th>Maximum Errors</th>
<th>Score x Weight = Final Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What month is it now (without looking at a calendar)?</td>
<td>1</td>
<td>______ x 4 = _____</td>
<td></td>
</tr>
</tbody>
</table>

Memory Phrase:
Repeat this phrase after me: ‘John Brown, 42 Market Street, Chicago’

<table>
<thead>
<tr>
<th>3. About what time is it (within 1 hour, without looking at a clock)?</th>
<th>1</th>
<th>______ x 3 = _____</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Count backwards from 20 to 1.</td>
<td>2</td>
<td>______ x 2 = _____</td>
</tr>
<tr>
<td>5. Say the months in reverse order.</td>
<td>2</td>
<td>______ x 2 = _____</td>
</tr>
<tr>
<td>6. Repeat the memory phrase</td>
<td>5</td>
<td>______ x 2 = _____</td>
</tr>
</tbody>
</table>

Total score:

Scoring: For items 1-3, the response is either correct (score 0) or incorrect (score 1). For items 4-6, add one point for each error (item 4 and 5 maximum error is 2; for item 6, maximum error is 5); total all
scores in “Final Score” column. Data from participants found to have gross cognitive impairment as determined by the Blessed Orientation-Memory-Concentration Score $\geq 11$ will be excluded from the analysis. Maximum score = 28.

IV. SCORING

Did the patient score $\geq 11$ on the Blessed Orientation-Memory-Concentration Test?

□ No
□ Yes $\rightarrow$ If yes, notify the patient’s treating physician

V. NUTRITION

What is the patient’s height? (from patient’s chart)  cm

What is the patient’s current weight? (from patient’s chart)  kg

What was the patient’s weight approximately 6 months ago? (from patient’s chart or patients self report)  kg

VI. QUESTIONS REGARDING THE QUESTIONNAIRES

A. Were any of the questions of the “CSGA – Research Team Questionnaire” difficult for you to administer?

□ No
□ Yes

If no, please proceed to the next question.

If yes, please indicate which questions were difficult to administer?
(Please mark all that apply)

□ KPS Healthcare Professional Rated (page 1)
□ Timed Up and Go (page 2)
□ Blessed Orientation-Memory-Concentration Test (page 2)
□ Other: Please specify _________________________________

B. Were any of the questions of the “CSGA – Patient” difficult for the patient to complete?

□ No
□ Yes

If no, please proceed to the next question

If yes, please indicate which questions were difficult for the patient to complete?
(Please mark all that apply)

□ Background Information (page 1)
□ Daily Activities (page 2-3)
□ Physical Activities (page 3)
□ Current Health Rating (page 4)
□ Falls (page 4)
□ Your Health (page 4-5) *(Mark all that apply)*
  □ 1. Your general health (page 4-5)
  □ 2. Medications (page 6)
□ Health Questionnaire (page 7-8)
□ Social activity (page 9)
□ Social support (page 10)

C. Was the patient able to complete the “CSGA – Patient” on his/her own?
□ Yes
□ No

If no, why? *(Please mark all that apply)*
□ Not literate (does not read or write)
□ Visual problem
□ Fatigue
□ Questions too difficult (above the patient’s reading ability)
□ Other: specify__________________________

D. Length of time to complete both the Patient and Research Team Questionnaires.

Length of time to complete healthcare professional questionnaire □□□ minutes

Length of time to complete patient questionnaire □□□ minutes

Total length of time to complete both questionnaires □□□ minutes

Completed by: __________________________

*(Last name, First name)*

Date Completed: __________________________
The Canadian Study of Health and Aging Clinical Frailty Scale (CSHA-CFS) – Research Team Questionnaire

NCCTG Number: _________________  Patient Initials (last, first)_________ Date: ______________

Directions: Please circle the category that best describes your patient’s feelings during the past week, including today.

The Canadian Study of Health and Aging Clinical Frailty Scale (CSHA-CFS)
(Rockwood et al. 2007)

1. Very fit – robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age
2. Well – without active disease, but less fit than people in category 1
3. Well, with treated comorbid disease – disease symptoms are well controlled compared with those in category 4
4. Apparently vulnerable – although not frankly dependent, these people commonly complain of being “slowed up” or have disease symptoms
5. Mildly frail – with limited dependence on others for instrumental activities of daily living
6. Moderately frail – help is needed with both instrumental and non-instrumental activities of daily living
7. Severely frail – completely dependent on others for the activities of daily living
8. Terminally ill
PATIENT QUESTIONNAIRE BOOKLET
ACTIVE TREATMENT, CURRENT CYCLE

You have been given a booklet to complete for this study. The booklet contains some questions about your quality of life and health status as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel and tolerate treatment.

1. The booklet contains two set of questions:
   – Neurotoxicity Symptom Experience Diary (8 questions)
   - Patient Reported Outcomes – Adverse Events (9 questions)

2. Directions on how to complete the set of questions is written at the top of the set.

3. Please complete the booklet during your scheduled clinic visit and return it to your nurse or your physician.

Thank you for taking the time to help us.
Neurotoxicity Symptom Experience Diary

NCCTG Number: _________________  Patient Initials (last, first)_________ Date: ______________

Directions: Please circle the one number (0-10) for each item below that best describes you.

1. Did you experience sensitivity to touching cold items within the last 24 hours?
   0 1 2 3 4 5 6 7 8 9 10
   Not at all        As bad as it can be

2. Did you experience discomfort swallowing cold liquids within the last 24 hours?
   0 1 2 3 4 5 6 7 8 9 10
   Not at all        As bad as it can be

3. Did you notice any throat discomfort within the last 24 hours?
   0 1 2 3 4 5 6 7 8 9 10
   Not at all        As bad as it can be

4. Did you experience any fever or chills within the last 24 hours?
   0 1 2 3 4 5 6 7 8 9 10
   Not at all        As bad as it can be

5. Did you suffer from muscle cramps within the last 24 hours?
   0 1 2 3 4 5 6 7 8 9 10
   Not at all        As bad as it can be

6. Did you have difficulties walking within the last 24 hours?
   0 1 2 3 4 5 6 7 8 9 10
   Not at all        As bad as it can be

7. Did you have any difficulties buttoning your shirt or tying shoe-laces within the last 24 hours?
   0 1 2 3 4 5 6 7 8 9 10
   Not at all        As bad as it can be

8. Did you experience any neurologic side effects that we did not mention?
   ____No    ____Yes, please list______________________________
Patient Reported Outcomes – Adverse Events

Directions: Please circle your answers to the following questions about your symptoms.

1. In the last 7 days, how OFTEN did you have diarrhea:

   1  2  3  4  5
   Never  Rarely  Occasionally  Frequently  Almost constantly

2. In the last 7 days, what was the SEVERITY of your diarrhea at its WORST:

   1  2  3  4  5
   None  Mild  Moderate  Severe  Very severe

3. In the last 7 days, what was the SEVERITY of your fatigue, tiredness, or lack of energy at its WORST:

   1  2  3  4  5
   None  Mild  Moderate  Severe  Very severe

4. In the last 7 days, how much did fatigue, tiredness, or lack of energy INTERFERE with your usual or daily activities:

   1  2  3  4  5
   Not at all  A little bit  Somewhat  Quite a bit  Very much

5. In the last 7 days, what was the SEVERITY of your hand-foot syndrome (a rash of the hands and feet that can cause cracking, peeling, redness, or pain) at its WORST:

   1  2  3  4  5
   None  Mild  Moderate  Severe  Very severe

6. In the last 7 days, how OFTEN did you have nausea:

   1  2  3  4  5
   Never  Rarely  Occasionally  Frequently  Almost constantly

7. In the last 7 days, what was the SEVERITY of your nausea at its WORST:

   1  2  3  4  5
   None  Mild  Moderate  Severe  Very severe

8. In the last 7 days, what was the SEVERITY of your numbness or tingling in your hands or feet at its WORST:

   1  2  3  4  5
   None  Mild  Moderate  Severe  Very severe

9. In the last 7 days, how much did numbness or tingling in your hands or feet INTERFERE with your usual or daily activities:

   1  2  3  4  5
   Not at all  A little bit  Somewhat  Quite a bit  Very much
PATIENT QUESTIONNAIRE BOOKLET
ACTIVE TREATMENT, EVERY 3 MONTHS

You have been given a booklet to complete for this study. The booklet contains some questions about your quality of life and health status as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel and tolerate treatment.

1. The booklet contains two sets of questions:
   a. Fatigue/Uniscale Assessments (2 questions)
   b. Linear Analogue Self Assessment (LASA) Scale (4 questions)
   c. EQ-5D Assessment (6 questions)

2. Directions on how to complete each set of questions are written on the top of each set.

3. Please complete the booklet during your scheduled clinic visit and return it to your nurse or your physician.

Thank you for taking the time to help us.
Fatigue/Uniscale Assessments

NCCTG Number: _________________  Patient Initials (last, first)_________  Date: ______________

Directions: Please circle the one number (0-10) for each item below that best describes you.

How would you describe:

1. your level of fatigue, on the average in the past week including today?

   0 1 2 3 4 5 6 7 8 9 10
   No Fatigue                      Fatigue as bad as it can be

2. your overall quality of life in the past week including today?

   0 1 2 3 4 5 6 7 8 9 10
   As bad as it can be             As good as it can be
Linear Analogue Self Assessment (LASA) Scale

NCCTG Number: _________________  Patient Initials (last, first)_________ Date: ______________

Directions: Please circle the number (0-10) best reflecting your response to the following that describes your feelings during the past week, including today.

How would you describe:

1. your overall Quality of Life?

   0  1  2  3  4  5  6  7  8  9  10
   As bad as it can be       As good as it can be

2. your overall mental (intellectual) well-being?

   0  1  2  3  4  5  6  7  8  9  10
   As bad as it can be       As good as it can be

3. your overall physical well-being?

   0  1  2  3  4  5  6  7  8  9  10
   As bad as it can be       As good as it can be

4. your level of fatigue, on the average?

   0  1  2  3  4  5  6  7  8  9  10
   No fatigue               Constant tiredness
EQ-5D Assessment

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

**Mobility**
- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

**Self-Care**
- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

**Usual Activities** (e.g. work, study, housework, family or leisure activities)
- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

**Pain/Discomfort**
- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

**Anxiety/Depression**
- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed
EQ-5D Assessment (continued)

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.
PATIENT QUESTIONNAIRE BOOKLET
OBSERVATION PHASE

You have been given a booklet to complete for this study. The booklet contains some questions about your quality of life and health status as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel and tolerate treatment.

1. The booklet contains eight sets of questions:
   a. Neurotoxicity Symptom Experience Diary (8 questions)
   b. Patient Reported Outcomes – Adverse Events (9 questions)
   c. Cancer-Specific Geriatric Assessment (56 questions)
   d. NCCTG Brief Frailty Inventory (7 questions)
   e. Fatigue/Uniscale Assessments (2 questions)
   f. Linear Analogue Self Assessment Scale (4 questions)
   g. EQ-5D Assessment (6 questions)
   h. Was It Worth It (7 questions)

2. Directions on how to complete each set of questions are written on the top of each set.

3. Please complete the booklet during your scheduled clinic visit and return it to your nurse or your physician.

Thank you for taking the time to help us.
Neurotoxicity Symptom Experience Diary

NCCTG Number: _________________  Patient Initials (last, first) ___________  Date: _______________

Directions: Please circle the one number (0-10) for each item below that best describes you.

1. Did you experience sensitivity to touching cold items within the last 24 hours?
   
   0 1 2 3 4 5 6 7 8 9 10
   Not at all  As bad as it can be

2. Did you experience discomfort swallowing cold liquids within the last 24 hours?
   
   0 1 2 3 4 5 6 7 8 9 10
   Not at all  As bad as it can be

3. Did you notice any throat discomfort within the last 24 hours?
   
   0 1 2 3 4 5 6 7 8 9 10
   Not at all  As bad as it can be

4. Did you experience any fever or chills within the last 24 hours?
   
   0 1 2 3 4 5 6 7 8 9 10
   Not at all  As bad as it can be

5. Did you suffer from muscle cramps within the last 24 hours?
   
   0 1 2 3 4 5 6 7 8 9 10
   Not at all  As bad as it can be

6. Did you have difficulties walking within the last 24 hours?
   
   0 1 2 3 4 5 6 7 8 9 10
   Not at all  As bad as it can be

7. Did you have any difficulties buttoning your shirt or tying shoe-laces within the last 24 hours?
   
   0 1 2 3 4 5 6 7 8 9 10
   Not at all  As bad as it can be

8. Did you experience any neurologic side effects that we did not mention?
   
   ___ No   ____ Yes, please list ____________________________________________
# Patient Reported Outcomes – Adverse Events

**Directions:** Please circle your answers to the following questions about your symptoms.

1. In the last 7 days, how OFTEN did you have **diarrhea:**

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>Rarely</td>
<td>Occasionally</td>
<td>Frequently</td>
<td>Almost constantly</td>
</tr>
</tbody>
</table>

2. In the last 7 days, what was the SEVERITY of your **diarrhea** at its WORST:

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Very severe</td>
</tr>
</tbody>
</table>

3. In the last 7 days, what was the SEVERITY of your **fatigue, tiredness, or lack of energy** at its WORST:

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Very severe</td>
</tr>
</tbody>
</table>

4. In the last 7 days, how much did **fatigue, tiredness, or lack of energy** INTERFERE with your usual or daily activities:

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>A little bit</td>
<td>Somewhat</td>
<td>Quite a bit</td>
<td>Very much</td>
</tr>
</tbody>
</table>

5. In the last 7 days, what was the SEVERITY of your **hand-foot syndrome** (a rash of the hands and feet that can cause cracking, peeling, redness, or pain) at its WORST:

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Very severe</td>
</tr>
</tbody>
</table>

6. In the last 7 days, how OFTEN did you have **nausea:**

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>Rarely</td>
<td>Occasionally</td>
<td>Frequently</td>
<td>Almost constantly</td>
</tr>
</tbody>
</table>

7. In the last 7 days, what was the SEVERITY of your **nausea** at its WORST:

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Very severe</td>
</tr>
</tbody>
</table>

8. In the last 7 days, what was the SEVERITY of your **numbness or tingling in your hands or feet** at its WORST:

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Very severe</td>
</tr>
</tbody>
</table>

9. In the last 7 days, how much did **numbness or tingling in your hands or feet** INTERFERE with your usual or daily activities:

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>A little bit</td>
<td>Somewhat</td>
<td>Quite a bit</td>
<td>Very much</td>
</tr>
</tbody>
</table>
Patient Instructions: If you are unable to complete the questionnaire, a member of your health care team will assist you. Please do not have a family member complete the questionnaire for you.

If this questionnaire was not completed at the specified timepoint, specify reason: (Please mark one)
□ Patient refused □ Patient withdrew consent □ Not done
□ Other, specify _________________________________________

A. BACKGROUND INFORMATION.

1. What is the highest grade you finished in school? (Please mark one box only.)
  □ 1-8 grades
  □ 9-11 grades
  □ High school graduate
  □ Some college
  □ Junior college degree
  □ College degree (B.A. / B.S.)
  □ Some post-college work
  □ Advanced degree

2. What is your marital status? (Please mark one box only.)
  □ Single, never married
  □ Married
  □ Separated
  □ Divorced
  □ Widowed

3. With whom do you live? (Please mark all that apply.)
  □ Wife / husband / partner
  □ Girlfriend / boyfriend
  □ Children
  □ Parent(s)/ parents(s)-in-law
  □ Live alone
  □ Others

4. What is your current employment status? (Please mark one box only.)
  □ Currently working full time
  □ Currently working part-time
  □ Homemaker
  □ Disabled
  □ Unemployed
  □ Retired
  □ Student
B. DAILY ACTIVITIES
(Older Americans Resource Scale for Instrumental Activities of Daily Living (Fillenbaum, G.G., et al., 1981))

PATIENT INSTRUCTIONS: Mark only one box per question.

1. Can you use the telephone…
   □ Without help, including looking up phone numbers and dialing;
   □ With some help (can answer phone or dial operator in an emergency, but need a special phone or help in getting the phone number or dialing); or
   □ Are you completely unable to use the telephone?

2. Can you get to places out of walking distance…
   □ Without help (drive your own car, or travel alone on buses or taxis);
   □ With some help (need someone to help you or go with you when traveling); or
   □ Are you unable to travel unless emergency arrangements are made for a specialized vehicle like an ambulance?

3. Can you go shopping for groceries or clothes (assuming you have transportation) …
   □ Without help (taking care of all shopping needs yourself, assuming you have transportation);
   □ With some help (need someone to go with you on all shopping trips); or
   □ Are you completely unable to do any shopping?

4. Can you prepare your own meals…
   □ Without help (plan and cook full meals yourself);
   □ With some help (can prepare some things but unable to cook full meals yourself); or
   □ Are you completely unable to prepare any meals?

5. Can you do your housework…
   □ Without help (can clean floors, etc);
   □ With some help (can do light housework but need help with heavy work); or
   □ Are you completely unable to do any housework?

6. Can you take your own medicines…
   □ Without help (in the right doses at the right time);
   □ With some help (able to take medicine if someone prepares it for you and/or reminds you to take it); or
   □ Are you completely unable to take your medicines?

7. Can you handle your own money…
   □ Without help (write checks, pay bills, etc.);
   □ With some help (manage day-to-day buying but need help with managing your checkbook and paying your bills); or
   □ Are you completely unable to handle money?
C. PHYSICAL ACTIVITIES
(Medical Outcomes Study, Physical Functioning Scale (Stewart, A.L., et al., 1992))

1. The following items are activities you might do during a typical day. Does your health limit you in these activities?

<table>
<thead>
<tr>
<th>Activities</th>
<th>Limited a lot</th>
<th>Limited a little</th>
<th>Not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Vigorous activities such as: running, lifting heavy objects,</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>participating in strenuous activities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Moderate activities such as: moving a table, pushing a vacuum</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>cleaner, bowling or playing golf</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Lifting or carrying groceries</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>d. Climbing several flights of stairs</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>e. Climbing one flight of stairs</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>f. Bending, kneeling, or stooping</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>g. Walking more than a mile</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>h. Walking several blocks</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>i. Walking one block</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>j. Bathing or dressing yourself</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>
D. CURRENT HEALTH RATING  
(Patient Karnofsky Performance Status (Loprinzi, C.L., et al., 1994))

Which one of the following phrases best describes you at this time? *(Please mark one box only.)*

- □ Normal, no complaints, no symptoms of disease
- □ Able to carry on normal activity, minor symptoms of disease
- □ Normal activity with effort, some symptoms of disease
- □ Care for self, unable to carry on normal activity or to do active work
- □ Require occasional assistance but able to care for most of personal needs
- □ Require considerable assistance for personal care
- □ Disabled, require special care and assistance
- □ Severely disabled, require continuous nursing care

E. FALLS
How many times have you fallen in the last 6 months? □□□

F. YOUR HEALTH  
(Older Americans Resource Scale for Instrumental Activities of Daily Living (Fillenbaum, G.G., et al., 1981))

1. Your General Health  
**Patient Instructions:** Do you have any of the following illnesses at the present time, and if so, how much does it interfere with your activities: Not at all, Somewhat or A Great Deal? *(Mark the one box that best reflects your answer.)*

**If you have this illness:**
How much does it interfere with your activities?

<table>
<thead>
<tr>
<th>Illness</th>
<th>No</th>
<th>Yes</th>
<th>Not at All</th>
<th>Somewhat</th>
<th>A Great Deal</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Other cancers or leukemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Arthritis, rheumatism or other connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Glaucoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Emphysema or chronic bronchitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. High blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f. Heart disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g. Circulation trouble in arms or legs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>h. Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2. How is your eyesight (with glasses or contacts)? *(Mark only one box)*

- □ Excellent
- □ Good
- □ Fair
- □ Poor
- □ Totally blind

If fair, poor or totally blind, how much does this interfere with your activities?

- □ Not at all
- □ Somewhat
- □ A great deal

3. How is your hearing (with a hearing aid, if needed)? *(Mark only one box)*

- □ Excellent
- □ Good
- □ Fair
- □ Poor
- □ Totally deaf

If fair, poor or totally deaf, how much does this interfere with your activities? *(Mark only one box)*

- □ Not at all
- □ Somewhat
- □ A great deal

4. Do you have any other physical problems or illnesses (other than listed in questions 1-3) at the present time that seriously affect your health?

- □ No

- □ Yes, specify: ________________________________________________________________

If yes, how much does this interfere with your activities?

- □ Not at all
- □ Somewhat
- □ A great deal
How many medications (either prescribed or over-the-counter), herbs or vitamins do you currently take?

Please list all prescribed or over-the-counter medicines, herbs or vitamins you are currently taking (doses not necessary).

1. _________________________________________________________________
2. _________________________________________________________________
3. _________________________________________________________________
4. _________________________________________________________________
5. _________________________________________________________________
6. _________________________________________________________________
7. _________________________________________________________________
8. _________________________________________________________________
9. _________________________________________________________________
10. _________________________________________________________________
11. _________________________________________________________________
12. _________________________________________________________________
13. _________________________________________________________________
14. _________________________________________________________________
15. _________________________________________________________________
G. HEALTH QUESTIONNAIRE.
(MHI-17 (Stewart and Ware, 1992))

INSTRUCTIONS: These questions are about how you have been feeling within the past two weeks. Please mark the box on each line that best reflects your situation.

<table>
<thead>
<tr>
<th>How much of the time during the past two weeks:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Has your daily life been full of things that were interesting to you?</td>
</tr>
<tr>
<td>2. Did you feel depressed?</td>
</tr>
<tr>
<td>3. Have you felt loved and wanted?</td>
</tr>
<tr>
<td>4. Have you been a very nervous person?</td>
</tr>
<tr>
<td>5. Have you been in firm control of your behavior, thoughts, emotions, feelings?</td>
</tr>
<tr>
<td>6. Have you felt tense or high-strung?</td>
</tr>
<tr>
<td>7. Have you felt calm and peaceful?</td>
</tr>
<tr>
<td>8. Have you felt emotionally stable?</td>
</tr>
<tr>
<td>9. Have you felt downhearted and blue?</td>
</tr>
<tr>
<td>10. Have you felt restless, fidgety, or impatient?</td>
</tr>
<tr>
<td>11. Have you been moody, or brooded about things?</td>
</tr>
<tr>
<td>12. Have you felt cheerful, lighthearted?</td>
</tr>
<tr>
<td>13. Have you been in low or very low spirits?</td>
</tr>
</tbody>
</table>
14. Were you a happy person? □ 1 □ 2 □ 3 □ 4 □ 5 □ 6

15. Did you feel that you had nothing to look forward to? □ 1 □ 2 □ 3 □ 4 □ 5 □ 6

16. Have you felt so down in the dumps that nothing could cheer you up? □ 1 □ 2 □ 3 □ 4 □ 5 □ 6

17. Have you been anxious or worried? □ 1 □ 2 □ 3 □ 4 □ 5 □ 6

H. SOCIAL ACTIVITY
(Medical Outcomes Study Social Support Survey (Sherbourne, C.D., et al., 1991))

1. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc)? (Please mark one box only.)

□ All of the time
□ Most of the time
□ Some of the time
□ A little of the time
□ None of the time

2. Compared to your usual level of social activity, has your social activity during the past 6 months decreased, stayed the same, or increased because of a change in your physical or emotional condition? (Please mark one box only.)

□ Much less socially active than before
□ Somewhat less socially active than before
□ About as socially active as before
□ Somewhat less limited than others
□ Much less limited than others

3. Compared to others your age, are your social activities more or less limited because of your physical health or emotional problems? (Please mark one box only.)

□ Much more limited than others
□ Somewhat more limited than others
□ About the same as others
□ Somewhat less limited than others
□ Much less limited than others

4. During the last 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors or groups? (Please mark one box only.)

□ Not at all
I. SOCIAL SUPPORT.
(Medical Outcomes Study Social Support Survey (Sherbourne, C.D., et al., 1991))

**INSTRUCTIONS:** People sometimes look to others for companionship, assistance or other types of support. How often is each of the following kinds of support available to you now if you need it? (Please mark the box on each line that best reflects your situation.)

<table>
<thead>
<tr>
<th>Item</th>
<th>None of the time</th>
<th>A little of the time</th>
<th>Some of the time</th>
<th>Most of the time</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Someone to help you if you were confined to bed</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>2. Someone you can count on to listen to you when you need to talk</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>3. Someone to give you good advice about a crisis</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>4. Someone to take you to the doctor if you needed it</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>5. Someone to give you information to help you understand a situation</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>6. Someone to prepare your meals if you were unable to do it yourself</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>7. Someone whose advice you really want</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>8. Someone to help you with daily chores if you were sick</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>9. Someone to share your most private worries and fears with</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>10. Someone to turn to for suggestions about how to deal with a personal problem.</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>11. Someone to confide in or talk to about yourself or your problem.</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>12. Someone who understands your problems</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>
J. QUESTIONS CONCERNING THE QUESTIONNAIRE

1. Were any of these questions difficult to understand?
   □ No
   □ Yes
   If Yes, which questions were they?
   __________________________________________________________
   __________________________________________________________
   __________________________________________________________

2. Was the time it took to answer all the questions too long, just right or too short?
   □ Too short → How long would you have liked the questionnaire to be? □ minutes
   □ Just right
   □ Too long → How long would you have liked the questionnaire to be? □ minutes
   Which items would you remove?
   __________________________________________________________
   __________________________________________________________

3. Did you find any of the questions upsetting?
   □ No
   □ Yes
   If Yes, which questions were they?
   __________________________________________________________
   __________________________________________________________
   __________________________________________________________
   Could you tell me why they were upsetting?
   __________________________________________________________
   __________________________________________________________

4. Do you think the questionnaire left out any questions that were important to ask?
NCCTG Brief Frailty Inventory

NCCTG Number: _________________  Patient Initials (last, first)_________ Date: ________________

Directions: Please circle the one number (0-10) for each question that describes how much your level of frailty, during the past week, has interfered with your:

1. General activity
   
   0 1 2 3 4 5 6 7 8 9 10
   Does not interfere
   Completely interferes

2. Mood
   
   0 1 2 3 4 5 6 7 8 9 10
   Does not interfere
   Completely interferes

3. Walking ability
   
   0 1 2 3 4 5 6 7 8 9 10
   Does not interfere
   Completely interferes

4. Normal work (includes both work outside the home and daily chores)
   
   0 1 2 3 4 5 6 7 8 9 10
   Does not interfere
   Completely interferes

5. Relations with other people
   
   0 1 2 3 4 5 6 7 8 9 10
   Does not interfere
   Completely interferes

6. Enjoyment of life
   
   0 1 2 3 4 5 6 7 8 9 10
   Does not interfere
   Completely interferes

7. Circle the one number that describes your level of frailty over the past week:
   
   0 1 2 3 4 5 6 7 8 9 10
   Not frail
   As frail as can be
## Fatigue/Uniscale Assessments

NCCTG Number: _________________  Patient Initials (last, first)_________  Date: ______________

Directions: Please circle the one number (0-10) for each item below that best describes you.

How would you describe:

1. your level of fatigue, on the average in the past week including today?

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No  Fatigue</td>
<td>Fatigue as bad as it can be</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. your overall quality of life in the past week including today?

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>As bad as it can be</td>
<td>As good as it can be</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Linear Analogue Self Assessment (LASA) Scale

NCCTG Number: _________________  Patient Initials (last, first)_________ Date: ______________

Directions: Please circle the number (0-10) best reflecting your response to the following that describes your feelings during the past week, including today.

How would you describe:

1. your overall Quality of Life?
   - 0 1 2 3 4 5 6 7 8 9 10
   - As bad as it can be
   - As good as it can be

2. your overall mental (intellectual) well-being?
   - 0 1 2 3 4 5 6 7 8 9 10
   - As bad as it can be
   - As good as it can be

3. your overall physical well-being?
   - 0 1 2 3 4 5 6 7 8 9 10
   - As bad as it can be
   - As good as it can be

4. your level of fatigue, on the average?
   - 0 1 2 3 4 5 6 7 8 9 10
   - No fatigue
   - Constant tiredness
EQ-5D Assessment

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

**Mobility**
- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

**Self-Care**
- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

**Usual Activities** (e.g. work, study, housework, family or leisure activities)
- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

**Pain/Discomfort**
- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

**Anxiety/Depression**
- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed
EQ-5D Assessment (continued)

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.
Was It Worth It (WIWI) Questionnaire

NCCTG Number: _________________  Patient Initials (last, first)_________ Date: ______________

Participating in a clinical trial / research study is a personal choice and an individual experience. We would like to get your feedback on your experience in this research study. Please respond to the following questions as indicated.

Directions: Please answer each question by circling Y (for yes), N (for no), or U (for uncertain).
1. Was it worthwhile for you to participate in this research study?  Y  N  U
2. If you had to do it over, would you participate in this research study again? Y  N  U
3. Would you recommend participating in this research study to others?  Y  N  U

Directions: Please respond to the following 4 items as indicated.
4. Overall, did your quality of life change by participating in this research study (circle one response)?
   It improved  It stayed the same  It got worse
5. Overall, how was your experience of participating in this research study (circle one response)?
   Better than I expected  The same as I expected  Worse than I expected
6. If there was one thing that could have been done to improve your experience in this research study, what would it be?

_______________________________________________________________________________
________________________________________________________________________________

7. Would you like to talk to someone about your concerns (circle one response)?  Yes  No
RESEARCH TEAM QUESTIONNAIRE BOOKLET
OBSERVATION PHASE

This booklet is to be completed by the research team (physician, institutional nurse, or CRA) on behalf of the patient prior to completion of the patient questionnaire booklet.

1. The booklet contains the following items:
   a. Cancer-Specific Geriatric Assessment – Research Team Questionnaire (14 questions)
      • Karnofsky Performance Scale (KPS)
      • Timed Up and Go (TUG)
      • Blessed Orientation-Memory-Concentration (BOMC) Test
   b. Canadian Study of Health and Aging Clinical Frailty Scale (CSHA-CFS) – Research Team Questionnaire (1 question)

2. Directions on how to complete each set of questions are written on the top of each set.

3. Please complete this booklet prior to the patient’s completion of the Patient Questionnaire Booklet corresponding to this visit.

Thank you for taking the time to help us.
Cancer Specific Geriatric Assessment – Research Team  
Version date June 7, 2011

I. This form completed by: (Please mark all that apply)  
- □ Physician  
- □ Nurse  
- □ CRA

If form was not completed at specified timepoint, specify reason: (mark one)  
- □ Patient refused  
- □ Patient withdrew consent  
- □ Not done  
- □ Other, specify _________________________________________

II. FUNCTIONAL STATUS

A. KPS  (Healthcare professional rated)  
(Karnofsky, D.A. et al., 1948)

Directions: Please rate your assessment of patient’s Karnofsky Performance Status as of date this form is completed.  (Scale is listed below.)

□□□ %

<table>
<thead>
<tr>
<th>%</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Able to carry on normal activity and able to work. No special care is needed.</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some signs or symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self. Unable to carry on normal activity or do active work</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most of his/her needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospitalization is indicated although death not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospitalization necessary; active supportive treatment necessary</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes progressing rapidly</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>
B. TIMED UP AND GO (TUG)
(Podsiadlo, D., et al., 1991)

INSTRUCTIONS: The timed “Up and Go” measures, in seconds, the time it takes for an individual to stand up from a standard arm chair (approximate seat height of 46 cm [approximately 1.5 ft]), walk a distance of 3 meters (approximately 10 feet), turn, walk back to the chair and sit down again. The subject wears his/her regular footwear and uses their customary walking aid (none, cane, walker, etc.) No physical assistance is given. The subject starts with his/her back against the chair, his/her arm resting on the chair’s arm, and his/her walking aid in hand. She/He is instructed that on the word “go”, she/he is to get up and walk at a comfortable and safe pace to a line on the floor 3 meters (approximately 10 feet) away, turn, and return to the chair and sit down again. The subject walks through the test once before being timed in order to become familiar with the test. Either a wrist watch with a second hand or a stopwatch can be used to time the performance.

Time required to complete the Timed Up and Go: □□□□□ seconds

III. COGNITION

BLESSED ORIENTATION-MEMORY-CONCENTRATION (BOMC) TEST
(Kawas, C., et al., 1991)

<table>
<thead>
<tr>
<th>Patient's Response</th>
<th>Maximum Errors</th>
<th>Score x Weight = Final Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. What year is it now (without looking at a calendar)?</td>
<td>1</td>
<td>_____ x 4 = _____</td>
</tr>
<tr>
<td>8. What month is it now (without looking at a calendar)?</td>
<td>1</td>
<td>_____ x 3 = _____</td>
</tr>
<tr>
<td><strong>Memory Phrase:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeat this phrase after me: ‘John Brown, 42 Market Street, Chicago’</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. About what time is it (within 1 hour, without looking at a clock)?</td>
<td>1</td>
<td>_____ x 3 = _____</td>
</tr>
<tr>
<td>10. Count backwards from 20 to 1.</td>
<td>2</td>
<td>_____ x 2 = _____</td>
</tr>
<tr>
<td>11. Say the months in reverse order.</td>
<td>2</td>
<td>_____ x 2 = _____</td>
</tr>
<tr>
<td>12. Repeat the memory phrase</td>
<td>5</td>
<td>_____ x 2 = _____</td>
</tr>
</tbody>
</table>

| Total score: | |

Scoring: For items 1-3, the response is either correct (score 0) or incorrect (score 1). For items 4-6, add one point for each error (item 4 and 5 maximum error is 2; for item 6, maximum error is 5); total all
scores in “Final Score” column. Data from participants found to have gross cognitive impairment as determined by the Blessed Orientation-Memory-Concentration Score $\geq 11$ will be excluded from the analysis. Maximum score = 28.

IV. SCORING

Did the patient score $\geq 11$ on the Blessed Orientation-Memory-Concentration Test?

□ No

□ Yes $\Rightarrow$ If yes, notify the patient’s treating physician

V. NUTRITION

What is the patient’s height? (from patient’s chart) □□□ cm

What is the patient’s current weight? (from patient’s chart) □□□ kg

What was the patient’s weight approximately 6 months ago? (from patient’s chart or patients self report) □□□ kg

VI. QUESTIONS REGARDING THE QUESTIONNAIRES

B. Were any of the questions of the “CSGA – Research Team Questionnaire” difficult for you to administer?

□ No

□ Yes

If no, please proceed to the next question.

If yes, please indicate which questions were difficult to administer?

(Please mark all that apply)

□ KPS Healthcare Professional Rated (page 1)

□ Timed Up and Go (page 2)

□ Blessed Orientation-Memory-Concentration Test (page 2)

□ Other: Please specify _________________________________

B. Were any of the questions of the “CSGA – Patient” difficult for the patient to complete?

□ No

□ Yes

If no, please proceed to the next question.

If yes, please indicate which questions were difficult for the patient to complete?

(Please mark all that apply)

□ Background Information (page 1)
□ Daily Activities (page 2-3)
□ Physical Activities (page 3)
□ Current Health Rating (page 4)
□ Falls (page 4)
□ Your Health (page 4-5) *(Mark all that apply)*
  □ 1. Your general health (page 4-5)
  □ 2. Medications (page 6)
□ Health Questionnaire (page 7-8)
□ Social activity (page 9)
□ Social support (page 10)

C. Was the patient able to complete the “CSGA – Patient” on his/her own?
□ Yes
□ No

If no, why? *(Please mark all that apply)*
□ Not literate (does not read or write)
□ Visual problem
□ Fatigue
□ Questions too difficult (above the patient’s reading ability)
□ Other: specify_________________________________________________

D. Length of time to complete both the Patient and Research Team Questionnaires.

Length of time to complete healthcare professional questionnaire □ □ □ minutes

Length of time to complete patient questionnaire □ □ □ minutes

Total length of time to complete both questionnaires □ □ □ minutes

Completed by: ____________________________

(Last name, First name)

Date Completed: ____________________________
The Canadian Study of Health and Aging Clinical Frailty Scale (CSHA-CFS) – Research Team Questionnaire

NCCTG Number: _________________  Patient Initials (last, first)_________ Date: ______________

Directions: Please circle the category that best describes your patient’s feelings during the past week, including today.

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Very fit</td>
<td>robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age</td>
</tr>
<tr>
<td>2. Well</td>
<td>without active disease, but less fit than people in category 1</td>
</tr>
<tr>
<td>3. Well, with treated comorbid disease</td>
<td>disease symptoms are well controlled compared with those in category 4</td>
</tr>
<tr>
<td>4. Apparently vulnerable</td>
<td>although not frankly dependent, these people commonly complain of being “slowed up” or have disease symptoms</td>
</tr>
<tr>
<td>5. Mildly frail</td>
<td>with limited dependence on others for instrumental activities of daily living</td>
</tr>
<tr>
<td>6. Moderately frail</td>
<td>help is needed with both instrumental and non-instrumental activities of daily living</td>
</tr>
<tr>
<td>7. Severely frail</td>
<td>completely dependent on others for the activities of daily living</td>
</tr>
<tr>
<td>8. Terminally ill</td>
<td></td>
</tr>
</tbody>
</table>
Procedure for Obtaining a Urine Protein/Creatinine (UPC) Ratio

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

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

Protein and creatinine concentrations should be available on standard reports of urinalyses, not dipsticks. If protein and creatinine concentrations are not routinely reported at an Institution, their measurements and reports may need to be requested.
Research Base Instructions for Biospecimen Processing in BAP Shared Resource

Study Number: N0949

Summary Table of Research Blood/Blood Products Being Received in BAP for This Protocol

<table>
<thead>
<tr>
<th>Collection tube description and/or additive (color of tube top)</th>
<th>Volume to be collected per tube (number of tubes to be collected)</th>
<th>Blood product to be processed in BAP</th>
<th>Baseline, prior to treatment</th>
<th>After 6 weeks of treatment</th>
<th>At time patient discontinues treatment</th>
<th>Shipping conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDTA (purple)</td>
<td>10 mL (1)</td>
<td>DNA, WBCs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Cold pack</td>
</tr>
<tr>
<td>EDTA (purple)</td>
<td>~1.5 mL (3)</td>
<td>Plasma</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Frozen</td>
</tr>
<tr>
<td>EDTA (purple)</td>
<td>1 mL (1)</td>
<td>WBCs(^1)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Frozen</td>
</tr>
<tr>
<td>No Additive (red)</td>
<td>~1.5 mL (3)</td>
<td>Serum</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Frozen</td>
</tr>
</tbody>
</table>

\(^1\)WBCs, white blood cells

1. Record receipt of specimens.

2. For all time points, frozen aliquots (i.e., serum, plasma, WBCs) will be stored at \(-80^\circ C\) for banking.

3. For “Baseline” sample, DNA will be extracted and WBCs will be isolated from one EDTA tube using the protocol entitled “Extracting Samples on the AutoGen”. DNA will be stored at 4°C until a box is full and then transferred and stored in a \(-80^\circ C\) freezer for banking. WBCs will be stored at \(-80^\circ C\) for banking.