

**A Multicenter Study of the Anti-VEGF Monoclonal Antibody Bevacizumab (Avastin®)  
Plus 5-Fluorouracil/ Leucovorin in Patients with Metastatic Colorectal Cancers  
That Have Progressed After Standard Chemotherapy**

**Sponsored by:** Cancer Therapy Evaluation Program  
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**Commercially Available Agents:** 5-Fluorouracil; Calcium Leucovorin (Citraovorum Factor)

### Important Contact Information

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**TRC Protocol Website:**

<http://spitfire.emmes.com/study/trc/>

For access to the protocol, registration forms, data reporting forms and instructions

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**To Submit IRB Approval, Registration Form, and, when applicable, Lottery Entry Forms:**

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**To Report Serious Adverse Events through AdEERS and for Questions on Adverse Event Reporting:**

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**SCHEMA**

**Eligibility** (see Section 3.1 for complete listing)

- ✓ Locally advanced or metastatic colorectal adenocarcinoma
- ✓ Progressive disease after irinotecan-based and oxaliplatin-based chemotherapy for metastatic disease
- ✓ ≥18 years of age
- ✓ PS 0-2 (ECOG); Karnofsky ≥ 60%
- ✓ Adequate organ function
- ✓ Absence of non-healing wound, uncontrolled hypertension, thromboembolism, active bleeding or CNS disease

**Treatment Plan**

Patients on this study may be treated with either Regimen A or Regimen B (below) as desired. However, choice of the regimen and the starting dose level should be determined at study entry.

**Regimen A (Bevacizumab + Roswell Park 5-FU/LV)**

Bevacizumab	5 mg/kg	IV infusion over 90 minutes Day 1, every 2 weeks
Leucovorin	500 mg/m <sup>2</sup>	IV infusion over 120 minutes Day 1, weekly x 6, every 8 weeks
5-FU	500 mg/m <sup>2</sup>	IV bolus (slow push) 1 hour after leucovorin Day 1, weekly x 6, every 8 weeks
5-FU (-1)*	400 mg/m <sup>2</sup>	Same as above
5-FU (-2)*	320 mg/m <sup>2</sup>	Same as above
<b>One cycle = 8 weeks</b>		
* For patients who could only tolerate 5-FU at dose levels (-1) or (-2) in prior 5-FU therapy, starting dose at the previously tolerated level is permitted for this protocol.		

**Regimen B (Bevacizumab + de Gramont 5-FU/LV)**

Bevacizumab	5 mg/kg	IV infusion over 90 minutes Day 1, every 2 weeks
Leucovorin	400 mg/m <sup>2</sup>	IV infusion over 120 minutes Day 1 and Day 2, every 2 weeks
5-FU	400 mg/m <sup>2</sup> /D 600 mg/m <sup>2</sup> /D	IV bolus <b>followed by</b> IV infusion continuously over 22 hours Day 1 and Day 2, every 2 weeks
5-FU (-1)*	320 mg/m <sup>2</sup> /D 500 mg/m <sup>2</sup> /D	Same as above
5-FU (-2)*	240 mg/m <sup>2</sup> /D 400 mg/m <sup>2</sup> /D	Same as above
<b>One cycle = 8 weeks</b>		
* For patients who could only tolerate 5-FU at dose levels (-1) or (-2) in prior 5-FU therapy, starting dose at the previously tolerated level is permitted for this protocol.		

**Duration of Therapy**

Therapy continues until:

- progressive disease\*
- unacceptable adverse events
- patient decision to withdraw study therapy
- death

\* Patients should not receive more than 1 cycle (8 weeks) of 5-FU/LV/bevacizumab unless there is clinical evidence that they are benefiting from the treatment. Benefit is defined as stable disease (SD), PR or CR as well as no increase in the size of any measurable or non-measurable lesion, and no new sites of disease.

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## 1. OBJECTIVES

- 1.1 To evaluate the response rate of bevacizumab (Avastin<sup>®</sup>) combined with 5-FU/LV for patients with locally advanced or metastatic colorectal cancers who have disease progression after irinotecan- and oxaliplatin-based regimens.
- 1.2 To evaluate the time to progression and overall survival for patients with locally advanced or metastatic colorectal cancer receiving bevacizumab (Avastin<sup>®</sup>) combined with 5-FU/LV after previous therapies with irinotecan- and oxaliplatin-based regimens.
- 1.3 To further evaluate the safety of bevacizumab when administered with a “bolus” 5-FU/LV regimen and with a “continuous infusion” 5-FU/LV regimen in patients previously treated with oxaliplatin and irinotecan.

## 2. BACKGROUND

### 2.1 The Treatment Referral Center

This Treatment Referral Center (TRC) protocol describes a multicenter, open-label study of bevacizumab, 5-fluorouracil (5-FU), and leucovorin (LV) in patients with advanced or metastatic colorectal cancer who are no longer benefiting from standard first- and second-line therapy.

The TRC mechanism was established in 1991 to handle inquiries for availability of investigational agents from physicians seeking treatment options for their patients. The purpose of the TRC is to make reasonable treatment options available to these physicians and their patients with emphasis on referral to Cooperative Group or Cancer Center studies. For specified diseases, the TRC identifies those stages and clinical settings for which there is clinical evidence suggesting that a new treatment option employing a not yet approved agent should be made available. These investigational treatment options are made available through the NCI Comprehensive and Clinical Cancer Centers as TRC protocols. Inquiring physicians wishing to have the investigational treatment for their patient are referred to the closest Cancer Center.

Based on the outcome of a major national study (AVF2107, Section 2.3.3.2), the NCI has made arrangements for the investigational agent, bevacizumab, in combination with 5-FU and LV to be available in the setting of a clinical trial for patients with advanced or metastatic colorectal cancer who have been previously treated with irinotecan- and oxaliplatin-based therapy. This protocol is being offered to all NCI-designated Comprehensive and Clinical Cancer Centers as well as additional institutions selected to achieve equitable geographic availability. Physicians, who contact the TRC seeking bevacizumab for their patients, will be referred to the nearest participating institution.

In the initial phase of the protocol, a maximum of 125 patients will be accrued. If preliminary data indicate that the treatment regimen is likely to be active, the protocol will be open to further accrual until bevacizumab is commercially available (see Section 10.0 Statistical Considerations). Initially, all eligible patients should be able to enter the study. If the demand exceeds the available supply of agent, eligible patients will be randomly selected by a lottery system based on enrollment of approximately 50 patients per month. The NCI will notify the participating centers should the lottery system be activated.

### 2.2 Treatment of Colon Cancer with Chemotherapy

It was estimated that approximately 129,000 new cases of colorectal cancer would be diagnosed and 56,000 deaths would occur due to colorectal cancer in the United States in 1999 (Landis et al. 1999). Approximately 70% of colorectal cancer patients present with disease that is potentially curable by surgical resection (August et al. 1984). However, the

prognosis for the 30% who present with advanced or metastatic disease and for the 20% who relapse following resection is poor. The median survival for those with metastatic disease was 12–14 months (Advanced Colorectal Cancer Meta-Analysis Project 1992). With newer first-line treatment, overall survival has improved to about 20 months, as reported from the N9741 intergroup trial led by the North Central Cancer Treatment Group (see Section 2.2.3).

### 2.2.1 Chemotherapy with 5-fluorouracil (5-FU) plus leucovorin

Until recently, the standard treatment for metastatic colorectal cancer in the United States has been chemotherapy with 5-FU plus leucovorin (Advanced Colorectal Cancer Meta-Analysis Project 1992; Moertel 1994). The method of 5-FU administration has ranged from bolus intravenous (IV) injection to continuous IV infusion. Commonly used regimens include the following:

- LV 20 mg/m<sup>2</sup> days 1-5, 5-FU 425 mg/m<sup>2</sup> q 4-5 wks (*Mayo 5-FU/LV Regimen*) (Poon et al. 1989)
- LV infusion 500 mg/m<sup>2</sup> over 2 hrs, 5-FU IV bolus 600 mg/m<sup>2</sup>, wkly X 6, then 2 wks rest (*Roswell-Park Regimen*) (Petrelli et al. 1989)
- LV 200 mg/m<sup>2</sup> over 2 hrs followed by 5-FU IV bolus 400 mg/m<sup>2</sup> plus 5-FU 600 mg/m<sup>2</sup> over 22 hrs, days 1 & 2, q 2 wks (*de Gramont Regimen*) (de Gramont et al. 1997)
- LV 500 mg/m<sup>2</sup> over 2 hrs followed by 5-FU 2600 mg/m<sup>2</sup> over 24 hrs weekly x 6 then 2 wks rest (AIO Regimen) (Kohne et al. 1998).

Clinical trials comparing the Mayo Clinic and Roswell Park regimens have not demonstrated a difference in efficacy although they were underpowered to do so (Buroker et al. 1994; Poon et al. 1989). The adverse event profiles of the two regimens, however, are different. The Mayo Clinic regimen results in more leukopenia and stomatitis and the Roswell Park regimen is associated with more frequent diarrhea. Patients with newly diagnosed metastatic colorectal cancer receiving either regimen can expect a median time to disease progression (TTP) of 4–5 months and a median survival of 12–14 months (Petrelli et al. 1989; Advanced Colorectal Cancer Meta-Analysis Project 1992; Buroker et al. 1994; Cocconi et al. 1998).

In a comparison of the de Gramont and Mayo Clinic regimens (total patient number = 433), the former had a 32.6% response rate and the latter a 14.4% response rate (de Gramont et al. 1997). The TTP was 27.6 weeks vs. 22 weeks in favor of the de Gramont regimen ( $p=0.0012$ ). Overall survival times were not different between the two arms. Grade 3-4 adverse events were significantly lower with the infusional regimen.

5-FU, particularly administered as a continuous infusion, has been tested in both second- and third-line settings in several small trials. The response rates varied between studies, ranging from 2-10%. More recent data on infusional 5-FU, however, indicated that the response rates were lower, between 0 to 1.6% in patients with irinotecan-refractory disease (Rothenberg et al. 2003; Garay et al. 2003).

### 2.2.2 Chemotherapy with 5-FU/LV/irinotecan

The CTP-11-based regimen most widely used in the US is the **IFL** regimen (also known as the “Saltz regimen”), which consists of irinotecan 125 mg/m<sup>2</sup>, 5-FU 500 mg/m<sup>2</sup> IV bolus, and LV 20 mg/m<sup>2</sup> IV bolus weekly for 4 out of 6 weeks. The study comparing IFL to 5-FU/LV demonstrated significantly longer progression-free survival (7.9 vs. 4.3 months,  $p = 0.004$ ), a higher response rate, and longer overall survival (median 14.8 months vs. 12.6 months,  $p = 0.04$ ). In addition, Douillard et al. (2000) studied irinotecan combined with the de Gramont 5-FU/LV regimen, as compared to “bolus” 5-FU/LV, using the same schedule. The patients receiving the irinotecan-containing regimen demonstrated significantly better outcome in terms of TTP (median 6.7 months vs. 4.4 months,  $p < 0.001$ ), response rate, and overall survival (median 17.4 vs. 14.1 months,  $p = 0.031$ ). The addition of irinotecan was associated with an increase in grade 3/4 diarrhea, grade 3/4 vomiting, grade 4

neutropenia, and asthenia compared with 5-FU/LV alone.

Both of these irinotecan-based regimens are licensed for use in the United States, with the IFL regimen being more widely prescribed.

### 2.2.3 Chemotherapy with oxaliplatin with infusional 5-FU/LV

More recently, oxaliplatin, in combination with infusional 5-FU/LV, was approved by the Food and Drug Administration (FDA) for the treatment of patients with metastatic colorectal cancer who have progressive disease after first-line treatment with bolus 5-FU and irinotecan. A commonly used oxaliplatin regimen was developed by de Gramont (FOLFOX4) and is composed of oxaliplatin 85 mg/m<sup>2</sup> and the de Gramont regimen of infusional 5-FU/LV. This regimen is repeated on two consecutive days every 2 weeks.

The FOLFOX4 regimen was evaluated in a phase 3 randomized intergroup trial (N9741) as a first-line therapy for metastatic colorectal cancer. The three treatment arms evaluated in the N9741 trial were irinotecan/bolus 5-FU/LV (IFL; n= 264), oxaliplatin with de Gramont 5-FU/LV (FOLFOX4; n=267), and a combination of oxaliplatin and irinotecan (IROX; n=265).

The updated results from the N9741 trial were presented at the Oral Presentation Session for Colorectal Cancer Malignancies at the 2003 American Society of Clinical Oncology meeting. These results showed that outcomes for patients receiving FOLFOX4 were significantly better than for the standard arm, IFL, with a median overall survival of 19.5 months vs. 14.1 months (p = 0.0001). Response rate and TTP were also superior for the FOLFOX arm (see Table below). Furthermore, the safety profile was more favorable for the FOLFOX arm compared to either IFL or IROX, except for paresthesias (Goldberg et al. 2003).

#### **Comparison of IFL and FOLFOX as First-line Treatment for Advanced Colorectal Cancer**

(Updated results based on an oral presentation after the abstract by Goldberg et al. 2003)

	<b>5-FU/LV/irinotecan IFL Regimen (n = 264)</b>	<b>5-FU/LV/oxaliplatin FOLFOX4 Regimen (n = 267)</b>	<b>p-Value</b>
<b>Response rate</b>	31%	45%	0.002
<b>Median TTP</b>	6.9 months	8.7 months	0.0014
<b>Median Survival</b>	14.8 months	19.5 months	0.0001

Oxaliplatin has also been evaluated in the second-line setting for patients with irinotecan-refractory disease. In an 821-patient, randomized, three-arm, second-line study of oxaliplatin plus infusional 5-FU vs. 5-FU alone vs. oxaliplatin alone, the combination arm demonstrated a statistically significant improvement in response rate (9.9% vs. 0% vs. 1%, p<0.0001). The median TTP was also prolonged in the combination arm (4.6 months) as compared to 5-FU alone (2.7 months) or oxaliplatin alone (1.6 months) (Rothenberg et al. 2003).

## 2.3 Bevacizumab Background

### 2.3.1 Angiogenesis and vascular endothelial growth factor (VEGF)

Folkman and others have provided compelling evidence linking tumor growth and metastases with angiogenesis (Folkman 1997). Angiogenesis is regulated by a diverse group of endogenous pro-angiogenic and anti-angiogenic factors [reviewed in Kerbel and Folkman, 2002]. Of the identified angiogenic factors, vascular endothelial growth factor (VEGF; also known as vascular permeability factor) is the most potent and specific and has been identified as a crucial regulator of both normal and pathologic angiogenesis (Ferrara and Davis-Smyth 1997). VEGF produces a number of biologic effects, including

endothelial cell mitogenesis and migration as well as induction of proteinases, leading to remodeling of the extracellular matrix, increased vascular permeability, and maintenance of survival for newly formed blood vessels (Ferrara and Davis-Smyth 1997).

Increased expression of VEGF has been measured in most human tumors examined to date (Ferrara and Davis-Smyth 1997). Specifically, in colorectal cancer, increased VEGF expression correlates with invasiveness, vascular density, metastasis, recurrence, and prognosis (Takahashi et al. 1995, 1997; Warren et al. 1995; Radinsky and Ellis 1996; Tokunaga et al. 1998). In addition, levels of VEGF in the ascites of patients with metastatic colorectal cancer are markedly elevated. This suggests that VEGF-induced vascular permeability may contribute to the formation of malignant ascites (Zebrowski et al. 1999).

### 2.3.2 Bevacizumab (Avastin<sup>®</sup>) – general information

To test the hypothesis that inhibition of VEGF in patients with cancer results in clinical benefit, a recombinant humanized version of a murine anti-human VEGF monoclonal antibody, named bevacizumab (Avastin<sup>®</sup>), was created (Presta et al. 1997). Bevacizumab has been advanced into clinical development by Genentech, Inc. for use in oncology indications. The agent is also being co-developed under a Cooperative Research and Development Agreement (CRADA) with the Cancer Therapy and Evaluation Program at the National Cancer Institute.

#### 2.3.2.1 Non-clinical toxicology

In cynomolgus monkey studies, twice weekly IV treatments with bevacizumab (doses up to 50 mg/kg) were well tolerated with no overt signs of acute side effects (Christian 1999; Ryan et al. 1999). In all active treatment groups, animals with open growth plates showed epiphyseal dysplasia. Focal to diffuse chondroid necrosis and linear fissuring of the cartilaginous growth plate were also observed. In addition, females treated with 10 or 50 mg/kg twice weekly had decreased ovarian and uterine weights that were associated with the absence of corpora lutea. These findings were expected considering the known role of VEGF in formation of the corpora lutea and of the growing bone (Ferrara et al. 1998). Minor changes in some organ weights were noted in the 4-week study but were not reproduced in the 13- or 26-week studies. No antibodies against bevacizumab were detected.

To assess the effects of bevacizumab on wound healing, rabbits were given partial thickness dermal wounds on their ears or backs and treated with bevacizumab every other day for 2 weeks at doses from 0.5 to 50 mg/kg per day (Leach and Shopp 1997). Dose-related inhibition of wound healing was exhibited following treatment with rhuMAb VEGF. Maximal inhibition was observed at a dose level of 10 mg/kg per day.

No specific tissue cross-reactivity with human, cynomolgus monkey, or rabbit tissue was observed with 400 µg/mL bevacizumab.

#### 2.3.2.2 Clinical development of bevacizumab - overview

Bevacizumab, as single agent or in combination regimens, has been evaluated in phase 1 to phase 3 clinical trials in a variety of solid tumors (Chen et al. 2001), including colorectal tumors (see Section 2.3.3). Pharmacokinetics appeared to be linear at doses above 1 mg/kg, with a half-life of ~15 days. Pharmacokinetic interaction with chemotherapy has not been observed (Kabbinarav et al. 2003). Commonly used dosing schedules of bevacizumab are 5 or 10 mg every 2 weeks, or 15 mg every 3 weeks (i.e. 2.5 or 5 mg/kg per week).

Single agent activity of bevacizumab has been demonstrated in renal cell carcinoma (RCC) in a phase 2 randomized, double-blinded, placebo-controlled study, in which

110 patients with advanced RCC were randomized to receive bevacizumab 3 mg/kg every 2 weeks, 10 mg/kg every 2 weeks, or placebo. A significant prolongation in time to progression (TTP) was observed in the high-dose arm compared to the placebo control arm (hazards ratio=2.55,  $P=.0002$ ). Tumor response evaluation identified four partial responses in the bevacizumab high-dose treatment arm (RR=10%) (Yang et al. 2002).

In patients with breast cancer, bevacizumab has been shown to induce a modest rate of objective responses (Sledge et al. 2000). In a phase 3 trial of bevacizumab in combination with capecitabine as second- or third-line therapy in patients with metastatic breast cancer, the tumor response rate was enhanced in the combination arm compared to capcitabine alone (20% vs. 9%); however, there was no difference in TTP between the two arms (Miller et al. 2002). A phase 3 trial of bevacizumab and chemotherapy as first-line therapy for advanced or metastatic breast cancer is on-going.

A phase 2 trial of bevacizumab monotherapy was conducted in patients with androgen-independent prostate cancer (Reese et al. 2001). In this study, no objective partial or complete responses were observed, and no patients achieved >50% decline in prostate-specific antigen (PSA). There were some mixed responses and four patients (27%) experienced transient declines in PSA of <50%.

**2.3.3 Clinical trials of bevacizumab in combination with chemotherapy in patients with advanced colorectal cancer**

**2.3.3.1 Phase 2 study of bevacizumab and 5-FU/LV in untreated metastatic colorectal cancer (Study AVF0780g)**

Study AVF0780g was a phase 2, open-label, randomized trial to evaluate the efficacy, safety, and pharmacokinetics of bevacizumab combined with 5-FU/LV in patients with previously untreated metastatic colorectal cancer (Kabbnavar et al. 2003). Patients were randomized to one of three treatment arms: control arm (5-FU/LV alone), 5 mg/kg bevacizumab plus 5-FU/LV, or 10 mg/kg bevacizumab plus 5-FU/LV. 5-FU was administered according to the Roswell Park regimen. The primary efficacy endpoints were TTP and best-confirmed response as determined by an independent review facility that was blinded to treatment assignment. Although the study was not designed or powered to compare efficacy, the combination arm (with 5 mg/kg bevacizumab) suggested a trend towards higher response rate as well as a longer time to progression and overall survival compared to the control arm.

	<b>5FU/LV (n = 36)</b>	<b>5-FU/LV/Bevacizumab 5 mg/kg (n = 35)</b>	<b>5-FU/LV/Bevacizumab 10 mg/kg (n = 33)</b>
<b>Best-Confirmed RR</b>	6 (17%)	14 (40%, $p=0.03$ )	8 (24%)
<b>Median TTP</b>	5.2 mos.	9.0 mos. ( $p=0.005$ )	7.2 mos.
<b>Median Survival</b>	13.6 mos.	21.5 mos. ( $P=0.135$ )	16.1 mos.

In this study, 21 patients in the placebo arm crossed-over to receive single agent bevacizumab and two achieved a partial response in the cross-over phase. Selected grade 3/4 adverse events that occurred on this study are shown in Table 2.3.4a.

**2.3.3.2 Phase 3 trial of bevacizumab combined with IFL as a first-line therapy for patients with metastatic colorectal cancer (AVF2107)**

Study AVF2107 was a 925-patient, randomized, multicenter, double-blind, placebo-controlled trial evaluating the addition of bevacizumab to IFL chemotherapy (irinotecan/5-FU/LV) in first-line treatment of patients with metastatic colorectal cancer. A third arm (5-FU/LV/bevacizumab) was originally included in the design. This

arm was discontinued at the recommendation of an independent data monitoring committee after an interim analysis showed that the IFL/bevacizumab arm had an adverse event profile comparable to the other two arms.

A total of 815 patients were entered on either the IFL/bevacizumab arm (n=403) or the IFL/placebo arm (n=412) of the study. The addition of bevacizumab (5 mg/kg IV q2 weeks) to the IFL regimen resulted in a statistically and clinically significant improvement in all endpoints examined: median overall survival (15.6 vs. 20.3 months, HR 0.65), median progression-free survival (6.2 vs. 10.6 months), objective response rate (34.7% vs. 44.9%) and response duration (7.1 vs. 10.4 months) (Hurwitz et al. 2003). These results are summarized in the table below.

	<b>IFL/ bevacizumab (n = 403)</b>	<b>IFL/ placebo (n = 412)</b>	<b>HR (p-Value)</b>
<b>Response Rate</b>	44.9%	34.7%	(0.0029)
<b>Median TTP</b>	10.6 months	6.2 months	(0.00001)
<b>Median Survival</b>	20.3 months	15.6 months	0.65 (0.00003)

In the 5-FU/LV/bevacizumab arm (n=110), which was closed to accrual at a planned early interim analysis), the efficacy of this combination was suggested by the finding of a median survival of 18.3 months, a median progression-free-survival of 8.8 months, and a response rate of 40%.

The main adverse events reported in this randomized trial that were considered to be possibly attributable to bevacizumab are listed in Table 2.3.4b. Hypertension was more frequent in the bevacizumab-containing arm; however, the rates of proteinuria, thrombosis, and bleeding were similar across all treatment arms. There was an excess of bowel perforation events noted in the IFL/bevacizumab arm (six subjects) as compared to the IFL/placebo arm (no events).

**2.3.3.3 Phase 3 trial of bevacizumab with FOLFOX4 as second-line therapy for patients with advanced colorectal cancer (ECOG 3200)**

This NCI-sponsored phase 3 cooperative group trial, led by the Eastern Cooperative Oncology Group (ECOG), was designed to evaluate bevacizumab in combination with an oxaliplatin-based regimen as second-line therapy for patients with advanced colorectal cancer previously treated with irinotecan and 5-FU/LV. This study contained three treatment arms: oxaliplatin/de Gramont infusional 5-FU/LV (FOLFOX4) plus bevacizumab, FOLFOX4, and bevacizumab alone. The primary endpoint is overall survival. The bevacizumab alone arm was terminated early, as recommended by the independent data monitoring board, after an interim analysis indicated that survival in patients receiving bevacizumab alone was inferior to that of the other two arms. The study completed patient accrual to the FOLFOX4 and FOLFOX4/bevacizumab arms in April 2003. Results are pending.

**2.3.4 Adverse events associated with bevacizumab therapy**

In theory, inhibition of VEGF could result in a number of adverse events: increased incidence of bleeding (including bleeding into cancerous lesions), delayed wound healing, detrimental effects on blood vessel integrity in response to tissue ischemia, altered menstruation and/or ovulation, potential infertility, deleterious effects on embryogenesis, chondroid necrosis at the growth plate, increased susceptibility to bone fractures due to potential linear fissure at the growth plate (a possible risk in subjects with growing bones), and exacerbation of previous cytotoxic chemotherapy-related adverse events.

In practice, some of these anticipated adverse events, as well as a number of unanticipated adverse events, have been observed in bevacizumab clinical trials. Life-threatening adverse events reported in clinical trials with bevacizumab to date include hemorrhage, thrombosis, and bowel perforation. Other adverse events observed include proteinuria, hypertension, headache, epistaxis, and infusional or hypersensitivity reactions.

Information on selected adverse events reported in two randomized colorectal cancer trials that included treatment with bevacizumab is presented in Tables 2.3.4a and 2.3.4b. A comprehensive list of bevacizumab-related adverse events can be found in Section 6.1.2. A more detailed description of adverse events is available in the Investigator's Brochure for bevacizumab.

Hemorrhage: Life-threatening and fatal hemorrhagic events have been reported in clinical trials with bevacizumab. In a phase 2 study in non-small cell lung cancer, 6 cases of life threatening hemoptysis or hematemesis were reported among 66 patients treated with bevacizumab and chemotherapy. Four of these events were fatal (Novotny et al. 2001). Serious bleeding has also been observed in the central nervous system, gastrointestinal tract, and other organs. Many, but not all of these serious bleeding episodes, were associated with tumor involvement.

Thrombosis: Venous and arterial thromboses have been reported in the form of lower extremity deep vein thrombosis, pulmonary embolism, mesenteric vein thrombosis, cerebral ischemia, and mesenteric ischemia. The attribution of these events to bevacizumab is uncertain with the available data. In the randomized phase 3 trial of IFL with and without bevacizumab (given at 5 mg/kg every two weeks), the frequencies of thromboembolic events were comparable in the two arms (19% vs. 16%) (Hurwitz et al. 2003).

Proteinuria: This event is common (20%) and has been seen in all bevacizumab clinical trials to date. The severity of proteinuria ranged from clinically silent, transient, trace proteinuria to, in rare instances, nephrotic syndrome. Grade 3 proteinuria is also rare. In two patients in whom renal biopsy was performed, the pathology showed membranous proliferative glomerulonephritis.

Hypertension: This event is also attributable to bevacizumab and is common (about 20%), often requiring initiation of or increase in hypertensive medication. The most commonly used anti-hypertensive therapies were angiotensin-converting enzyme inhibitors or calcium channel blockers. Less commonly used therapies included beta-blockers and diuretics. In most cases, blood pressure can be controlled with routine oral medication while bevacizumab is continued. However, rare episodes of hypertensive crisis have been reported.

As noted in the phase 3 trial in metastatic colon cancer comparing IFL to IFL/bevacizumab, bowel perforation, although rare, was increased in the bevacizumab-containing arm compared to chemotherapy alone (1.5% vs. 0%) (Hurwitz et al. 2003). Bowel perforation and bowel anastomotic dehiscence or skin wound dehiscence have also been reported in NCI-sponsored bevacizumab trials. Although these events were likely related to co-existing factors such as tumor involvement, recent invasive procedures, or bowel inflammation, contribution of bevacizumab to these events cannot be excluded. Partial delay in wound healing has been demonstrated in animal models treated with anti-VEGF antibodies. It is possible that bevacizumab may delay or compromise wound healing in patients.

**Table 2.3.4a: Selected Grade 3/4 Adverse Events:  
Phase 2 Randomized Study of 5-FU/LV ± Bevacizumab**  
(Adapted from Kabbinavar et al. 2003)

Adverse Event	5-FU/LV	5-FU/LV/Bevacizumab	
	(n = 35)	Bevacizumab 5 mg/kg (n = 35)	Bevacizumab 10 mg/kg (n = 32)
GI hemorrhage	0	0	3
Hypertension	0	3	8
Thrombotic events	1	5	2
Diarrhea	13	10	10
Leukopenia	1	2	1
Infection	0	0	1
Abdominal pain	1	3	4
Weight loss	0	1	0
Headache	0	0	1
Rash	0	1	0

**Table 2.3.4b  
Selected Safety Results:  
Phase 3 Trial of IFL plus Bevacizumab or Placebo**  
(adapted from Hurwitz et al. 2003)

Adverse Event*	IFL/Placebo (n=412)	IFL/Bevacizumab (5mg/kg q2 weeks) (n=403)
Grade 3/4 bleeding	2.5%	3.1%
Any thromboembolism	16.1%	19.3%
Grade 3 proteinuria	0.8%	0.8%
Grade 3 hypertension	2.3%	10.9%
Bowel perforation	0%	1.5%

\* Uncorrected for differential time on therapy

## 2.4 Rationale for the current study

5-FU, irinotecan, and oxaliplatin are three approved and active agents for the treatment of advanced colorectal cancer. In particular, both irinotecan and oxaliplatin have demonstrated clinical benefit in either the first-line or second-line setting. However, no standard treatment options are available for patients with progressive disease following irinotecan- and oxaliplatin-based treatment.

Given the proven clinical benefit conferred by the addition of bevacizumab to IFL chemotherapy (irinotecan/5-FU/LV) in patients with untreated metastatic colorectal cancer, the current study is designed to evaluate the potential benefit of combining bevacizumab with additional chemotherapy (5-FU/LV) as a third-line treatment option for patients who have progressive disease after irinotecan- and oxaliplatin-based chemotherapy regimens. The two 5-FU/LV schedules used in this study (Roswell Park bolus regimen and de Gramont infusional regimen) have been tested in combination with bevacizumab in other studies, and the adverse event profiles were acceptable.

This study is intended to be complimentary to the on-going and planned evaluation of bevacizumab in the first- and second-line treatment of metastatic colorectal cancer. Currently,

data are not yet available on the value of bevacizumab in combination with the newer and more effective first-line chemotherapy regimen for metastatic colorectal cancer, FOLFOX. An NCI-sponsored cooperative group phase 3 trial has been planned to address this question. It also remains to be determined (in the recently closed cooperative group trial, E3200) whether the addition of bevacizumab to FOLFOX is beneficial in the second-line setting.

The Treatment Referral Center mechanism is being used to provide access to this third-line trial by physicians and patients across the United States. It is the intent of this TRC protocol to make the 5-FU/LV/bevacizumab treatment available within the limitation of agent availability until bevacizumab becomes commercially available. However, since the efficacy of this study regimen in the third-line setting is unknown and treatment-related adverse events are expected, early stopping rules will be implemented if there is lack of activity in the first 35-100 evaluable patients (see Section 10.0 Statistical Considerations).

### 3. PATIENT SELECTION

#### 3.1 Eligibility Criteria

- 3.1.1 Patients must have histologically or cytologically documented locally advanced or metastatic colorectal adenocarcinoma not curable by surgery or amenable to radiation therapy with curative intent.

Patients with a history of colorectal cancer treated by surgical resection who develop radiological or clinical evidence of metastatic cancer do not require separate histological or cytological confirmation of metastatic disease, provided the diagnosis of the primary lesion was documented and there is no ambiguity regarding the nature and the source of apparent metastasis.

- 3.1.2 Patients must have received treatment with standard chemotherapy regimens (including oxaliplatin and irinotecan), as defined by:

- Investigator-assessed disease progression during or following **irinotecan-based** therapy for metastatic disease, OR relapse within 6 months of concluding adjuvant therapy with an **irinotecan-based** regimen;

#### AND

- Investigator-assessed disease progression during or following **oxaliplatin-based** therapy for metastatic disease, OR relapse within 6 months of concluding adjuvant therapy with an **oxaliplatin-based** regimen

- 3.1.3 Age  $\geq$ 18 years

- 3.1.4 Performance status: ECOG 0-2 (Karnofsky  $\geq$  60%; see Appendix A.)

- 3.1.5 Patients must have recovered from side effects that might interfere with the protocol therapy, and:
- $\geq$  4 weeks must have elapsed from the time of major radiotherapy (e.g., chest or bone palliative RT)
  - $\geq$  3 weeks must have elapsed from the last administration of cytotoxic agent
  - $\geq$  8 weeks after the last administration of monoclonal antibody therapy

- 3.1.6 Patients must have adequate organ function as defined below:
- absolute granulocyte count (AGC)  $\geq 1,500/\mu\text{L}$  ( $\geq 1.5 \times 10^9/\text{L}$ )
  - platelets  $\geq 100,000/\mu\text{L}$  ( $\geq 100 \times 10^9/\text{L}$ )
  - hemoglobin  $\geq 9 \text{ gm/dL}$  ( $\geq 90 \text{ g/L}$ )  
[patients may be transfused to meet this requirement]
  - creatinine  $\leq 1.5 \times \text{ULN}$
  - Urine dipstick for proteinuria  $< 1+$  (i.e., either 0 or trace).  
[If urine dipstick is 1+, then a 24-hour urine for protein must demonstrate  $< 500 \text{ mg of protein/24 hours}$  to allow participation in the study]
  - total bilirubin  $\leq 1.5 \text{ mg/dL}$  ( $\leq 25.65 \mu\text{mol/L}$ )
  - aspartate aminotransferase (AST)  $< 5 \times \text{ULN}$
  - alkaline phosphatase  $< 5 \times \text{ULN}$
  - PT INR  $\leq 1.5 \times \text{ULN}$
  - PTT  $\leq \text{ULN}$
- 3.1.7 Bevacizumab may pass the placenta and be secreted in milk, and may be detrimental to fetal and infant development. In addition, it is unknown whether anti-VEGF therapy is also teratogenic.
- For these reasons, pregnant or nursing women should not be enrolled in this study. Women of child-bearing potential and men must agree to use adequate contraception during study participation, and for at least 3 months after the conclusion of bevacizumab therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.
- 3.1.8 Ability to understand and the willingness to sign a written informed consent document.

### 3.2 Exclusion Criteria

- 3.2.1 Patients may not have received prior bevacizumab therapy
- 3.2.2 Patients may not be receiving any other investigational agents.
- 3.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to bevacizumab as well as other agents used in the study.
- 3.2.4 Uncontrolled intercurrent illness including, but not limited to the following:
- active infection
  - uncontrolled high blood pressure
  - symptomatic congestive heart failure
  - unstable angina pectoris
  - cardiac arrhythmia
  - myocardial infarction  $< 6$  months prior to registration
  - New York Heart Association classification III or IV (Appendix B)
  - psychiatric illness/social situations that would limit compliance with study requirements.
- 3.2.5 History or evidence of presence of CNS disease (e.g., any brain metastases, primary brain tumor, seizures not controlled with standard medical therapy, or history of stroke)

- 3.2.6 Patients must not be on therapeutic anticoagulation. Prophylactic anticoagulation (e.g. low dose coumadin) of venous access devices is allowed provided that the requirement for PT INR or PTT is met.
- 3.2.7 Any invasive procedures as defined below:
- Major surgical procedure, open biopsy, or significant traumatic injury **within 6 weeks** prior to Day 1 of treatment,
  - Fine needle aspirations or core biopsies within 7 days prior to Day 1 of treatment
  - Anticipation of need for major surgical procedure during the course of the study;
- 3.2.8 Chronic, daily treatment with aspirin (>325 mg/day) or non-steroidal anti-inflammatory medications (of the kind known to inhibit platelet function at doses used to treat chronic inflammatory diseases).
- 3.2.9 Serious, non-healing wound (including wounds healing by secondary intention), ulcer, or bone fracture
- 3.2.10 Evidence of bleeding diathesis or coagulopathy
- 3.2.11 Patients with immune deficiency are at increased risk of lethal infections when treated with marrow-suppressive therapy. Therefore, HIV-positive patients receiving combination anti-retroviral therapy are excluded from the study because of possible pharmacokinetic interactions with bevacizumab or other agents administered during the study. Appropriate studies will be undertaken in patients receiving combination anti-retroviral therapy when indicated.

### 3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this treatment study. There is no evidence thus far for differing treatment outcomes based on gender or ethnicity; however, the data will be scrutinized for evidence of any such differences.

## 4. TREATMENT PLAN

### 4.1 Agent Administration

Reported adverse events and potential risks for bevacizumab, 5-FU, and LV are described in Section 6. **Appropriate dose modifications/interruption for bevacizumab and 5-FU should be implemented in the setting of related adverse events according to the guidelines described in Section 5.** No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy on this study.

**Patients should receive bevacizumab at the participating (enrolling) institutions. For treatment days when bevacizumab is not administered, the enrolling physician, at his/her discretion, may arrange for 5-FU/LV to be given by the patient's local oncologist.**

4.1.1 Treatment Regimens:

Patients on this study can be treated with either Regimen A or Regimen B as described below. The starting dose level of 5-FU can be the standard, (-1) or (-2) based on the dose level tolerated by the patient during prior 5-FU therapy. **However, the choice of the regimen and the starting dose level should be determined at study entry:**

**Regimen A: Bolus 5-FU/LV (Roswell Park Regimen) + Bevacizumab**

Bevacizumab	5 mg/kg	IV infusion over 90 minutes Day 1, every 2 weeks
Leucovorin	500 mg/m <sup>2</sup>	IV infusion over 120 minutes Day 1, weekly x 6, every 8 weeks
5-FU	500 mg/m <sup>2</sup>	IV bolus (slow push) 1 hour after leucovorin Day 1, weekly x 6, every 8 weeks
5-FU (-1)*	400 mg/m <sup>2</sup>	Same as above
5-FU (-2)*	320 mg/m <sup>2</sup>	Same as above
<b>One cycle = 8 weeks</b>		
* For patients who could only tolerate 5-FU at dose levels (-1) or (-2) in prior 5-FU therapy, starting dose at the previously tolerated level is permitted for this protocol.		

- Agent administration should occur in the order by which the agents are listed in the table (i.e., Day 1: Bevacizumab, LV, bolus 5-FU).
- The initial bevacizumab dose should be administered over a minimum of 90 minutes. If no adverse events occur, the second dose can be administered over a minimum of 60 minutes. Again, if no adverse events occur, the third and subsequent doses should be administered over a minimum of 30 minutes. The infusions should be made with a volumetric infusion device. If infusion-related adverse events occur, subsequent infusions should be administered over the shortest period that is well tolerated (see Section 6.1.3).
- To ensure complete delivery of bevacizumab, the IV infusion line must be flushed with 0.9% sodium chloride (see Section 6.1.3).

**Regimen B: Bevacizumab + Infusional 5-FU/LV (de Gramont Regimen)**

Bevacizumab	5 mg/kg	IV infusion over 90 minutes Day 1, every 2 weeks
Leucovorin	400 mg/m <sup>2</sup>	IV infusion over 120 minutes Day 1 and Day 2, every 2 weeks
5-FU	400 mg/m <sup>2</sup> /D 600 mg/m <sup>2</sup> /D	IV bolus <b>followed by</b> IV infusion continuously over 22 hours Day 1 and Day 2, every 2 weeks
5-FU (-1)*	320 mg/m <sup>2</sup> /D 500 mg/m <sup>2</sup> /D	Same as above
5-FU (-2)*	240 mg/m <sup>2</sup> /D 400 mg/m <sup>2</sup> /D	Same as above
<b>One cycle = 8 weeks</b>		
* For patients who could only tolerate 5-FU at dose levels (-1) or (-2) in prior 5-FU therapy, starting dose at the previously tolerated level is permitted for this protocol.		

- Agent administration should occur in the order by which the agents are listed in the table (i.e., Day 1: Bevacizumab, LV, 5-FU bolus, 5-FU CIV; Day 2: LV, 5-FU bolus, 5-FU CIV).
- The initial bevacizumab dose should be administered over a minimum of 90 minutes. If no adverse events occur, the second dose should be administered over a minimum of 60 minutes. Again, if no adverse events occur, the third and subsequent doses should be administered over a minimum of 30 minutes. The infusions should be made with a volumetric infusion device. If infusion-related adverse events occur, subsequent infusions should be administered over the shortest period that is well tolerated (see Section 6.1.3).
- To ensure complete delivery of bevacizumab, the IV infusion line must be flushed with 0.9% sodium chloride (see Section 6.1.3).

**4.2 General Patient Monitoring and Supportive Care Guidelines**

4.2.1 Patients should be carefully monitored during the treatment phase and then followed appropriately. Prior to each treatment, the patient should be carefully assessed, with special attention to blood pressure, proteinuria, and bleeding events as well as other adverse events. Decisions for retreatment or dose modifications/interruption should follow the guidelines in Section 5.0.

Patients who have an on-going study agent-related serious adverse event upon study completion or at discontinuation from the study will be contacted by the investigator or his/her designee every 2 weeks until the event is resolved or determined to be irreversible.

4.2.2 Hypertension: Blood pressure should be assessed at least weekly during the first cycle and before each administration of bevacizumab. Home monitoring is strongly encouraged. High blood pressure may require initiation or increase in hypertensive medication according to routine practice. Bevacizumab treatment modifications should follow instructions in Section 5.1.3.

4.2.3 Prophylactic anticoagulation: Prophylactic anticoagulation (e.g. 1 mg warfarin) is allowed on study. However, it is recommended that the prothrombin time be monitored carefully (at least monthly). Bevacizumab should be held for PT INR of > 1.5.

- 4.2.4 Growth factors: Routine prophylactic use of G-CSF is not recommended on this trial. Therapeutic or prophylactic G-CSF use in patients with serious neutropenic complications may be given at the investigator's discretion following the ASCO Guidelines.

#### 4.3 Duration of Therapy and Off-Therapy Criteria

Patients should not receive more than 1 cycle (8 weeks) of 5-FU/LV/bevacizumab unless there is clinical evidence that they are benefiting from the treatment. Benefit is defined as stable disease (SD), PR or CR as well as no increase in the size of any measurable or evaluable lesion, and no new sites of disease. In the absence of unacceptable adverse events, treatment may continue until one of the criteria below applies. All reasons for discontinuation of treatment must be documented in an off-study note (i.e., progression, adverse events, refusal, etc.).

Patients should be removed from study for any of the following criteria:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Criteria for treatment discontinuation as described in Sections 5.1 and 5.2 (dose and treatment modifications)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator.

### 5. DOSING DELAYS/DOSE MODIFICATIONS

Note: If a component of the study regimen is held or interrupted, the dose will be skipped and will not be made up.

Note: If 5-FU is permanently discontinued due to 5-FU-related adverse events, the patient may continue to receive bevacizumab on study at physician's discretion **provided** that other off-therapy criteria are not met (see Section 4.3 and Section 5.1). If bevacizumab is temporarily held for adverse events unrelated to chemotherapy, 5-FU may be given. However, if bevacizumab is permanently discontinued, the patient should be taken off study.

#### 5.1 Bevacizumab Treatment Modifications

*There will be no dose reduction for bevacizumab. All adverse events should be graded per the Common Terminology for Adverse Events – Version 3.0 (CTCAE.v3.0). Treatment should be interrupted or discontinued for certain adverse events, as described below:*

##### 5.1.1 Hemorrhage

- Grade 2: Hold bevacizumab until bleeding resolves (grade 0). The patient should be taken off study if bleeding of grade 2 or worse recurs.
- Grade 3-4: Discontinue bevacizumab; the patient should be taken off study.

- 5.1.2 Thrombosis: Patient should be taken off study in the event of arterial thrombosis. For venous thrombosis requiring systemic anticoagulation, the patient should also be taken off study.

- 5.1.3 Hypertension
- Hypertension should be treated with anti-hypertensive medication as per general practice.
  - For **controlled** hypertension (<160/90 mmHg): continue therapy.
  - For persistent or symptomatic hypertension: hold bevacizumab therapy. If treatment is delayed for > 4 weeks due to uncontrolled hypertension, patients should be taken off study.
  - Grade 4 hypertension: The patient should be taken off study.
- 5.1.4 Proteinuria: Proteinuria of  $\geq 2+$  (as determined by urine dipstick) requires holding bevacizumab treatment and performing a 24-hour urine collection to determine total protein.
- If proteinuria is < 2 g/24 hours, continue bevacizumab.
  - If proteinuria is > 2 g/24 hours, the patient should be taken off study.
  - If nephrotic syndrome (G4) occurs, the patient should be taken off study.
- 5.1.5 Coagulopathy Grade 3 or 4: discontinue bevacizumab; the patient should be taken off study.
- 5.1.5 LFT abnormality (SGOT/SGPT, bilirubin)
- Grade 3 or 4: hold bevacizumab until < grade 1. If there is no recovery within 3 weeks, the patient should be taken off study.
  - If grade 3 or 4 LFT abnormality recurs, the patient should be taken off study.
- 5.1.6 Platelet count < 50,000/mm<sup>3</sup>: hold bevacizumab. If platelet < 50,000/mm<sup>3</sup> persists for 3 weeks, the patient should be taken off study.
- 5.1.7 Allergic reactions and cytokine release syndrome/acute infusion reaction:
- Patients who develop grade 2 allergic reactions with bronchospasm, or any grade 3/4 allergic/ infusional reactions should be taken off study.
  - For milder infusional reactions, follow instructions for bevacizumab administration in section 6.1.3.
- 5.1.8 Other grade 3/4 non-hematological adverse events: If a patient develops any grade 3 non-hematological adverse events (except controllable nausea/vomiting), bevacizumab should be held until symptoms resolve to  $\leq$  grade 1. If a grade 3 adverse event persists for > 3 weeks or recurs after resumption of the therapy, the patient will be taken off study. For Grade 4 adverse events (except controllable nausea/vomiting), the patient should be taken off study.

**5.2 5-Fluorouracil and Leucovorin Modifications** (all adverse events will be graded per CTCAE.v3.0)

- **Regimen A** (Roswell Park; bolus 5-FU/bevacizumab) **dose reduction steps**  
Dose reduction steps

	Standard Dose	Dose Level (- 1)	Dose Level (- 2)	Dose Level (- 3)
<b>5-FU Bolus</b>	500 mg/m <sup>2</sup>	400 mg/m <sup>2</sup>	320 mg/m <sup>2</sup>	250 mg/m <sup>2</sup>
<b>LV</b>	500 mg/m <sup>2</sup> (No dose reduction; however, dose will be delayed if 5-FU is delayed.)			

- **Regimen B** (de Gramont; infusional 5-FU/bevacizumab)  
Dose reduction steps

	Standard Dose	Dose Level (- 1)	Dose Level (- 2)	Dose Level (- 3)
<b>5-FU Bolus</b>	400 mg/m <sup>2</sup> /D	320 mg/m <sup>2</sup> /D	240 mg/m <sup>2</sup> /D	200 mg/m <sup>2</sup> /D
<b>5-FU CI</b>	600 mg/m <sup>2</sup> /D	500 mg/m <sup>2</sup> /D	400 mg/m <sup>2</sup> /D	300 mg/m <sup>2</sup> /D
<b>LV</b>	400 mg/m <sup>2</sup> (No dose reduction; however, dose will be delayed if 5-FU is delayed.)			

The table on the next page describes the recommended dose modifications during a course of therapy and at the start of each subsequent course of therapy. All dose modifications should be based on the worst preceding adverse events.

**Recommended 5-FU Dose Modifications - Regimens A and B**

<p align="center"><b>Adverse Event NCI Grade (Value) (based on CTCAE v3.0)</b></p>	<p align="center"><b>Dose Level for Subsequent Cycles Based on Interval Adverse Events in Previous Course</b></p>	<p align="center"><b>At Time of Re-treatment</b></p>
<p><b>No adverse event</b></p>	<p>Maintain dose level</p>	<p>Maintain dose level</p>
<p><b>Neutropenia (ANC)</b> Grade 1-2 (ANC 1,000-1,499/mm<sup>3</sup>) Grade 3-4 (ANC &lt; 500-999/mm<sup>3</sup>)</p>	<p>Maintain dose level ↓ 1 dose level of 5-FU</p>	<p>If ANC &lt;1500 at start of cycle, hold and check weekly then treat based on interval adverse events. If ANC &lt;1500 after 2 weeks, discontinue 5-FU.</p>
<p><b>Neutropenic fever</b> Grade 4 neutropenia &amp; ≥ grade 2 fever</p>	<p>↓ 1 dose level of 5-FU</p>	
<p><b>Thrombocytopenia (PLT)</b> 75,000-100,000/mm<sup>3</sup> 50,000-75,000/mm<sup>3</sup> 20,000- 50,000/mm<sup>3</sup> &lt; 20,000/mm<sup>3</sup></p>	<p>Maintain dose level ↓ 1 dose level of 5-FU ↓ 2 dose levels of 5-FU Off 5-FU</p>	<p>If PLT &lt;75,000 at start of cycle, hold and check weekly then treat based on interval adverse events. If PLT &lt;75,000 after 3 weeks, discontinue 5-FU.</p>
<p><b>Diarrhea</b> Grade 1-2 Grade 3-4</p>	<p>Maintain dose level ↓ 1 dose level of 5-FU</p>	<p>If grade ≥2 diarrhea at start of cycle, hold and check weekly then treat based on interval adverse events. If grade ≥2 diarrhea after 2 weeks, discontinue 5-FU.</p>
<p><b>Other non-hematologic adverse events</b> (Exceptions: alopecia, fatigue, anorexia, nausea/vomiting controlled by anti-emetics)</p>	<p>the same recommendations as for diarrhea above.</p>	
<p><b>Important:</b></p> <ul style="list-style-type: none"> <li>• Patient is off 5-FU/LV therapy if an adverse event requires a dose reduction beyond the two dose-reduction steps or if an adverse event requires dose reduction below dose level (-3).</li> <li>• If a patient experiences adverse event(s) requiring a dose reduction at the start of the next course, then the dose will remain lowered for that entire subsequent course. If that course is completed with no further adverse events &gt; grade 2, then the dose may be increased, at the investigator's discretion, one level at a time during an entire course, and in the following courses, until the patient again experiences an adverse event &gt; grade 2. When this occurs, the dose will remain one level lower than the dose that caused the adverse event for all subsequent courses.</li> <li>• There will be no dose reduction for leucovorin. However, if 5-FU is delayed or discontinued, leucovorin will be delayed or discontinued.</li> </ul>		

## 6. PHARMACEUTICAL INFORMATION

### 6.1 Bevacizumab

- 6.1.1 **Other Names:** rhuMAb VEGF, Avastin®
- Classification:** Recombinant humanized monoclonal antibody
- Molecular Weight:** Approximate molecular weight is 149,000 daltons
- Mode of Action:** Bevacizumab blocks the binding of vascular endothelial growth factor (VEGF) to its receptors resulting in inhibition of angiogenesis.
- Description:** Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody, consisting of 93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and murine antigen-binding complementarily-determining regions.
- How Supplied:** Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration. Each 100 mg (25 mg/mL – 4 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.
- Preparation:** Vials contain no preservatives and are intended for single use only. The calculated dose should be placed in a sterile, empty IV bag and diluted with a sufficient amount of 0.9% sodium chloride for injection to obtain a final volume of 100 mL.
- Storage:** Upon receipt, bevacizumab should be stored in the refrigerator (2° to 8° C). Do not freeze. Do not shake.
- Stability:** Shelf-life studies of bevacizumab are on-going. The sterile single use vials contain no antibacterial preservatives. Therefore, vials should be discarded 8 hours after initial entry.
- Once diluted in 0.9% sodium chloride, solutions of bevacizumab must be administered within 8 hours.

**Route of Administration:** Intravenous

### 6.1.2 **Reported Adverse Events and Potential Risks (a comprehensive list):**

- Infusional or allergic reaction:** fever, chills, rigor, rash, urticaria, dyspnea
- Cardiovascular:** hypertension (including hypertensive crisis), hypotension, pericardial effusion\*, decrease in cardiac function \*
- Hematologic:** arterial and venous thrombosis/embolism (including pulmonary embolism, mesenteric vein thrombosis, ischemic bowel, cerebral vascular accident); hemorrhage (including epistaxis, CNS bleeding, GI bleeding, hemoptysis, pulmonary hemorrhage).
- Constitutional:** headache, infection without neutropenia, asthenia
- Skin:** rash, urticaria, delay in wound healing or dehiscence of healed wound
- Gastrointestinal:** nausea, vomiting, colitis, stomatitis/pharyngitis, intestinal

obstruction\*, bowel perforation, bowel anastomotic dehiscence.

**Hepatic:** LFT abnormalities  
**Pulmonary:** pulmonary infiltration\*, dyspnea  
**Renal/Genitourinary:** proteinuria, nephrotic syndrome  
**Musculoskeletal:** arthralgia, chest pain

\* indicates reported events where the relationship to bevacizumab is unclear

Note: Additional adverse events may be associated with combination chemotherapy.

### 6.1.3 Method of Administration:

The initial dose should be administered over a minimum of 90 minutes. If no adverse events occur, the second dose should be administered over a minimum of 60 minutes. If no adverse events occur after the second dose, all subsequent doses should be administered over a minimum of 30 minutes. If infusion-related adverse events occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

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

1. When the bevacizumab infusion is complete, an additional 50 mL of 0.9% sodium chloride for injection should be added to the bevacizumab infusion bag. The infusion should continue until a volume equal to that of the volume contained in the tubing has been administered.

**Or**

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

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

### 6.1.4 Availability

Bevacizumab is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. Bevacizumab is provided to the NCI under a Cooperative Research and Development Agreement (CRADA) between Genentech, Inc. and the DCTD, NCI (see Appendix C). Sufficient agent will be available for this protocol to treat about 50 patients/month. Unless there is evidence to suggest that the study regimen is ineffective, the protocol will remain open to patient accrual until about 1 month after bevacizumab has been approved by the FDA and commercial supplies have reached local wholesalers.

### 6.1.5 Agent Ordering

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that the agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of PMB-distributed agents between institutions (unless prior approval from PMB is obtained).

The CTEP-assigned protocol number must be used for ordering all CTEP-supplied

investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD, through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Due to limited agent supply, starter supplies will NOT be sent for this protocol. Once a patient has been enrolled and a TRC patient ID number (e.g., TRC-MD000-001) has been assigned, an initial protocol-specific supply of bevacizumab may be ordered by completing an NCI Clinical Drug Request Form (NIH-986) and faxing it to the Pharmaceutical Management Branch (PMB) at (301) 480-4612. The NCI Clinical Drug Request Form is available on the NCI home page (<http://ctep.cancer.gov>) or by calling PMB at (301) 496-5725. The TRC patient ID number must be listed in the "Patient or Special Code" field for all patients for whom bevacizumab is being ordered.

#### 6.1.6 Agent Accountability

The Investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record (DAR) Form. See the CTEP website for Policy and Guidelines for Accountability and Storage of Investigational Drugs at: <http://ctep.cancer.gov/requisition/guidelines.html>.

## 6.2 Commercial Agents

### 6.2.1 5-Fluouracil (5-FU)

**Product description:** Commercially available in 500 mg/10 mL ampules and vials, and 1 g/20 mL, 2.5 g/50 mL, and 5 g/100 mL vials.

**Preparation and storage:** Stable for prolonged periods of time at room temperature if protected from light. Note manufacturer's expiration date. Inspect for precipitate; if apparent, agitate vial vigorously or gently heat to not greater than 140°F in a water bath. Do not allow to freeze. Please refer to the package insert for preparation instructions.

**Route of administration:**

Regimen A: To be infused as an IV bolus (slow push).

Regimen B: To be infused as an IV bolus followed by an IV infusion via ambulatory pump of choice over 22 hours.

**Expected adverse events:** Expected adverse events that may be dose limiting include myelosuppression, diarrhea, and mucositis. Nausea, vomiting, anorexia, alopecia, cerebellar syndrome, dermatologic, and ophthalmic reactions also occur. Please refer to the package insert for a complete list of adverse events.

### 6.2.2 Leucovorin Calcium (LV)

**Product Description:** Commercially available as a lyophilized product in 50 mg, 100 mg, 200 mg, 350 mg, and 500 mg vials. Also available as a 10 mg/mL solution in 100 mg and 250 mg vials.

**Preparation and Storage:** Store the intact vials at controlled room temperature. Note manufacturer's expiration date. Reconstitute as per manufacturer's instructions. Solutions further diluted in normal saline, 5% dextrose, 10%

dextrose, Ringer's injection or Lactated Ringer's injection are stable for 24 hours at room temperature.

**Route of Administration:** IV over 2 hours (both Regimen A and Regimen B)

**Expected Adverse Events:** Nausea, diarrhea, thrombocytosis, rash, hives, pruritus, headache, and wheezing may occur. Please refer to the package insert for a complete list of adverse events.

7. **CORRELATIVE/SPECIAL STUDIES** - Not applicable.

8. **STUDY CALENDAR**

During study, patients will be seen by a physician every 4 weeks. The schedule for the tests and procedures associated with this protocol is provided below.

	Screen <sup>1</sup>	Treatment Period																Study Termination <sup>7</sup>
Cycle Number		Cycle 1 (week)								Cycle 2 through termination								
Week		1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8	
Informed consent	x																	
Medical history	x																	
Serum pregnancy test <sup>2</sup>	x																	
Complete physical exam	x	x				x				x				x				x
Vital signs, weight <sup>3</sup>	x	x		x		x		x		x		x		x		x		x
CBC /differential <sup>3</sup>	x	x		x		x		x		x		x		x		x		x
Serum LFT, BUN, creatinine <sup>3</sup>	x	x				x				x				x				x
Urinalysis for proteinuria <sup>4</sup>	x	x				x				x				x				x
PT/PTT <sup>5</sup>	x																	
Clinical assessment –for Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Tumor assessments <sup>6</sup>	x								x								x	x
Bevacizumab administration (Regimens A and B)		x		x		x		x		x		x		x		x		
5-FU/Leucovorin administration (Regimen A)		x	x	x	x	x	x			x	x	x	x	x	x			
5-FU/Leucovorin administration (Regimen B)		x		x		x		x		x		x		x		x		

1. Baseline evaluations are to be done ≤ 14 days prior to start of study therapy; scan/x-ray ≤ 28 days before the start of therapy. If the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of therapy.
2. Pregnancy test is for women with child-bearing potential only.
3. Vital signs (especially blood pressure), clinical status and laboratory tests should be reviewed before study treatment. Treatment modifications of bevacizumab and chemotherapy should follow guidelines in Sections 5.1 and 5.2.
4. Proteinuria of > 1+ on urinalysis should lead to determination of 24-hour urine protein (see Section 5.1.4).
5. PT/PTT should be repeated at least monthly if the patient is receiving warfarin.
6. If criteria of PR or CR are met, a confirmation by repeat assessments no less than 4 weeks apart is required before a PR or CR status is assigned (see Section 9.4.1).
7. Patients who have an on-going agent-related serious adverse event upon study completion or at discontinuation of the study will be contacted by the investigator or his/her designee every 2 weeks until the event is resolved or determined to be irreversible.

**9. MEASUREMENT OF EFFECT**

**For the purposes of this study, patients should be restaged every 8 weeks.**

**9.1. Definitions**

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy.

### 9.1.1 Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as  $\geq 20$  mm with conventional techniques (CT, MRI, x-ray) or as  $\geq 10$  mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

### 9.1.2 Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter  $< 20$  mm with conventional techniques or  $< 10$  mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

### 9.1.3 Target lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

### 9.1.4 Non-target lesions

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required but the presence or absence of each should be noted throughout follow-up.

## 9.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

**Clinical lesions.** Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

**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 is preferable.

**Conventional CT and MRI.** These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

**Ultrasound (US).** When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

**Endoscopy, Laparoscopy.** The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained.

**Tumor markers.** Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific additional criteria for standardized usage of prostate-specific antigen (PSA) and CA-125 response in support of clinical trials are being developed.

**Cytology, Histology.** These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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.

**9.3 Response Criteria**

**9.3.1 Evaluation of target lesions**

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

**9.3.2 Evaluation of non-target lesions**

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of “non-target” lesions only is exceptional, in such circumstances the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

9.3.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see Sections 9.3.1 and 9.4.1).

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note:

- C Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration.” **Every effort should be made to document the objective progression, even after discontinuation of treatment.**
- C In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (e.g., fine needle aspirate/biopsy) before confirming the complete response status.

9.4 Confirmatory Measurement/Duration of Response

9.4.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks (see Section 9.3.3).

9.4.2 Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

**9.4.3 Duration of Stable Disease**

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

**9.5 Progression-Free Survival**

Time-to-tumor progression is defined as the time from start of therapy to documentation of disease progression (see Section 9.3). Patients who die without documentation of progression will be considered to have had tumor progression at the time of death unless there is documented evidence that no progression occurred before death. Patients who fail to return for evaluation after beginning therapy will be non-evaluable for progression on the last day of therapy. Patients who experience major treatment violations will be censored for progression on the date the treatment violation occurred.

In patients with a confirmed CR who discontinue therapy and then restart therapy upon evidence of progression, time to tumor progression will be defined as the time from start of therapy to documentation of further disease progression following the re-initiation of therapy.

**9.6 Survival**

Survival will be measured from the day 1 of the study therapy.

**10. STATISTICAL CONSIDERATIONS**

**10.1 Response Variables (Objectives)**

**10.1.1 Primary Objective**

The primary objective of this protocol is to evaluate the response rate. Data will also be collected for time to progression, adverse events and overall survival associated with bevacizumab in combination with 5-FU/LV in patients who have progressive disease after treatment with irinotecan- and oxaliplatin-based chemotherapy regimens.

**10.1.2 Other Objectives**

Provide investigational therapy to physicians for the management of individual patients with advanced colorectal cancer who are no longer benefiting from standard, effective treatment regimens.

**10.2 Statistical Analysis**

**10.2.1 Study Design**

This is a multicenter, open-label, study of bevacizumab administered in combination with 5-FU/LV as third-line therapy for patients with metastatic colorectal cancer. Patients on this study can receive either of the following two regimens: Regimen A – bevacizumab/bolus 5-FU/LV (Roswell Park regimen) or Regimen B – bevacizumab/infusional 5-FU/LV (de Gramont regimen).

The following two-stage study design will be used.

	Cumulative number of responses	Decision
Stage 1: 35 patients*	0	The study regimen is inactive. Terminate the trial

	1 or more	Inconclusive result. Continue observation in more patients (Stage 2)
Stage 2: 65 patients (Total of 100 patients in Stage 1 and 2)*	4 or fewer	The study regimen is not effective. No further patient accrual
	5 or more	The regimen meets the target level of activity. Resume accrual until bevacizumab is commercially available
* Accrual will be suspended for response observation after completion of the stage 2 accrual, until $\geq 5$ responses have been documented. Accrual will not be suspended between stage 1 and stage 2. However, response data will be collected on an on-going basis. If cumulative data reveals no response in the first 35 evaluable patients, the study may be terminated before stage 2 has been completed.		

This approach allows for a distinction between response rates of 10% vs 2% with the probability of type I and type II errors both under 0.05. This design yields at least 95% power to continue the protocol beyond stage 2 if the true response rate is at least 10%, and at least 95% probability of terminating the protocol early if the true response rate is no more than 2%, with at least 49% probability of termination based on the initial 35 patients.

**10.2.1 Sample Size**

Allowing for 20% of ineligible or non-evaluable cases, a total of 125 patients will be accrued to the initial phase (stage 1 and stage 2). The accrual rate is expected to be approximately 50 patients/month. Thus, it is expected it would take about 3 months to accrue 125 patients. If activity is observed, accrual will resume at a maximum of 50 patients/month, without a cap on the total sample size, until bevacizumab is commercially available.

**10.2.3 Data Collection**

Data will be collected during the treatment of these patients as well as during their follow-up in order to gain additional information concerning the efficacy and adverse events of bevacizumab in this population. The primary indicator of efficacy will be the frequency of response, duration of time-to-progression and survival. Because overall survival is of interest, follow-up of these patients until death is required.

**10.3 Safety Analysis**

All patients who receive any amount of protocol treatment in this study will be included in the on-going safety analysis. The incidence of adverse events will be recorded and classified according to body region and severity. The safety analysis will be performed on the total sample size and in an explanatory fashion within the two protocol-specified treatment regimens.

SAEs will be collected through the *AdEERS system*, and the *Advanced Disease Off-Treatment Form*. Safety data will be monitored by the CTEP drug monitor on an on-going basis. Periodic review of safety and efficacy will also be conducted by the Principal Investigator together with staff members of the CTEP Investigational Drug Branch and the Clinical Investigations Branch.

## 10.4 Analysis of Primary Objectives

**Response:** The RECIST criteria will be used in the evaluation of response. The estimate of the overall response rate (as evaluated by the study investigator), together with 95% confidence intervals, will be computed based on the collected data. The response rate will be calculated as the ratio of the number of patients who demonstrated response divided by the number of patients evaluable for response.

**Evaluability for response:** patients will be considered evaluable for response if they meet the following criteria:

- The patient is eligible
- The patient has measurable disease
- The patient has received the study therapy

**Time-to-progression and Survival:** All patients will be followed for survival, which will be measured from the beginning of 5-FU/LV/ bevacizumab until death. Survival data for all patients still alive at the time of the analysis or lost to follow-up will be censored at the last contact date. Kaplan-Meier methodology will be used to obtain the survival estimates, median survival time, and 95% confidence intervals. Time-to-progression will be defined from the beginning of protocol therapy until documented progression.

The above analyses will be performed on the total sample and, in an exploratory fashion, within the two protocol-specified treatment regimens.

## 11. REGULATORY AND DATA REPORTING REQUIREMENTS

### 11.1 Adverse Event Reporting

11.1.1 **Mechanisms of Adverse Event (AE) reporting:** AEs in this trial are reported in two ways:

1. Serious Adverse Events (SAEs) that meet the criteria for Expedited Reporting should be reported through the AdEERS system (see Section 11.2); and
2. All AEs listed on the “*Advanced Disease Off-Treatment Form*” (Appendix D) that the patient experiences during the course of this study must be recorded on this form at the conclusion of study therapy, even if the AEs have already been reported through the AdEERS system.

11.1.2 **Grading of AEs** for this protocol will be based on the revised NCI Common Terminology Criteria for Adverse Events version 3.0 (**CTCAE v3.0**). All treatment areas should have access to a copy of the CTCAE v3.0. A copy of the CTCAE v3.0 can be downloaded from the CTEP website at: <http://ctep.cancer.gov/reporting/ctc.html>.

11.1.3 **Use the following guidelines for AE reporting:**

- Identify the grade of an AE using the CTCAE v3.0
- Determine whether the AE is “**Expected**” or “**Unexpected**” according to Table 11.2.2 (List of AdEERS “Expected AEs”) or is an exception to the AdEERS reporting (see Section 11.2.1)
- Determine the attributions of the AE.
  - Definite – The adverse event *is clearly related* to the study regimen
  - Probable – The adverse event *is likely related* to the study regimen
  - Possible – The adverse event *may be related* to the study regimen
  - Unlikely – The adverse event *is doubtfully related* to the study regimen

- Unrelated – The adverse event *is clearly NOT related* to the study regimen

**11.2 Expedited Adverse Event Reporting through AdEERS**

Questions about AdEERS reporting can be directed to AdEERSMD at 301-897-7476.

Expedited AE Reporting for this study is via AdEERS (Adverse Event Expedited Reporting System) and should follow the guidelines in Section 11.2.1. A more detailed description of the reporting procedures can be found in the “NCI Guidelines: Expedited Adverse Event Reporting Requirements for NCI Investigational Agents,” which can be downloaded from the CTEP website at: <http://ctep.cancer.gov/reporting/adeers.html>.

Expedited reports are submitted to CTEP via the secure AdEERS application which can be accessed via the CTEP website at: [https://webapps.ctep.nih.gov/openapps/plsql/qadeers\\_main\\$.startup](https://webapps.ctep.nih.gov/openapps/plsql/qadeers_main$.startup).

**Note: AdEERS reporting prior to 10/15/03:**

*CTCAE v3.0 will not be available on the AdEERS website prior to October 15, 2003. Until then, all AdEERS reporting will be associated with CTC v2.0. Please use the following guidelines:*

- *Refer to CTCAE v3.0 to find the AE that needs to be reported. Most, but not all, of the AE terms and categories in CTCAE v3.0 match those in CTC v2.0; (matching of the two versions can be found on <http://ctep.cancer.gov>).*
    - *If there is an exact match, use the appropriate CTC v2.0 AE and its grading scale for reporting.*
    - *If CTCAE v3.0 term and grade are different from CTC v2.0, use the “Other-Specify” AE term at the end of the appropriate CATEGORY and supply the correct CTCAE v3.0 terms and grades.*
- Example 1: Perforation (GI) in CTCAE v3.0 is not an AE term in CTCv2.0. Therefore, Perforation (GI) should be reported under “Other (specify)” under the GI Category in CTC v2.0.*
- Example 2: Hemorrhage (nose) in CTCAE v3.0 will be reported under Epistaxis in CTC v2.0.*

**11.2.1 AdEERS Expedited Reporting Guidelines for serious Adverse Events**

Attribution	Grade 2	Grade 3		Grade 4		Grade 5 <sup>a</sup>	
	Unexpected	Unexpected	Expected	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely		AdEERS if Hospitalized	AdEERS if Hospitalized	24-Hr Report and AdEERS	AdEERS	24-Hr Report and AdEERS	AdEERS
Possible, Probable, Definite	AdEERS	AdEERS	AdEERS if Hospitalized				
a. This includes all deaths within 30 days of the last dose of treatment with an investigational agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with an investigational agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must also be reported via AdEERS							

- 24-Hr Report: Please complete a 24-Hour Notification Report via the NCI AdEERS website (<http://ctep.cancer.gov/reporting/adeers/html>).
- AdEERS: Indicates an expedited report is to be submitted within 10 working days of learning of the event. Report through the same website above (<http://ctep.cancer.gov/reporting/adeers/html>)
- Hospitalization: Any grade 3, 4, or 5 adverse event that precipitates or prolongs a hospitalization must be submitted via AdEERS within 10 working days of learning of the event, regardless of requirements of the study phase, grade, the attribution, or whether the event is expected or unexpected.
- **See Table 11.2.2. for a list of AdEERS “Expected” AEs. See below for a list of “Exceptions” to AdEERS reporting for this protocol.**
- **Questions about AdEERS reporting can be directed to AdEERSMD at 301-897-7476**

**Exceptions to AdEERS reporting:**

The SAEs listed below Do NOT require AdEERS reporting, including hospitalization for these events

- Grade 1-4 neutrophils/granulocytes
- Grade 1-4 leukocytes
- Grade 1-4 febrile neutropenia
- Grade 1-4 diarrhea and associated electrolyte imbalances
- Grade 1-4 dehydration
- Grade 1-4 nausea/vomiting
- Grade 1-4 mucositis, or esophagitis, or somatitis/pharyngitis, or dysphagia
- Grade 1-4 fatigue
- Grade 1-3 rash: hand and foot reaction
- Grade 1-4 pain

11.2.2 List of AdEERS “Expected” AEs

<ul style="list-style-type: none"> <li>All Adverse Events listed below are defined as “<b>Expected</b>” for the purpose of Expedited Reporting. They should be reported as per Section 11.2.1</li> </ul>	
CTCAE v3.0 CATEGORY	Adverse Event Terms
BLOOD/BONE MARROW	Hemoglobin Platelets
CARDIAC (GENERAL)	Hypertension
CONSTITUTIONAL	Rigors/chills
DERMATOLOGY/SKIN	Rash/ Desquamation Hand-foot skin reaction Urticaria
GASTROINTESTINAL	Ileus
HEMORRHAGE	Hemorrhage/GI Hemorrhage/ nose Hemorrhage/other Hemorrhage/CNS Hemorrhage/ pulmonary
INFECTION	Infection (documented) with grade 1 or 2 neutropenia or normal ANC Infection (documented) with grade 3 or 4 neutropenia Infection with unknown ANC
METABOLIC/ LABORATORY	Proteinuria SGOT/SGPT
VASCULAR	Thrombosis/embolism

11.2.3 Secondary AML/MDS

Investigators are required to report cases of secondary AML/MDS occurring on or following treatment on NCI-sponsored protocols using the NCI/CTEP Secondary AML/MDS Report Form. This form can be downloaded from the CTEP website at: <http://ctep.cancer.gov/reporting/index.html>. Non-AML/MDS secondary malignancies should NOT be reported via AdEERS but should be submitted as part of the study results via routine CDUS reporting.

11.3 Data Reporting for this trial

11.3.1 Data reporting forms should be submitted as follows:

FORM	SUBMISSION SCHEDULE
Registration Form*	Prior to enrollment
Colorectal Cancer – Advanced Disease On-Study Form*	Within 14 days of initiation of protocol therapy.
Colorectal Cancer – Advanced Disease Off-Treatment Form*	Within 14 days of completion of protocol therapy
Colorectal Cancer - Long-term Follow-up Form*	Every 3 months during protocol treatment and every 6 months thereafter for 2 years or until death

\* A printout of these forms can be found in Appendix D. **These forms can be accessed at:** <http://spitfire.emmes.com/study/trc/>

11.3.2 **Data will be provided to the NCI by completing the forms using a web-based data entry system or forms can be sent to:**

TRC Data and Statistical Center  
The EMMES Corporation  
401 N. Washington Street, Suite 700  
Rockville, MD 20850  
Phone : (301) 251-1161  
Fax: (202) 478-0163  
E-mail: [TRCPM@emmes.com](mailto:TRCPM@emmes.com)  
Website: <http://spitfire.emmes.com/study/trc/>

11.3.3 **Patient records and quality assurance.**

As a quality assurance measure for the treatment delivered on this protocol, primary patient records may be reviewed. The records to be examined will be selected retrospectively and at random. Complete records must therefore be maintained on each patient treated on this protocol. These records should include the primary source documentation (e.g., laboratory report slips, X-ray reports, scan reports, pathology reports, physician notes, etc.) which confirm that:

11.3.3.1 The patient met each eligibility criterion.

11.3.3.2 Signed informed consent was obtained prior to enrollment.

11.3.3.3 Treatment was given according to protocol (e.g., dated notes about doses given; any reasons for dose modifications).

11.3.3.4 Adverse events were assessed according to protocol (e.g., laboratory report slips, etc.).

11.3.3.5 Response was assessed according to protocol (i.e., using X-rays, scan, lab reports, bone marrow aspiration/biopsy, dated notes on measurements and clinical assessment, as appropriate). If an objective response is documented for a patient, every effort should be made to obtain copies of the relevant scans for future review.

11.3.3.6 NCI Drug Accountability Records were maintained.

11.3.4 **Methods of Review:** In general, reviews will take place either via mail or through on-site audits. For data that may be pivotal in making future decisions regarding agent development or the treatment of this disease, investigator meetings may be held in Bethesda.

Mail review: Copies of selected reports which document critical data items will be requested by mail.

On-site audit: NCI staff or their official representatives may visit the treating physician's office and examine the primary patient records. The treating physician will be given at least two weeks notice of such a visit and notified of the patient records that will be requested for review at that time.

#### 11.4 Special Regulatory Considerations:

- 11.4.1 The Privacy Rule is a Federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information. It is administered and enforced by the Department of Health and Human Services (DHHS), Office for Civil Rights (OCR). The Privacy Rule complements existing regulations for the protection of human subjects as found in the Common Rule (45CFR46) and FDA Regulations (21CFR50); it does not modify nor replace these current regulations. Covered entities must comply with the Privacy Rule by April 14, 2003. **All institutions participating in this trial should comply with the HIPAA guidelines during the registration process and data reporting.**
- 11.4.2 This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines. Proof of local IRB approval must be provided to NCI before the site can activate the trial and register a patient. IRB approval should be submitted to TRC via fax at 301-402-4870 [Telephone 301-496-5725].

#### 12. REGISTRATION GUIDELINES:

**Important:**

- Patient must be registered within 2 weeks prior to initiation of study therapy.
- Before an institution can register a patient, the NCI must have received proof of local IRB approval of this protocol.
- Institutions registering a patient should follow the HIPAA requirements and guidelines.
- All enrolling physicians must be registered with the NCI (see Section 6.1.5).
- Registration instructions in Section 12.1 should be followed until the lottery system is activated upon further notification from the NCI.

##### 12.1 Registration procedures for the first 125 patients and BEFORE activation of the lottery system.

- 12.1.1 Until a lottery system is activated, **all possible candidates should be screened and enrolled by an enrolling physician at a participating center** (See guidelines and a schema on next page).

Primary physicians outside the participating centers may contact the Treatment Referral Center (TRC) at NCI (301-496-5725) to discuss the eligibility requirements for the protocol.

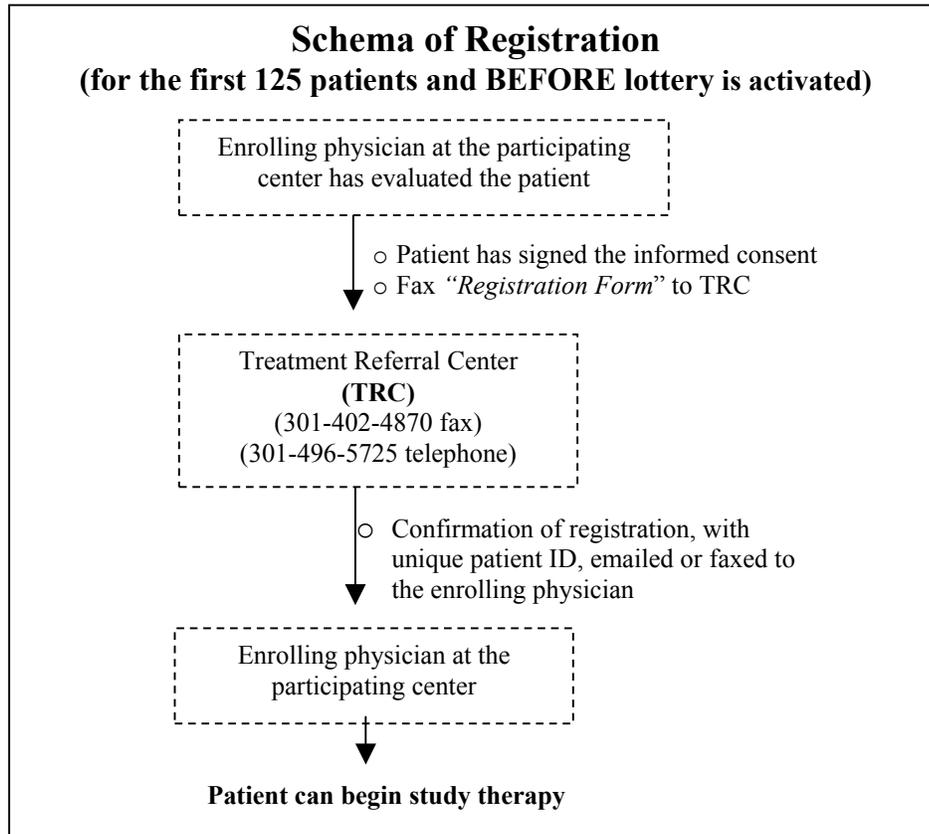
If a patient appears to be eligible and wants to participate in the study, the primary physician will be directed to an enrolling physician at the nearest participating center. The enrolling physician's contact information will be provided by the TRC.

- 12.1.2 **To enroll a patient**, the enrolling physician at the participating center must obtain a signed Informed Consent Form, and fax a completed and signed "*Registration Form*" to the Treatment Referral Center at **(301) 402-4870**. The "*Registration Form*" can **only** be accepted if it is signed and submitted by the enrolling physician at a participating center.

- 12.1.2.1 **After a patient is enrolled** (if eligible), a unique patient ID number will be assigned (i.e., TRC-MD000-001), and a confirmation of registration will be faxed or e-mailed to the enrolling physician at the participating site. Please note that a patient may **NOT** begin treatment with bevacizumab until a patient ID number is assigned and the confirmation of registration is received.

- 12.1.2.2 Upon initiation of study therapy, the enrolling physician must complete the “Advanced Disease On-Study Form” (Appendix D). This form should be submitted to TRC Data and Statistical Center at EMMES (through the web-based data entry system) within **14 days of starting therapy**.

TRC Data and Statistical Center  
 The EMMES Corporation  
 401 N. Washington Street, Suite 700  
 Rockville, MD 20850  
 Phone : (301) 251-1161  
 Fax: (202) 478-0163  
 E-mail: [TRCPM@emmes.com](mailto:TRCPM@emmes.com)  
 Website: <http://spitfire.emmes.com/study/trc/>



- 12.2 **Registration procedures AFTER the activation of lottery** (the following procedures for lottery enrollment are **NOT** to be used until NCI notifies the participating centers that the lottery system is activated)

If activity of this study regimen is observed (i.e., at least 5 responses seen in the first 100 evaluable patients), this protocol will continue to accrue patients until bevacizumab is commercially available. Since the agent supply of the agent is limited, there may be a need for random patient selection through a lottery system. If a lottery system is necessary, the NCI will notify the participating sites and referring physicians to follow the procedures for lottery enrollment as described below (**see Schema in Section 12.2.3.1**).

- 12.2.1 **To enter a patient in the lottery** for the trial, the *“Preliminary Eligibility Screening and Lottery Entry Form”* (Appendix E) should be signed and submitted by the enrolling physician at the participating center to the Treatment Referral Center (TRC) at **(301) 402-4870**. The patient must have also signed the *“Lottery Authorization Form”* (Appendix E) before the *“Preliminary Eligibility Screening and Lottery Entry Form”* can be submitted for lottery enrollment.

For referrals from primary physicians outside the participating centers, it is allowable for the enrolling physician at the participating center to enter the patient in the lottery before seeing the patient **provided** that the following procedures are followed: **(1)** the patient has signed the *“Lottery Authorization Form,”* **(2)** the primary physician has performed the eligibility screening and signed the *“Preliminary Eligibility Screening and Lottery Entry Form”* (which will be faxed to the enrolling physician), and **(3)** the enrolling physician at the participating center has reviewed and co-signed the *“Preliminary Eligibility Screening and Lottery Entry Form”*. Please note that this form is acceptable **only** if signed and submitted by the enrolling physician at the participating site.

- 12.2.2 The **selection program** will be run once a week. For any given week, patients entered into the lottery from the start-of-business on Monday (8:30 am Eastern Time) through the close-of-business on Friday (4:30 pm Eastern Time) will be eligible. The selection program will be run the following Monday and the enrolling physician will be notified of the results of the lottery prior to the close-of-business on Monday. It is estimated that the available supplies of bevacizumab are sufficient to allow approximately 50 patients per month (or 12-13 patients per week) to be randomly selected from the total number of eligible patients. All patients entered into the lottery will have an equal chance of being selected.

- 12.2.2.1 **If the patient is “selected” by lottery**, a unique patient ID number will be assigned (i.e., TRC-MD000-001), which will be faxed or e-mailed to the enrolling center. The patient must travel to the participating center for a complete evaluation by the enrolling physician and to receive the study treatment (5-FU / LV/ bevacizumab).

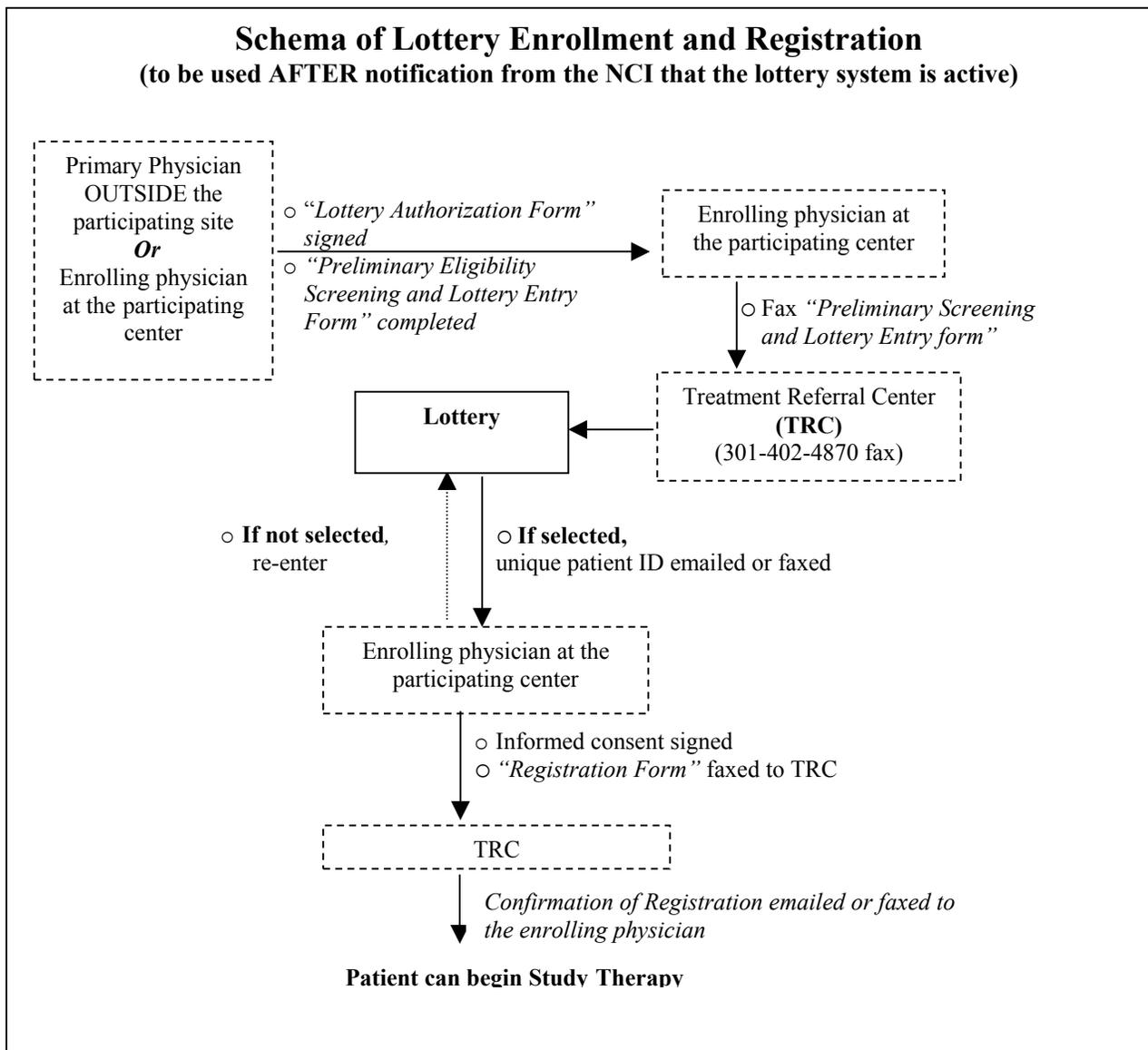
- 12.2.2.2 **Before** a patient is treated, the enrolling physician must obtain a signed *“Informed Consent Form”* and complete the *“Registration Form”* to confirm eligibility of the patient. The *“Registration Form”* must be faxed to TRC at (301) 402-4870 no more than **2 weeks** after the patient is selected by the lottery. **Please note that a patient may NOT begin treatment with bevacizumab until the “Registration Form” is submitted to TRC and a confirmation of registration is received by the enrolling physician.**

- 12.2.2.3 **Upon initiation of study therapy**, the enrolling physician must complete the *“Advanced Disease On-Study Form”* (Appendix D). This form should be submitted to TRC Data and Statistical Center at EMMES through the web-based data entry system **within 14 days of starting therapy.**

TRC Data and Statistical Center  
The EMMES Corporation  
401 N. Washington Street, Suite 700  
Rockville, MD 20850  
Phone : (301) 251-1161  
Fax: (202) 478-0163  
E-mail: [TRCPM@emmes.com](mailto:TRCPM@emmes.com)  
Website: <http://spitfire.emmes.com/study/trc/>

12.2.3 If the patient is “**not selected**”, the patient can be re-entered in the lottery for the following week’s selection **provided** that he/she still meets the eligibility requirements and still desires to be entered on the protocol. The re-entry process will be repeated until he/she is selected.

12.2.3.1 By close-of-business on Monday (4:30 pm Eastern Time), the enrolling physician will receive a spreadsheet listing the patients they registered the preceding week who were not selected. **The enrolling physician should indicate on the spreadsheet those patients who are no longer eligible for the trial or do not wish to re-enter the lottery for the following week.** The spreadsheet should be returned to EMMES via fax at (202) 478-0163 or by e-mail ([TRCPM@Emmes.com](mailto:TRCPM@Emmes.com)) prior to close-of-business on Wednesday (4:30 pm Eastern Time). Those patients whom the enrolling physician wishes to treat with an alternate treatment regimen should NOT be re-entered in the lottery.



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## Model Informed Consent

**TITLE: Protocol TRC-0301: A Multicenter Study of the Anti-VEGF Monoclonal Antibody Bevacizumab (Avastin<sup>®</sup>) Plus 5-Fluorouracil/Leucovorin in Patients with Metastatic Colorectal Cancer that Have Progressed after Standard Chemotherapy**

### **PARTICIPANTS:**

You are being asked to take part in this research study because you have advanced cancer of the colon or rectum that has grown even after standard treatment.

This is a clinical trial (a type of research study). Clinical trials include only patient who choose to take part. This is an important form. Please read it carefully. It tells you what you need to know about this study. Please take your time to make your decision. Discuss it with your friends and family. If you agree to take part in this research study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. It also means that you want to take part in this study.

### **Why is this study being done?**

The purpose of this clinical trial is to find out if adding bevacizumab (Avastin<sup>®</sup>), an experimental agent, to a chemotherapy regimen of 5-fluorouracil and leucovorin is useful for patients who have already received standard chemotherapy for their advanced cancer of the colon or rectum. Bevacizumab is an agent that blocks the action of a protein called “vascular endothelial growth factor”, or VEGF. It was designed to decrease a tumor’s blood supply and reduce its growth. Bevacizumab is not yet approved for commercial use by the US Food and Drug Administration (FDA).

Researchers conducted a large clinical study using bevacizumab in the United States. They added bevacizumab to one of the standard chemotherapy regimens for patients with untreated metastatic colorectal cancer. The group of patients who received bevacizumab combined with chemotherapy survived longer than the patients who received chemotherapy alone.

Although the addition of bevacizumab was shown to help patients with untreated metastatic colorectal cancer, we do not yet know if adding bevacizumab to chemotherapy is also useful for patients who have already received standard chemotherapy for their advanced colorectal cancer. That is what this study will try to find out.

### **How many people will take part in the study?**

Between 35 and 125 patients will take part in the study initially. If it appears that bevacizumab in combination with 5-fluorouracil and leucovorin is useful in patients whose advanced colorectal cancer has grown even after standard treatment, the study will remain open until bevacizumab becomes commercially available in the United States.

## What is involved in the study?

The study will involve the following tests and treatment procedures. Some of these tests would be done even if you did not take part in the study.

### Tests

- Blood tests – before study and every 4 weeks while on study
- Physical examination – before study and every 4 weeks while on study
- X-rays or scans for tumor measurement – before study and every 8 weeks while on study
- Urinalysis – before treatment and every 4 weeks during treatment

### TREATMENT

All the drugs used in this study to treat your cancer (5-fluorouracil, leucovorin, and bevacizumab) will be given through the vein (intravenously) while you are in the doctor's office or clinic. The doses of the drugs may be changed if you experience side effects.

You will receive all the study drugs using one of two treatment schedules, depending on whether the 5-fluorouracil (5-FU) is given to you as a “bolus” (Regimen A) or a “continuous infusion” (Regimen B). Your doctor will review your previous treatment history and current medical condition, and decide with you which way to administer 5-FU and at what dose. Each treatment schedule is described below.

#### Regimen A (Study treatment with “Bolus” administration of 5-FU):

Each cycle of treatment consists of 8 weeks.

- Bevacizumab will be given through the vein on Day 1 every 2 weeks throughout the study.
  - The first infusion of bevacizumab will be given over 90 minutes. If you tolerate this well, the second time it is given, the infusion time will be shortened to 60 minutes. If the second infusion is well tolerated, all subsequent infusions will be shortened to 30 minutes.
- Leucovorin (LV) and 5-FU will be given once a week for 6 weeks out of the 8-week cycle. That is: 5-FU/LV on Day 1 of week 1 through week 6; no 5-FU/LV during weeks 7 and 8.
  - LV will be given through your vein over 2 hours, followed by a “bolus” or shorter infusion of 5-FU.

#### Regimen B (Study treatment with “Continuous Infusion” of 5-FU):

Each cycle of treatment consists of 8 weeks.

- Bevacizumab will be given through the vein on Day 1 every 2 weeks throughout the study.
  - The first time bevacizumab is administered, it will be given over 90 minutes. If you tolerate this well, the second time it is given, the infusion time will be shortened to 60 minutes. If the second infusion is well tolerated, all subsequent infusions will be shortened to 30 minutes.
- The leucovorin will be given through a vein over 2 hours on Day 1 and Day 2, every two weeks. 5-FU will be given as an injection followed by a “continuous infusion” over 22 hours on Day 1 and Day 2, every 2 weeks.
  - The 22-hour infusion of 5-FU will be given using a special catheter in your vein (referred to as a “central catheter” or “port”) and a small portable infusion pump. The placement of

the central catheter will be done by a surgeon or other medical professional trained in catheter placement.

## How long will I be in the study?

You will be in the study as long as you benefit from the study treatment and do not have unacceptable side effects. Your doctor may decide to stop your participation in the study if:

- Your cancer worsens
- You have serious side effects
- Your health otherwise worsens
- New information on treating cancer of the colon or rectum becomes available.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to your cancer doctor first.

**The Cancer Center Physicians would also like to follow your progress after you have stopped the study treatment. They will contact you or your primary physician/oncologist every 6 months to find out how you are doing.**

## What are the risks of the study?

While on the study, you are at risk for the following side effects. You should discuss these with your cancer doctor. There may also be other side effects that we cannot predict. Other drugs may be given to make side effects less serious and less uncomfortable. Many side effects go away shortly after the intravenous injections are over, but in some cases side effects can be serious or long-lasting or fatal.

### **5-Fluorouracil with Leucovorin:**

#### Very Likely

- Low numbers of white blood cells (may make you likely to get infections)
- Low numbers of platelets (may make you more likely to have bruising or bleeding)
- Low numbers of red blood cells (may make you feel weak or tired)
- Diarrhea, nausea, vomiting, dehydration; loss of appetite
- Fatigue
- Abdominal pain or cramps
- Mouth sores
- Nail changes, skin darkening
- Temporary hair loss
- Infection

#### Less Likely

- Watery eyes, eye irritation, blurred vision
- Nose stuffiness
- Hives, itching, rash
- Shortness of breath
- Headache
- Blistering of the palms of the hands and soles of the feet

#### Rare but serious

- Unsteadiness of movement

- Severe, life-threatening diarrhea
- Heart attack or chest pain

**Bevacizumab (Avastin®):**Very Likely:

- Nose bleeds
- High blood pressure - In most patients, blood pressure can be controlled with routine medications taken by mouth while bevacizumab is continued. However, uncontrolled hypertension and hypertension resulting in disturbance of organ function have rarely been reported.
- Fatigue
- Rash
- Headache

Less Likely

- Bleeding, including bleeding in the tumor, the lung, stomach and intestines, brain, tumor, and other parts of the body
- Blood clots: blood clots can occur in the veins or in the blood supply to the brain, heart or other organs. Rarely, formation of blood clots in the veins or arteries can be life-threatening or fatal
- Leakage of protein in the urine, which can rarely lead to damage to the kidney
- Blood in the urine
- Reactions associated with infusion of the drug: rash, chills, fever, rigor
- Watery eyes, nasal stuffiness
- Palpitations (rapid heart beat), slowing of your heart
- Shortness of breath, cough
- Generalized pain and pain at the tumor site
- Constipation

Rare but serious

- Serious or fatal bleeding or blood clots
- Bowel perforation and bowel anastomotic dehiscence. Bowel perforation occurs when an opening exists in the bowel wall allowing bowel contents to spill into the abdomen. Bowel anastomotic dehiscence is a breakdown in the surgical connection between two pieces of bowel. These events are rare but can be life-threatening or fatal. In the recent large randomized clinical trial, bowel perforation events were noted in 6 patients (or 1.5%) who received bevacizumab with chemotherapy, compared to no bowel perforations in the group of patients receiving chemotherapy alone.
- Decrease in heart function
- Worsening of fluid collections surrounding the heart
- Worsening of fluid within the tissues of the lung
- Delayed or poor wound healing
- Severe allergic reaction
- Damage to the liver

**Risks/Side Effects Insertion of a Central Venous Catheter/Port:** Risks associated with central venous catheters are not likely but may occur. These risks include infection and bleeding. Rarely, perforation of the lung may occur. The risks associated with this procedure will be reviewed in detail with you by the individual who places the catheter.

**Risks/Side Effects of Intravenous Injection:** Escape of chemotherapy drug from the vein where the injection is given is not likely but, if it occurs, may cause inflammation in the area of the injection.

### **Reproductive Risks**

Because the drugs in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. Men who are able to father a child and women who can become pregnant must use a birth control plan during this study and for at least 3 months after the last dose of bevacizumab. Ask your doctor about counseling and more information about preventing pregnancy.

Women who are capable of becoming pregnant must have a negative pregnancy test before taking part in this study.

Since the drug may also affect a breast-fed infant, you should not nurse your baby while on this study and for at least 3 months after the last dose of bevacizumab.

## **Are there benefits to taking part in this study?**

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with colon cancer in the future.

## **What other options are there?**

Instead of being in this study, you have these options:

- Treatment with other chemotherapy drugs
- Other experimental chemotherapy or investigational drugs
- No therapy at this time with comfort care only – with comfort care only, treatments are directed only at reducing symptoms, relieving suffering, and maximizing comfort, dignity, and control. In comfort care only, treatment is not directed at curing, slowing, or reversing your disease.

Please talk to your cancer doctor about these and other options. Please ask any questions you may have and take as much time as you need to make your decision.

## **What about confidentiality?**

This study is being conducted by the National Cancer Institute. Although study results may be published, your confidentiality will be maintained. Your name or information identifying you will not be released without written permission unless required by law. Medical records related to this study may be shown to Genentech, Inc. (the manufacturer of bevacizumab), the National Cancer Institute, The EMMES Corporation (the data management and statistical center for this study), or the Food and Drug Administration and other federal regulatory agencies and/or their designated representatives. Records of patient progress while on the study will be kept in a confidential file.

## **What are the costs?**

The Division of Cancer Treatment and Diagnosis of the National Cancer Institute will provide you with the investigational agent bevacizumab free of charge, through an agreement with the bevacizumab manufacturer, Genentech, Inc. If bevacizumab becomes commercially available while

you are being treated, there is a possibility that you may be asked to purchase subsequent supplies. However, every effort will be made to provide adequate supplies of bevacizumab free of charge to you to complete the study treatment.

The drugs 5-fluorouracil and leucovorin are commercially available. You and/or your health care plan will be responsible for all costs associated with that part of the treatment.

Certain tests and examinations will need to be done regularly to monitor safety and to measure the treatment effect. These tests include physical examinations, x-rays, scans, urine tests, and blood tests.

Costs for these tests and examinations will be billed to you and/or your health care plan. The use of medications or other types of treatment to help control side effects could also result in added costs to you and/or your health care plan. ***Some health insurance plans may not cover certain procedures and medical treatments. You should check with your insurance company before enrollment to see if insurance coverage is available under your plan.***

Taking part in this study may lead to added costs to you and your insurance company. Please ask about any unexpected added costs or insurance problems. In the case of injury or illness resulting from this study, emergency medical treatment is available, but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

## **What are my rights as a participant?**

Taking part in this study is voluntary. You may choose not to take part in the study. If you do decide to take part, you may leave the study at any time. Choosing not to take part, or leaving the study, will not result in any penalty or loss of benefits to which you are entitled.

Your doctor or the investigators may stop you from taking part in this study at any time if it is in your best interest, if you do not follow the study rules, or if the study is stopped.

Your doctor or the investigator will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

## **Whom do I call if I have questions or problems?**

For any questions about the study or a research-related injury, please contact your cancer doctor  
          Name(s)           at           Telephone Number          .

For questions about your rights as a research participant, please contact the           Name of Center            
Institutional Review Board (which is a group of people who review the research to protect your rights  
at           Telephone Number          .

[And if available, list patient representative (or other individual who is not on the research team or IRB).]

**Where do I get more information?**

You may call the National Cancer Institute's Cancer Information Service at:  
**1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615**

Visit the NCI's Web Sites at:

<http://www.cancer.gov/>

**You will get a copy of this form. You can also request a copy of the protocol (full study plan).**

**I have had an opportunity to have my questions answered. I have been given a copy of this form. I agree to participate in this study.**

\_\_\_\_\_  
(Date)

\_\_\_\_\_  
(Signed and Printed Name of Participant)

\_\_\_\_\_  
(Date)

\_\_\_\_\_  
(Signed and Printed Name of Individual Obtaining Consent)

**APPENDIX A**

**Performance Status Criteria**

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

**APPENDIX B**

**New York Heart Association Classifications**

Clinical Evaluation of Functional Capacity of Patients  
with Heart Disease in Relation to Ordinary Physical Activity

<u>Class</u>	<u>Cardiac Symptoms</u>	<u>Limitations</u>	<u>Need for Additional Rest*</u>	<u>Physical Ability to work**</u>
I	None	None	None	Full time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, and any activity increases discomfort	Extreme	Marked	Unable to work

\*To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.

\*\*At accustomed occupation or usual tasks.

Reference: Bruce, R. A.: Mod. Concepts Cardiovasc. Dis. 25:321, 1956. (Modified from New York Heart Association, 1953).

**APPENDIX C****Cooperative Research and Development Agreement (CRADA)**

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

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient participating on the study or patient's family member, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from <http://ctep.cancer.gov>.
2. For a clinical protocol where there is an investigational Agent used in combination with (an) other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data".):
  - a. NCI must provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
  - b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval, or commercialize its own investigational agent.
  - c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational agent.
3. Clinical Trial Data and Results and Raw Data developed under a collaborative agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate. All data made available will comply with HIPAA regulations.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to

Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract, and/or press release/ media presentation should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI  
6130 Executive Boulevard, Suite 7111  
Rockville, MD 20852  
FAX 301-402-1584  
E-mail: [anshers@ctep.nci.nih.gov](mailto:anshers@ctep.nci.nih.gov)

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

## APPENDIX D

### Registration and DATA REPORTING FORMS

- ✓ TRC-0301 Registration Form
- ✓ TRC-0301 Colorectal Cancer - Advanced Disease On-Study Form
- ✓ TRC-0301 Colorectal Cancer – Long-term Follow-up Form
- ✓ TRC-0301 Colorectal Cancer - Advanced Disease Off-Treatment Form

These forms are available at <http://spitfire.emmes.com/study/trc/Forms/forms.html>

**A Multicenter Study of the Anti-VEGF Monoclonal Antibody Bevacizumab (Avastin®)  
Plus 5-Fluorouracil/ Leucovorin in Patients with Metastatic Colorectal Cancers  
that have Progressed After Standard Chemotherapy**

To enter a participant into the study, fax the completed form to TRC at 301-402-4870.

**Referring Physician (if applicable):**

Investigator Name: \_\_\_\_\_  
 NCI Investigator Number: \_\_\_\_\_  
 NCI Site Code: \_\_\_\_\_  
 Institution Name: \_\_\_\_\_  
 Address: \_\_\_\_\_  
 Phone: (     ) \_\_\_\_\_  
 Fax: (     ) \_\_\_\_\_

**Cancer Center Physician:**

Investigator Name: \_\_\_\_\_  
 NCI Investigator Number: \_\_\_\_\_  
 NCI Site Code: \_\_\_\_\_  
 Institution Name: \_\_\_\_\_  
 Address: \_\_\_\_\_  
 Phone: (     ) \_\_\_\_\_  
 Fax: (     ) \_\_\_\_\_

**Patient Demographics / Pre-Treatment Characteristics**

Patient's First Initial  Patient's Last Initial

Patient Gender  1-Male  2-Female  9-Unknown

Patient Race *(check all that apply)*  
 White  Black or African American  
 Native Hawaiian or Other Pacific Islander  Asian  
 American Indian or Alaska Native  Unknown

Patient Ethnicity *(check one)*  
 1-Hispanic or Latino  
 2-Non Hispanic  
 9-Unknown

Patient's ZIP Code (USA)  Country of Residence (if not USA)

Patient Height (cm)  Patient Weight (kg) . Body Surface Area (m<sup>2</sup>) .

Date Signed Informed Consent Obtained:    (MM/DD/YYYY)

Method of Payment *(check one) (U.S. only)*  
 Private  Military Sponsored  
 Medicare  (including CHAMPUS or TRICARE)  
 Medicare/Private  Veterans Sponsored  
 Medicaid  Self pay (no insurance)  
 Medicaid & Medicare  No means of payment (no insurance)  
 Military or Veterans  Other  
 Sponsored NOS  Unknown

**For use by TRC-DSC only**

Assigned case number: TRC -  -

--	--

***Patient Initials (First, Last)***

No  Yes

1. Written informed consent has been obtained.

No  Yes

2. The patient has histologically or cytologically documented locally advanced or metastatic colorectal adenocarcinoma not curable by surgery or amenable to radiation therapy with curative intent.

Patients with a history of colorectal cancer treated by surgical resection who develop radiological or clinical evidence of metastatic cancer do not require separate histological or cytological confirmation of metastatic disease provided the diagnosis of the primary lesion was documented and there is no ambiguity regarding the nature of the source of apparent metastasis.

No  Yes

3. Patients must have received treatment with standard, effective chemotherapy regimens (including oxaliplatin and irinotecan), as defined by:

Investigator-assessed disease progression during or following irinotecan-based therapy for metastatic disease, OR relapse within 6 months of concluding adjuvant therapy with irinotecan-based regimen;

**AND**

Investigator-assessed disease progression during or following oxaliplatin-based therapy for metastatic disease, OR relapse within 6 months of concluding adjuvant therapy with oxaliplatin-based regimen;

No  Yes

4. The patient's performance status is 0-2, or Karnofsky  $\geq$  60%

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

1 =Restricted in physically strenuous activity but ambulatory

2 =Ambulatory and capable of all selfcare but unable to carry out any work activities

3 =Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours (**not eligible**)

4 =Completely disabled (**not eligible**)

No  Yes

5. The patient is greater than or equal to 18 years of age.

Patient Birth Date       (MM/DD/YYYY)

No  Yes/NA

6.  $\geq$  4 weeks must have elapsed from the time of major radiotherapy (e.g., chest or bone palliative RT) and the patient has recovered from side effects that might interfere with the protocol therapy.

No  Yes/NA

7.  $\geq$  3 weeks must have elapsed from the last administration of cytotoxic agent and the patient has recovered from side effects that might interfere with the protocol therapy.

No  Yes/NA

8.  $\geq$  8 weeks must have elapsed from the last administration of monoclonal antibody therapy and the patient has recovered from side effects that might interfere with the protocol therapy.

No  Yes

9. Does the patient have adequate organ function as defined below:

(Must be obtained within 14 days prior to registration)

No  Yes

Date of last lab \_\_\_\_\_ Absolute granulocyte count (AGC)  $\geq$  1,500/ $\mu$ L.

No  Yes

Date of last lab \_\_\_\_\_ Platelets  $\geq$  100,000/ $\mu$ L.

No  Yes

Date of last lab \_\_\_\_\_ Hemoglobin  $\geq$  9.0 gm/dL (patients may be transfused to achieve this requirement).

No  Yes

Date of last lab \_\_\_\_\_ Creatinine  $\leq$  1.5 x ULN.

No  Yes

Date of last lab \_\_\_\_\_ Urine dipstick for proteinuria < 1+ (i.e. either trace or zero) OR if 1+ then 24 hour urine for protein is <500 mg

No  Yes

Date of last lab \_\_\_\_\_ Total bilirubin  $\leq$  1.5 mg/dL (regardless of whether patients have liver involvement secondary to tumor)

No  Yes

Date of last lab \_\_\_\_\_ Aspartate aminotransferase (AST) < 5 x institutional upper limit of normal (ULN).

No  Yes

Date of last lab \_\_\_\_\_ Alkaline phosphatase < 5 x ULN.

No  Yes

Date of last lab \_\_\_\_\_ PT INR  $\leq$  1.5 x ULN.

No  Yes

Date of last lab \_\_\_\_\_ PTT  $\leq$  ULN.

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***Patient Initials (First, Last)***

No     Yes/NA

10. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) for the duration of study therapy and for at least 3 months after the last dose of bevacizumab. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

**Exclusion Criteria:**

No     Yes

11. The patient has received prior bevacizumab therapy.

No     Yes

12. The patient is receiving concurrent investigational agents.

No     Yes

13. The patient has a history of allergic reactions attributed to compounds of similar chemical or biologic composition to bevacizumab as well as other agents used in the study.

No     Yes

14. Ongoing or active infection.

No     Yes

15. Uncontrolled high blood pressure.

No     Yes

16. Symptomatic congestive heart failure.

No     Yes

17. Unstable angina pectoris.

No     Yes

18. Cardiac arrhythmia.

No     Yes

19. Myocardial infarction  $\leq$  6 months prior to registration.

No     Yes

20. New York Heart Association classification III or IV (Appendix B).

No     Yes

21. Psychiatric illness/social situations that would limit compliance with study requirements.

No     Yes

22. Pregnant or nursing women.

No     Yes

23. History or evidence of presence of CNS disease (e.g., any brain metastases, primary brain tumor, seizures not controlled with standard medical therapy or history of stroke).

No     Yes

24. Patients must not be on therapeutic anticoagulation. (Prophylactic anticoagulation of venous access devices is allowed provided that the requirement for INR or PTT is met).

No     Yes

25. Major surgical procedure, open biopsy, or significant traumatic injury within 6 weeks prior to Day 1 of treatment.

No     Yes

26. Fine needle aspirations or core biopsies within 7 days prior to Day 1 of treatment.

No     Yes

27. Anticipation of need for major surgical procedure during the course of the study.

No     Yes

28. Chronic, daily treatment with aspirin ( $>325$  mg/day) or nonsteroidal anti-inflammatory medications (of the kind known to inhibit platelet function at doses used to treat chronic inflammatory disease).

No     Yes

29. Serious, nonhealing wound (including wound healing by secondary intention), ulcer, or bone fracture.

No     Yes

30. Evidence of bleeding diathesis or coagulopathy.

No     Yes

31. Patient is HIV positive and on combined anti-retroviral therapy

\_\_\_\_\_  
Investigator's Signature

Today's Date

MM		DD		YYYY	

**TRC-0301**  
Clinical Site

**COLORECTAL CANCER – ADVANCED DISEASE ON-STUDY FORM**

Protocol

Subject

Form  
Form Version

*This form is to be submitted within 14 days of initiation of protocol therapy.*

**TRC-0301 Treatment Regimen**

Please select the regimen chosen by the treating Cancer Center physician:

- Regimen A - Roswell Park (Bevacizumab + bolus 5-FU/LV)
- Regimen B - de Gramont (Bevacizumab + infusional 5-FU/LV)

Treatment starting dose:

- 0 - Roswell Park 5FU 500 mg/m<sup>2</sup>; de Gramont 5FU 400 mg/m<sup>2</sup>, 600 mg/m<sup>2</sup>
- 1 - Roswell Park 5FU 400 mg/m<sup>2</sup>; de Gramont 5FU 320 mg/m<sup>2</sup>, 500 mg/m<sup>2</sup>
- 2 - Roswell Park 5FU 320 mg/m<sup>2</sup>; de Gramont 5FU 240 mg/m<sup>2</sup>, 400 mg/m<sup>2</sup>

**Current Disease Description**

- |  |                              |                             |
|--|------------------------------|-----------------------------|
| Is the Primary Site or tumor bed involved? | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Lung?                                      | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Liver?                                     | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Other Abdominal?                           | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Bone?                                      | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Brain?                                     | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Distant Skin/Subcutaneous Tissue?          | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Other?                                     | <input type="checkbox"/> Yes | <input type="checkbox"/> No |

If Yes, Specify Other Site(s) \_\_\_\_\_

Please indicate the disease status:

- 1- Measurable disease only
- 2- Non-measurable disease only
- 3- Both measurable and non-measurable disease

COLORECTAL CANCER – ADVANCED DISEASE ON-STUDY FORM

Protocol

Subject

Form  
Form Version

**Prior Treatment**

- Prior Surgery?  Yes  No
- Prior Radiation Therapy?  Yes  No
- Prior Adjuvant Chemotherapy?  Yes  No
- Prior Adjuvant Immunotherapy?  Yes  No

Please indicate primary reason for discontinuing **irinotecan**-based therapy (please select one):

- Investigator assessed disease progression
- Toxicity
- Relapse within 6 months of concluding adjuvant therapy
- Other

If Other, specify reason \_\_\_\_\_

Please indicate primary reason for discontinuing **oxaliplatin**-based therapy (please select one):

- Investigator assessed disease progression
- Toxicity
- Relapse within 6 months of concluding adjuvant therapy
- Other

If Other, specify reason \_\_\_\_\_

**Comments**

Comments \_\_\_\_\_  
\_\_\_\_\_

TRC-0301  
Clinical Site

COLORECTAL CANCER – ADVANCED DISEASE OFF-TREATMENT FORM

Protocol

Subject

Form  
Form Version

This form is to be completed within 14 days after completion of protocol therapy

Treatment Schedule – Systemic Therapy

First Date (any modality of) Protocol Therapy was Given        
MM DD YYYY

Last Date Chemotherapy was Given        
MM DD YYYY

Last Date Bevacizumab was Given        
MM DD YYYY

Total Number of Cycles Given (One cycle = 8 weeks)

Were there any dose modifications or additions/omissions to protocol treatment (for this reporting period)?

Yes, planned (i.e., the treatment was changed according to protocol guidelines)

Yes, unplanned (i.e., the treatment change was not part of protocol guidelines)

Name of Therapy \_\_\_\_\_

Reason for Therapy Modification \_\_\_\_\_

No

Unknown

Primary Reason Treatment Ended

- Disease progression, relapse during active treatment
- Toxicity/side effects/complications
- Death on study
- Patient withdrawal or refusal after beginning protocol therapy
- Patient withdrawal or refusal prior to beginning protocol therapy
- Alternative therapy
- Patient off treatment for other complicating disease
- Lost to follow-up
- Disease progression before active treatment
- Other

If Other, specify reason \_\_\_\_\_

TRC-0301  
Clinical Site

COLORECTAL CANCER – ADVANCED DISEASE OFF-TREATMENT FORM

Protocol

Subject

Form  
Form Version

Response Assessment

Has the patient achieved a response?  Yes  No

*If Yes:*

Partial Response (PR) First Observed Date

MM DD YYYY

Complete Response (CR) First Observed Date

MM DD YYYY

Date PR or CR First Confirmed

MM DD YYYY

(must be at least 4 weeks from the first date of response)

Check here if no confirmatory scans done

Check here if confirmatory scans did not show continued response

Has the patient developed a first progression (or relapse)?

Yes

Progressive Disease (PD) Observed Date

MM DD YYYY

Progressive Disease Documentation (check all that apply)

- Target Lesions (At least a 20% increase in the Sum of Longest Diameters of Target Lesions, taking as reference the smallest sum recorded since the treatment started)
- Nontarget Lesions (Unequivocal progression of existing nontarget lesions)
- Appearance of one or more new lesions
- Other, specify \_\_\_\_\_

No

Date Response Last Documented

MM DD YYYY

Non-Protocol Therapy

Are there plans for the patient to receive subsequent therapy for this cancer?  Yes  No

If Yes, specify planned subsequent therapy \_\_\_\_\_

TRC-0301  
Clinical Site

COLORECTAL CANCER – ADVANCED DISEASE OFF-TREATMENT FORM

Protocol

Subject

Form  
Form Version

**Adverse Events** (Report the worst grade during the entire course of therapy. Use only CTCAE v3.0 terms)

CTC Adverse Event Term – Hematologic	CTC Adverse Event Grade (Only report Grade 4-5 for hematologic)	
Hemoglobin (Hgb)	<input type="checkbox"/>	
Leukocytes (total WBC)	<input type="checkbox"/>	
Neutrophils / Granulocytes (ANC/AGC)	<input type="checkbox"/>	
Platelets	<input type="checkbox"/>	
CTC Adverse Event Term – Non-Hematologic	CTC Adverse Event Grade (Only report Grade 3-5 for non-hematologic)	
Cardiac ischemia/infarction	<input type="checkbox"/>	Hemorrhage (lung/bronchus, or hemoptysis) <input type="checkbox"/>
Hypertension	<input type="checkbox"/>	Hemorrhage/nose <input type="checkbox"/>
LV dysfunction	<input type="checkbox"/>	Hemorrhage (other) <input type="checkbox"/>
Fatigue	<input type="checkbox"/>	ALT/AST <input type="checkbox"/>
Hand and foot	<input type="checkbox"/>	Bilirubin <input type="checkbox"/>
Rash/desquamation	<input type="checkbox"/>	Febrile neutropenia <input type="checkbox"/>
Wound complications	<input type="checkbox"/>	Infection w/grade 3 or 4 neutropenia <input type="checkbox"/>
Diarrhea	<input type="checkbox"/>	Infection w/o neutropenia <input type="checkbox"/>
Fistula	<input type="checkbox"/>	Infection w/ unknown ANC <input type="checkbox"/>
Mucositis/stomatitis	<input type="checkbox"/>	Proteinuria <input type="checkbox"/>
Perforation (GI)	<input type="checkbox"/>	Dyspnea <input type="checkbox"/>
Hemorrhage(CNS)	<input type="checkbox"/>	Thrombosis/embolism <input type="checkbox"/>
Hemorrhage (GI)	<input type="checkbox"/>	Thrombosis/embolism (vascular access related) <input type="checkbox"/>
Other toxicities (only report grade 3 or higher using CTCAE v3.0)		
1. _____	<input type="checkbox"/>	
2. _____	<input type="checkbox"/>	
3. _____	<input type="checkbox"/>	
4. _____	<input type="checkbox"/>	
5. _____	<input type="checkbox"/>	
6. _____	<input type="checkbox"/>	

**Comments (optional)**

Comments \_\_\_\_\_

TRC-0301  
Clinical Site

COLORECTAL CANCER – LONG-TERM FOLLOW-UP FORM

Protocol

Subject

Form  
Form Version

This form is to be submitted every 3 months during protocol treatment and every 6 months thereafter for 2 years or until death.

Vital Status

Patient's Vital Status       *Alive*                       *Dead*                       *Lost to follow-up*

Date of Last Contact or Death               

MM                      DD                      YYYY

Cause of death     *Disease progression*     *Unrelated to tumor progression*

Disease Follow-Up Status

Has the patient been taken off the study therapy?     *Yes*                       *No*

If No, please answer the following:

Has the patient achieved a response?     *Yes*                       *No*

*If Yes:*

Partial Response (PR) First Observed Date               

MM                      DD                      YYYY

Complete Response (CR) First Observed Date               

MM                      DD                      YYYY

Date PR or CR First Confirmed               

MM                      DD                      YYYY

(must be at least 4 weeks from the first date of response)

Check here if no confirmatory scans done

Check here if confirmatory scans did not show continued response

Date of Last Tumor Assessment               

MM                      DD                      YYYY

Disease status as of last tumor assessment     *CR*     *PR*     *SD*

Ongoing Toxicity:

Has the patient experienced (prior to initiation of non-protocol therapy) any severe (Grade ≥3), long term toxicity that has not been previously reported?

*Yes*     *No*     *Unknown*

If Yes, Describe: \_\_\_\_\_

Notice of New Primary

Has a new primary cancer or MDS (*myelodysplastic syndrome*) been diagnosed that has not been previously reported?       *Yes*                       *No*

Date of Diagnosis               

MM                      DD                      YYYY

Site(s) of New Primary \_\_\_\_\_

*(If new primary site is AML/MDS, please submit NCI AML/MDS form.)*

Comments

Comments \_\_\_\_\_

\_\_\_\_\_

## APPENDIX E

### Lottery Enrollment Forms

- ✓ TRC-0301 Preliminary Eligibility Screening and Lottery Entry Form
- ✓ TRC-0301 Lottery Authorization Form (model form)

These forms are available at <http://spitfire.emmes.com/study/trc/Forms/forms.html>

**A Multicenter Study of the Anti-VEGF Monoclonal Antibody Bevacizumab (Avastin®)  
Plus 5-Fluorouracil/ Leucovorin in Patients with Metastatic Colorectal Cancers  
that have Progressed After Standard Chemotherapy**

*This form is used for Entry to the Lottery, and should be submitted by the enrolling site to TRC via fax at 301-402-4870.*

**Referring Physician (if applicable):**

Investigator Name: \_\_\_\_\_  
 NCI Investigator Number: \_\_\_\_\_  
 NCI Site Code: \_\_\_\_\_  
 Institution Name: \_\_\_\_\_  
 Address: \_\_\_\_\_  
 Phone: (     ) \_\_\_\_\_  
 Fax: (     ) \_\_\_\_\_

**Cancer Center Physician:**

Investigator Name: \_\_\_\_\_  
 NCI Investigator Number: \_\_\_\_\_  
 NCI Site Code: \_\_\_\_\_  
 Institution Name: \_\_\_\_\_  
 Address: \_\_\_\_\_  
 Phone: (     ) \_\_\_\_\_  
 Fax: (     ) \_\_\_\_\_

**Patient Demographics / Pre-Treatment Characteristics**

Patient's First Initial	[                      ]	Patient's Last Initial	[                      ]
Patient Gender	<input type="checkbox"/> 1-Male	<input type="checkbox"/> 2-Female	<input type="checkbox"/> 9-Unknown

- No     Yes    1. Have local HIPAA guidelines been followed in obtaining authorization for release of Protected Health Information (PHI)?
- No     Yes    2. Has the patient signed the Lottery Authorization Form?
- No     Yes    3. The patient has histologically or cytologically documented locally advanced or metastatic colorectal adenocarcinoma not curable by surgery or amenable to radiation therapy with curative intent.
- Patients with a history of colorectal cancer treated by surgical resection who develop radiological or clinical evidence of metastatic cancer do not require separate histological or cytological confirmation of metastatic disease provided the diagnosis of the primary lesion was documented and there is no ambiguity regarding the nature of the source of apparent metastasis.
- No     Yes    4. Patients must have received treatment with standard, effective chemotherapy regimens (including oxaliplatin and irinotecan), as defined by:
- Investigator-assessed disease progression during or following irinotecan-based therapy for metastatic disease, OR relapse within 6 months of concluding adjuvant therapy with irinotecan-based regimen;  
**AND**  
 Investigator-assessed disease progression during or following oxaliplatin-based therapy for metastatic disease, OR relapse within 6 months of concluding adjuvant therapy with oxaliplatin-based regimen;
- No     Yes    5. The patient's performance status is 0-2, or Karnofsky  $\geq$  60%
- 0 = Fully active, able to carry on all pre-disease performance without restriction
  - 1 = Restricted in physically strenuous activity but ambulatory
  - 2 = Ambulatory and capable of all selfcare but unable to carry out any work activities
  - 3 = Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours (**not eligible**)
  - 4 = Completely disabled (**not eligible**)

<b>For use by TRC-DSC only</b>	
Assigned case number:	TRC - [    ] [    ] [    ] [    ] [    ] - [    ] [    ] [    ]

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**Patient Initials (First, Last)**

- No  Yes      6. The patient is greater than or equal to 18 years of age.  
Patient Birth Date 

--	--	--	--	--	--

 (MM/DD/YYYY)
- No  Yes/NA      7.  $\geq 4$  weeks must have elapsed from the time of major radiotherapy (e.g., chest or bone palliative RT) and the patient has recovered from side effects that might interfere with the protocol therapy.
- No  Yes/NA      8.  $\geq 3$  weeks must have elapsed from the last administration of cytotoxic agent, and the patient has recovered from side effects that might interfere with the protocol therapy.
- No  Yes/NA      9.  $\geq 8$  weeks must have elapsed from the last administration of monoclonal antibody therapy, and the patient has recovered from side effects that might interfere with the protocol therapy.
- No  Yes      10. Does the patient have adequate organ function as defined below:  
(Must be obtained within 14 days prior to registration)
- No  Yes      Date of last lab \_\_\_\_\_ Absolute granulocyte count (AGC)  $\geq 1,500/\mu\text{L}$ .
- No  Yes      Date of last lab \_\_\_\_\_ Platelets  $\geq 100,000/\mu\text{L}$ .
- No  Yes      Date of last lab \_\_\_\_\_ Hemoglobin  $\geq 9.0$  gm/dL (patients may be transfused to achieve this requirement).
- No  Yes      Date of last lab \_\_\_\_\_ Creatinine  $\leq 1.5$  x ULN.
- No  Yes      Date of last lab \_\_\_\_\_ Urine dipstick for proteinuria  $< 1+$  (i.e. either trace or zero) OR if 1+ then 24 hour urine for protein is  $< 500$  mg
- No  Yes      Date of last lab \_\_\_\_\_ Total bilirubin  $\leq 1.5$  mg/dL (regardless of whether patients have liver involvement secondary to tumor)
- No  Yes      Date of last lab \_\_\_\_\_ Aspartate aminotransferase (AST)  $< 5$  x institutional upper limit of normal (ULN).
- No  Yes      Date of last lab \_\_\_\_\_ Alkaline phosphatase  $< 5$  x ULN.
- No  Yes      Date of last lab \_\_\_\_\_ PT INR  $\leq 1.5$  x ULN.
- No  Yes      Date of last lab \_\_\_\_\_ PTT  $\leq$  ULN.
- No  Yes/NA      11. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) for the duration of study therapy and for at least 3 months after the last dose of bevacizumab. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

**Exclusion Criteria:**

- No  Yes      12. The patient has received prior bevacizumab therapy.
- No  Yes      13. The patient is receiving concurrent investigational agents.
- No  Yes      14. The patient has a history of allergic reactions attributed to compounds of similar chemical or biologic composition to bevacizumab as well as other agents used in the study.
- No  Yes      15. Ongoing or active infection.
- No  Yes      16. Uncontrolled high blood pressure.
- No  Yes      17. Symptomatic congestive heart failure.
- No  Yes      18. Unstable angina pectoris.
- No  Yes      19. Cardiac arrhythmia.
- No  Yes      20. Myocardial infarction  $\leq 6$  months prior to registration.
- No  Yes      21. New York Heart Association classification III or IV (Appendix B).
- No  Yes      22. Psychiatric illness/social situations that would limit compliance with study requirements.
- No  Yes      23. Pregnant or nursing women.
- No  Yes      24. History or evidence of presence of CNS disease (e.g., any brain metastases, primary brain tumor, seizures not controlled with standard medical therapy or history of stroke).

***Patient Initials (First, Last)***

- No  Yes 25. Patients must not be on therapeutic anticoagulation. (Prophylactic anticoagulation of venous access devices is allowed provided that the requirement for INR or PTT is met).
- No  Yes 26. Major surgical procedure, open biopsy, or significant traumatic injury within 6 weeks prior to Day 1 of treatment.
- No  Yes 27. Fine needle aspirations or core biopsies within 7 days prior to Day 1 of treatment.
- No  Yes 28. Anticipation of need for major surgical procedure during the course of the study.
- No  Yes 29. Chronic, daily treatment with aspirin (>325 mg/day) or nonsteroidal anti-inflammatory medications (of the kind known to inhibit platelet function at doses used to treat chronic inflammatory disease).
- No  Yes 30. Serious, nonhealing wound (including wound healing by secondary intention), ulcer, or bone fracture.
- No  Yes 31. Evidence of bleeding diathesis or coagulopathy.
- No  Yes 32. Patient is HIV positive and on combined anti-retroviral therapy

I have verified the eligibility information above and completed this form.

\_\_\_\_\_  
Signature of the physician who completed the form

Date       
MM DD YYYY

I have reviewed the eligibility information above and believe this patient to be an appropriate candidate for the lottery.

\_\_\_\_\_  
Signature of the enrolling TRC physician

Date       
MM DD YYYY

## TRC-0301 Model Lottery Authorization Form

The purpose of this form is to provide background information on a research study entitled "TRC-0301: A Multicenter Study of the Anti-VEGF Monoclonal Antibody Bevacizumab (Avastin®) Plus 5-Fluorouracil/ Leucovorin in Patients with Metastatic Colorectal Cancers That Have Progressed After Standard Chemotherapy". This study is also referred to as TRC-0301 for short. After reading this form you should be able to understand the process for participating in this study.

The purpose of this clinical trial is to find out if adding bevacizumab (Avastin®), an experimental agent, to a standard chemotherapy regimen (5-fluorouracil and leucovorin) is useful for patients who have previously received standard chemotherapy for their advanced cancer of the colon or rectum. Bevacizumab, the drug we are testing, was designed to decrease a tumor's blood supply and reduce its growth. Bevacizumab is not yet approved by the US Food and Drug Administration (FDA).

The National Cancer Institute (NCI) is offering this research study to all NCI-designated Cancer Centers and additional institutions selected to achieve geographical balance. Primary physicians or primary oncologists seeking bevacizumab for their patients will screen their patients for eligibility and contact the Treatment Referral Center within the NCI. Physicians will then be referred to the nearest participating institution. The supply of bevacizumab is limited, so if the demand exceeds the available supply, a process similar to a lottery will randomly select eligible patients. If a lottery is needed and you are not selected in the first week, your name will automatically be re-entered for following lotteries provided you still qualify for the study and want to participate.

Note that you do not need to be seen by the Cancer Center physician before eligibility has been determined for entry to lottery. However, your primary physician and the Cancer center physician should discuss the eligibility requirements and complete the "Eligibility Screening Worksheet" to determine if you are likely to qualify for the study

Please understand that this form does not take the place of the informed consent for the study. This form does not guarantee that you will be selected to receive the research drug. By signing this form you: 1) Agree that you understand the lottery process and 2) Agree to have information about your health history released to the NCI.

**I have had an opportunity to have my questions answered. I have been given a copy of this form. I agree to participate in the TRC-0301 Lottery and to have my health information needed to determine my eligibility for the study sent to the enrolling physician and the NCI.**

\_\_\_\_\_  
(Date)

\_\_\_\_\_  
(Signature of Participant)

\_\_\_\_\_  
(Date)

\_\_\_\_\_  
(Signature of Individual Explaining the Form)