A RANDOMIZED PHASE II STUDY OF HEPATIC ARTERIAL INFUSION WITH FLOXURIDINE AND DEXAMETHASONE IN COMBINATION WITH INTRAVENOUS SYSTEMIC CHEMOTHERAPY, WITH OR WITHOUT BEVACIZUMAB (A MONOCLONAL ANTIBODY TO VASCULAR ENDOTHELIAL GROWTH FACTOR-A), IN PATIENTS WITH RESECTED HEPATIC METASTASES FROM COLORECTAL CANCER

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**** Eligible to obtain patient informed consent***

Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

One MSK site	
Basking Ridge	**Follow Up Only**
Commack	**Follow Up Only**
Nassau	**Follow Up Only**
Westchester	**Follow Up Only**
Manhattan	**All Protocol Activities**

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This phase II study aims to assess the efficacy of HAI in combination with systemic chemotherapy plus or minus systemic Bevacizumab in patients with completely resected hepatic metastases from colorectal cancer. The protocol includes biological correlative studies.

The primary objective of this study is to assess whether the addition of concurrent intravenous Bevacizumab to hepatic arterial infusion (HAI) plus systemic chemotherapy increases the time to progression for patients who have undergone hepatic resection. We will also be assessing toxicity for this treatment, as well as survival. The secondary objectives are (1) to assess toxicity, (2) to determine survival, (3) to assess the expression pattern of VEGFR1, VEGFR2, and VEGFR3 and their cognate ligands (including VEGF-A, VEGF-B, VEGF-C, VEGF-D, and P1GF), and correlate with patient progression and survival following therapy, and (4) to compare baseline tissue levels of vascular endothelial growth factor (VEGF) with baseline, interim, and post-treatment end plasma levels of VEGF.

This study is based on the hypothesis that the growth and progression of metastatic liver lesions are dependent on the factors that support angiogenesis and lymphangiogenesis. As signaling molecules regulating these two processes are driven by three different tyrosine kinase receptors, namely VEGFR1, VEGFR2, and VEGFR3, we propose to assess the expression pattern of these receptors and their cognate ligands including VEGF-A, VEGF-B, VEGF-C, VEGF-D and P1GF, in the metastatic lesions. Since Bevacizumab selectively blocks the activity of VEGF-A, but not VEGF-C and VEGF-D or P1GF, these studies will provide important information as to whether inhibition of VEGF-A/VEGFR-2 signaling pathway is sufficient to block tumor angiogenesis and lymphangiogenesis within the liver lesions.

Intense expression of VEGF has been demonstrated in liver metastases. Inhibition of VEGF may lead to improved progression-free and overall survival. Fresh tissue from normal liver tissue and liver metastases will be available at surgery to measure VEGF levels. By evaluating a number of different VEGF receptors we can see if certain receptors are seen more often and may therefore be more predictive of TTP and overall survival.

A total of 80 patients whose liver metastases have been completely resected will be 1:1 randomized to two treatment arms: one group will receive HAI FUDR with systemic chemotherapy; the other will receive the same treatment plus Bevacizumab. The primary objective of the study is to determine whether the addition of Bevacizumab improves disease-free survival. In our last trial using adjuvant HAI + systemic chemotherapy after liver resection, 70% of those patients were disease-free at one year. If the one-year progression-free survival probability in the Bevacizumab arm is 80% or higher, we will consider this a sign of potentially improved efficacy and an encouragement for a larger comparative study. The decision to initiate such a study will depend on many factors, including tolerability of the regimen.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1.1 To determine whether the addition of concurrent intravenous Bevacizumab to HAI plus systemic chemotherapy increases the time to progression in patients with completely resected hepatic metastases from colorectal cancer.

2.1.2 To assess toxicity.

2.1.3 To determine survival.

2.1.4 To assess the expression pattern of VEGFR1, VEGFR2 (angiogenesis), and VEGFR3 (lymphangiogenesis) and their cognate ligands (VEGF-A, VEGF-C, VEGF-D), and correlate with patient progression and survival following hepatic resection and therapy. Frozen and paraffin-fixed tissue from the liver metastases will be available at surgery to measure these values.

2.1.5 To compare plasma levels of VEGF-A, VEGF-C, VEGF-D, and CD133+ VEGFR2+ circulating endothelial progenitors with baseline, interim, and post-treatment end plasma levels of VEGF, and correlate with progression and survival.

3.0 BACKGROUND AND RATIONALE

There are almost 150,000 new cases of colorectal cancer each year in the United States. Approximately 60% of patients develop hepatic metastases, and 15% are suitable for surgical resection. Of those who are able to undergo resection, 5-year survival is approximately 30%. The patients most likely to be cured by resection of hepatic metastases are those with isolated lesions, node-negative primary tumor, and margins on the metastasectomy specimen of > 1cm. Of those patients whose disease recurs after resection of their liver metastases, approximately half go on to fail in the liver, the other half systemically.

3.1 Hepatic Resection

About 200 patients each year undergo surgery at MSKCC for treatment of hepatic metastases, and approximately 100 undergo resection. Our older single institution experience with liver resection documents the efficacy of this aggressive approach with an actuarial two-year survival of 75%, but a two-year disease-free survival of only 21.2% in the subset of patients who underwent complete resection of colorectal liver metastases. Combined multi-institutional data from the registry of hepatic metastases was similar, with two-year actuarial survival and disease-free survivals of 65% and 35% respectively. These studies were conducted without standardized adjuvant chemotherapy post-surgical resection.

3.2 Rationale for Treatment

3.2.1 Regional Chemotherapy

Ackerman has demonstrated that microscopic metastases less than 1mm in size derive their blood supply from the portal circulation. As tumors begin to grow they induce the development of new vessels. Tumors measuring 1 to 2mm are encircled by new vessels derived from both the arterial and portal circulation, which mix freely. Tumors greater than 3mm have a well-developed arterial circulation. Metastases that remain after hepatic resection are probably in the range of 2 to 3mm and are therefore not detectable by the ultrasound scanning technique, which has a resolution of 5mm.

Presumably, these metastases derive most of the their blood supply from the arterial circulation. Therefore, adjuvant chemotherapy to the liver for resected hepatic metastases should be given via arterial circulation.

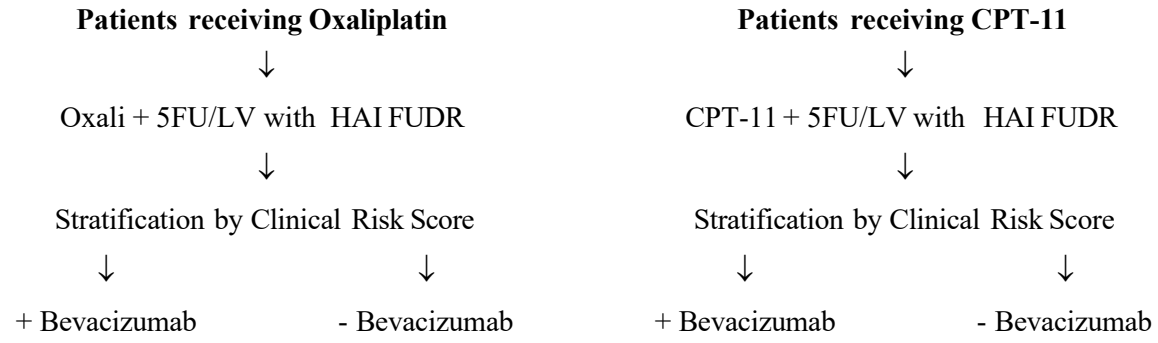
3.2.2 Adjuvant Therapy after Hepatic Resection

Of patients who undergo complete resection of hepatic metastases from colorectal cancer, 5-year actuarial overall survival is only 33-50%, with a 5-year disease-free survival of only 22%. Therefore, approximately 75% of resected patients will recur, with 50% recurring in the liver and 50% recurring elsewhere. Of those patients who do recur, approximately 80% will do so in the first two years.

A recent randomized study at MSKCC compared hepatic arterial infusion (HAI) and systemic therapy versus systemic chemotherapy alone. The study revealed a significant increase in hepatic disease-free survival in those patients who received HAI therapy in addition to systemic. At 2 years, hepatic progression-free survival was 89% and 37% for the HAI + SYS vs. SYS alone groups. Progression-free survival (PFS) was 50% and 35% for HAI + SYS vs. SYS at 2 years. Median PFS was 31 and 17 months, respectively. Updated survival analysis reveals a median survival of 5.6 years for the HAI and 4.7 years for systemic alone.

3.3 Systemic Chemotherapy

Available since the late 1950s, 5-Fluorouracil (5FU) has proven the single most active drug in the treatment of gastrointestinal carcinoma. Strategies developed to enhance the proliferative effects of 5FU have included various treatment schedules, biochemical modulation, and the addition of synergistic drugs. Recently two new agents – Oxaliplatin and Irinotecan – have been identified, and are commonly used as first-line therapy. There are now multiple options available for second-line therapy. Rothenberg et al. demonstrated that a second-line treatment with FOLFOX4 for patients with metastatic colorectal cancer who had progressed after IFL therapy was superior to treatment with LVFU2 in terms of recurrence and time to progression. Additionally, salvage therapy with irinotecan has been shown to be effective for patients who have had progression following adjuvant 5FU-based therapies (Rothenberg, 2004). Adjuvant trials after liver resection at our institution using either systemic oxaliplatin plus HAI or systemic CPT-11 plus HAI produced similar recurrence rates. Since these drugs have been available for a number of years, and since many of our patients will have received one or the other, we propose to offer the option in this trial of receiving either systemic drug with HAI, plus or minus Bevacizumab. Patients having had prior oxaliplatin will generally receive CPT-11 + 5FU/LV and HAI. However, patients who have not had more than 4 months of prior oxaliplatin and have tolerated it well can receive FOLFOX again.



3.4 Oxaliplatin

Numerous trials have studied Oxaliplatin in combination with 5FU and LV. The response rate ranged from 28% to 53% in the treated patients with a 3.5% to 5.8% complete response rate. A similar response rate was obtained in first- and second-line therapy. De Gramont et al. used 5FU + LV via a two-day infusion and added Oxaliplatin at 100mg/m^2 when patients progressed; he obtained a 10/20 (45%) response rate among those who progressed while receiving 5FU and LV.

The addition of Oxaliplatin in combination with 5FU and LV has also been tested in a randomized fashion. Two hundred patients from 15 centers were randomized to receive 5FU at 700mg/m^2 for five days and LV 300 mg/m^2 for five days with peaks at 4 A.M. Oxaliplatin was given at 125 mg/m^2 in half of the patients. Those who received the Oxaliplatin had a significant increase in response rate, 53% versus 16%. The response was confirmed at nine weeks in 34% versus 12%, respectively. The median disease-free survival was 7.7 versus 4.6 months respectively.

Another regimen (FOLFOX2) consisted of Oxaliplatin 100 mg/m2 as a two-hour infusion on day one, LV 500 mg/m2 as a two-hour infusion, followed by 5FU 24-hour infusion 1.5 g/m2 for two cycles and increased to 2 g/m2 for two consecutive days every two weeks in case of no toxicity in first two cycles. Forty-six patients were treated, all with disease progression on LV and 5FU therapy for metastatic disease, or relapse less than 6 months after the end of adjuvant therapy. One complete response (CR) and 20 partial responses (PRs) were observed for an overall response rate of 46%. Twenty-two patients had prior documented progression while receiving the same schedule of LV and 5FU as the one used in the FOLFOX2 regimen, and among them, ten had PRs (45%).

3.5 Irinotecan (CPT-11)

Numerous phase I and II studies have demonstrated the safety and broad anti-tumor activity of irinotecan. Irinotecan has demonstrated efficacy in 5-fluorouracil refractory colon cancer in trials performed in the United States. In an intent-to-treat analysis of the pooled data from three single-agent studies (P&U studies 01, 3R, 06), 14.5% of the patients (28/193) receiving irinotecan at 125 mg/m2 achieved a partial or complete response, and 53.9% of the patients (104/193) demonstrated stable disease. The median duration of response for this group of patients was 5.2 months (range, 2.6 to 15.1 months). A United Kingdom phase III trial of irinotecan versus best supportive care in 5-fluorouracil refractory colon cancer demonstrated a significant improvement in overall one year survival in patients randomized to received irinotecan (36% versus 14%, p=0.001). In the United States, irinotecan is now approved therapy for 5-fluorouracil refractory colon cancer.

Irinotecan has also been evaluated in previously untreated colorectal cancer patients (46-48), as well as in a randomized trial for adjuvant therapy. At Memorial Hospital, a phase II trial for 41 previously untreated patients with metastatic colorectal cancer demonstrated a 32% partial response rate. The median time to tumor progression was 4 months, and the medial survival time was 10.9 months. The most common adverse side effects were grade 3 of 4 late (occurring > 24 hours post-infusion) diarrhea (27%), leukopenia (12%), neutropenia (20%), and nausea/vomiting (9.8%). The incidence of grade 3 or 4 late diarrhea, initially 56% (10/18), was reduced to 9% (2/23) with early and frequent use of loperamide and diphenhydramine. The North Central Center Treatment Group sponsored a multicenter phase II study of 31 patients with previously untreated colorectal cancer, and demonstrated a 29% partial response rate. The median duration of response for these patients was 4.4 months, and median survival time was 11.7 months. Irinotecan has recently been approved by ODAC for the initial treatment of untreated metastatic colon cancer, and is currently being tested in the adjuvant setting for resected colorectal cancer (CALGB 89803).

3.6 Angiogenesis Inhibition

The growth of solid tumors is dependent on angiogenesis. Delivery of oxygen and nutrients by the new vessels is a rate-limiting step for tumor cell proliferation and therefore becomes a target for anti-tumor therapy.

Vascular endothelial growth factor (VEGF), and endothelial cell-specific mitogen, is an important mediator of angiogenesis. VEGF is a glycoprotein whose dominant isoform has a molecular mass of -45,000 daltons. Other angiogenic factors have been identified, but VEGF appears to be most potent and specific. Two VEGF receptors have been identified: Flt-1 and KDR. These receptors are found almost exclusively on endothelial cells.

VEGF gene expression is substantially increased in the majority of human tumors when compared with the surrounding tumor-free tissues. Direct evidence for a role of VEGF in tumorigenesis has been provided by studies showing that a murine anti-VEGF neutralizing antibody, alone or in combination with cytotoxic chemotherapy, is able to inhibit the in vivo growth of a variety of human tumor cell lines derived from breast, colon, ovary, lung, and other tissues.

3.7 Bevacizumab (rhuMAb VEGF)

Bevacizumab is a recombinant humanized anti-VEGF-A monoclonal antibody composed of human IgG1 framework and antigen-binding complementarity-determining regions from a murine monoclonal antibody (rhuMAb VEGF A.4.6.1) that blocks binding of human VEGF-A to its receptors. Approximately 93% of the amino acid sequence, including most of the antibody framework, is derived from human IgG1.

3.7.1 Pre-clinical Studies:

This antibody has been shown to recognize all isoforms of VEGF. It fails to recognize other peptide growth factors tested (fibroblast growth factor, epidermal growth factor, hepatocyte growth factor, platelet-derived growth factor, and nerve growth factor). The binding affinity and specificity of rhuMAb VEGF (Bevacizumab) are essentially equivalent to those of its murine counterpart.

a. In vitro and in vivo VEGF studies:

A correlation has been noted between the degree of tumor vascularization and the level of VEGF mRNA expression. In virtually all specimens examined, VEGF mRNA is expressed in tumor cells but not in endothelial cells. In contrast, as previously noted, mRNAs for the two VEGF receptors, Flt-1 and KDR, are up-regulated in endothelial cells associated with the tumor. These findings are consistent with the hypothesis that VEGF is primarily a paracrine mediator. Freeman et al. suggested that lymphocytes infiltrating the tumor might constitute an additional source of VEGF that contributes to tumor angiogenesis

b. In vivo efficacy studies:

In agreement with the hypothesis that inhibition of neovascularization is the mechanism of tumor suppression, the density of blood vessels was significantly lower in sections of tumors from antibody-treated animals compared with control. These findings provided a direct demonstration that inhibition of the action of endogenous VEGF may result in suppression of tumor growth in

vivo. The combination of anti-VEGF treatment and cisplatin or doxorubicin resulted in markedly enhanced biological activity against tumors compared with the activity of either agent alone.

Clinical Experience

3.7.2 Phase I/II Efficacy Results:

Antitumor activity has been demonstrated in multiple tumor types and with both single-agent Bevacizumab and combination therapy. Objective responses have been reported in the breast cancer trial (AVF0776g), including a complete response of supraclavicular nodal disease and partial responses of cervical node, liver, and skin-subcutaneous disease. In the NSCLC trial (AVF0757g), the data support that Bevacizumab at a dose of 15 mg/kg every 3 weeks and in combination with Carboplatin/Paclitaxel chemotherapy, increases response rates and prolongs time to disease progression compared with chemotherapy alone.

In Study AVF0780g (colorectal cancer), based on blinded assessments by an independent review facility, the hazard of experiencing disease progression was reduced by 57% in subjects receiving 5 mg/kg Bevacizumab plus 5-FU/Leucovorin alone (p=0.005). Improvements in response rate and median survival were also seen for subjects treated with 5 mg/kg Bevacizumab plus 5-FU/Leucovorin versus 5-FU/Leucovorin alone.

In the randomized, open-label, active-controlled, Phase III study AVF2119g (metastatic breast cancer), the results of the primary efficacy analysis showed that treatment with the combination of Bevacizumab plus Capecitabine did not result in a statistically significant prolongation in progression-free survival compared with Capecitabine alone. There was a statistically significant increase in objective response rate (secondary endpoint); however, this did not result in an improvement in progression-free survival.

In the randomized, double-blind, placebo-controlled phase III study AVF2107g, in the first-line treatment of metastatic colorectal cancer, the addition of Bevacizumab (5mg/kg IV q2 weeks) to the Irinotecan/5-Fluorouracil/Leucovorin (IFL) chemotherapy regimen resulted in a statistically and clinically significant improvement in median survival as compared to the IFL + placebo control arm (15.6 vs 20.3 months, HR 0.65, p=0.00003). Improvements in median progression-free survival (6.2 vs 10.6 months, p=0.00001), objective response rate (34.7% vs 44.9%, p=0.0029) and response duration (7.1 vs 10.4 months, p=0.0014) were also achieved with the addition of Bevacizumab to IFL chemotherapy.

Safety of Bevacizumab:
Completed phase II and phase III studies of Bevacizumab have further defined the safety profile of this agent in subjects with metastatic malignancies. Toxicities related to Bevacizumab are listed in detail in section 11.2. For further information regarding safety and adverse event rates, please refer to the Bevacizumab investigator's brochure.

3.7.3 Rationale for HAI FUDR + Dex and Systemic Chemotherapy, +/- Bevacizumab:

Intense expression of vascular endothelial growth factor (VEGF) mRNA in human liver metastases has been demonstrated, and increased VEGF levels in patients correlates with invasiveness and prognosis. By combining Bevacizumab with HAI and systemic treatment, we seek to obtain better control of hepatic and extrahepatic progression, thereby enhancing patient survival. This study is based on the hypothesis that the growth and progression of metastatic liver lesions are dependent on the factors that support angiogenesis and lymphangiogenesis. As

signaling molecules regulating these two processes are driven by three different tyrosine kinase receptors – namely VEGFR1, VEGFR2 and VEGFR3 – we propose to assess the expression pattern of these receptors and their cognate ligands including VEGF-A, VEGF-B, VEGF-C, VEGF-D and P1GF, in the metastatic lesions. Since Bevacizumab selectively blocks the activity of VEGF-A, but not VEGF-C and VEGF-D or P1GF, these studies will provide important information as to whether inhibition of the VEGF-A/VEGFR-2 signaling pathway is sufficient to block tumor angiogenesis and lymphangiogenesis within the liver lesions.

3.7.5 Evaluation of Molecular Markers and Tumor Specimens:

Permission from patients entering the study will be obtained for liver biopsy of normal and tumor liver tissue at the time of surgery to be sent to Dr. Solit's lab at Memorial Sloan Kettering for evaluation of the expression pattern of VEGFR1, VEGFR2, and VEGFR3 and their cognate ligands (including VEGF-A, VEGF-B, VEGF-C, VEGF-D, and P1GF). Evaluation of PAR-1, PAR-2, PTEN, p53 will be performed at the Pathology Core Facility of the Memorial Sloan Kettering Cancer Center.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

A total of 80 patients whose liver metastases have been completely resected will be randomized 1:1 to two arms: patients in Arm A will receive Bevacizumab in addition to HAI plus systemic chemotherapy, and patients randomized to Arm B will receive HAI plus systemic chemotherapy alone. Those patients who are chemo-naïve, or who have received chemotherapy regimens which did not include oxaliplatin, will receive oxaliplatin + 5FU/LV and HAI; patients having had prior oxaliplatin will generally receive CPT-11 + 5FU/LV and HAI. However, patients who have not had more than 4 months of prior oxaliplatin and have tolerated it well can receive FOLFOX again. Patients in both arms will be treated for a total of 6 cycles (7.5 months).

Cycle Schema q5 weeks			
Day 1	*Day 15*	*Day 29*	*Day 36 (Day 1 of next cycle)*
Pump Therapy	**Systemic Therapy***	**Systemic Therapy***	**Pump Therapy**
FUDR + Dexamethasone (14 day infusion)	Pump Emptied Saline	Pump Emptied Saline	FUDR + Dexamethasone (14 day infusion)

* For patients randomized to receive Bevacizumab, the dose will be: **5 mg/kg IV, over 10 minutes**. Bevacizumab will be given on Days 15 and 29 only.

The following systemic doses will be used:

1. For patients who will receive Oxaliplatin, the systemic treatment plan will be:

	SYSTEMIC		
	Oxaliplatin *(mg/m2) IV, over 2 hrs*	***5 FU*** *(mg/m2) Cont. infusion per day x 2 days*	***Leucovorin*** *(mg/m2) IV, over 2 hrs*
Total dose:	85	2000*	400

2. For patients who will receive Irinotecan, the systemic treatment plan will be:

	SYSTEMIC		
	Irinotecan *(mg/m2) IV, over 30 mins*	***5 FU*** *(mg/m2) Cont. infusion per day x 2 days*	***Leucovorin*** *(mg/m2) IV, over 30 mins*
Total dose:	150	2000*	400

** Patients who have already been enrolled on this study prior to 6/27/08 (when we amended the protocol to increase the 5-FU dose from 900 mg/m2 to 1000 mg/m2 per day over 2 days, for a total of 2000 mg/m2) will be able to receive 1000 mg/m2 of 5 FU, unless toxicity has occurred at 900 mg/m2.*

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 FUDR

5.1.1 Floxuridine (FUDR) is an antimetabolite that blocks the methylation of deoxyuridylic acid interfering with the synthesis of DNA. It is also incorporated into RNA and interferes with its function. The drug is metabolized in the liver.

5.1.2 FUDR is commercially available from Roche and Adria Laboratories in 500 mg/10 cc ampules. It is stable (protected from light) and is a colorless aqueous solution. Store at room temperature.

5.1.3 Toxicities associated with the intrahepatic administration of FUDR include biliary sclerosis, hepatic enzyme elevation, gastric ulcers.

5.2 Oxaliplatin

5.2.1 Oxaliplatin functions as an antineoplastic agent by forming platinum-DNA adducts which, if not excised, will prevent further DNA synthesis and/or transcription and thereby lead to cell death.

5.2.2 The freeze-dried powder is reconstituted by adding 10 to 20 ml (for the 50-mg vials) or 20-40 ml (for the 100-mg vials) of water for injection or 5% glucose solution and then by diluting in an infusion solution of 250 ml or 500 ml of 5% glucose solution.

The reconstitution or final dilution must never be performed with a sodium chloride solution.

5.2.3 Do not combine with alkaline medications or media (such as basic solutions of 5FU, Trometamol) which cause Oxaliplatin to degrade. Do not use for the preparation of administration needles or intravenous infusion sets containing aluminum items (risk of degradation of Oxaliplatin upon contact with aluminum).

5.2.4 *Freeze-dried powder:* The compound may be stored for two years at room temperature protected from light.

Reconstituted solution: In 5% glucose solution or water for injection in the original vial, the solution may be stored for 24 to 48 hours at +2° /+8° C.

5.3 Irinotecan

5.3.1 Irinotecan (CPT-11) is a semi-synthetic derivative of camptothecin that possesses greater aqueous solubility, greater *in vitro* and *in vivo* activity, and is associated with less severe and more predictable toxicity than camptothecin. Both camptothecin and CPT-11 are potent inhibitors of topoisomerase I, a nuclear enzyme that plays a critical role in DNA replication and transcription.

5.3.2 CPT-11 will be diluted with 250 ml of 5% Dextrose (D5W) and infused intravenously over 30 minutes. Nothing else should be added to the infusate. No other diluent is to be used.

5.3.3 CPT-11 vials must be stored in a cool, dry place, protected from light in a locked cabinet accessible only to authorized individuals. CPT-11 is relatively stable against heat and light but becomes slightly unstable against light in aqueous solution. It is stable for at least three years at room temperature. CPT-11 is stable for at least 24 hours in glass bottles or plastic bags when mixed with D5W.

5.3.4 Phase I and II studies of CPT-11 have reported neutropenia and diarrhea as the dose-limiting toxicities. It is expected that these toxicities will also be encountered in this trial. Other Grade 2-3 toxicities seen in phase I trials include nausea and vomiting, anorexia, abdominal cramping, cumulative asthenia, thrombocytopenia, renal insufficiency, increase in transaminase level and hair loss.

5.4 Flourouracil

5.4.1 Antimetabolite that will be administered by MSKCC guidelines.

5.4.2 Toxicity: Nausea, vomiting, stomatitis, diarrhea, dermatitis, alopecia, leukopenia, and thrombocytopenia.

5.5 Leucovorin Calcium (Folinic Acid)

5.5.1 Leucovorin calcium is a stable reduced formyl derivative and the active form of folic acid.

5.5.2 The only adverse reaction reported for Leucovorin has been rare cases of allergic sensitization.

5.6 Dexamethasone

5.6.1 Dexamethasone is an adrenocortical steroid, used for chronic inflammation, neoplastic and autoimmune diseases; used in HAI treatment as an agent to prevent liver damage.

5.6.2 Common potential side effects include anxiety, mood alteration/lability, hyperglycemia, insomnia, peripheral edema, myopathy (with chronic use), acne, hirsutism.

5.7 Bevacizumab (rhuMab VEGF)

Description:

Humanized monoclonal antibody produced from genetically engineered cells, and designed to block the action of a protein called vascular endothelial growth factor (VEGF). Bevacizumab belongs to a family of drugs called angiogenesis inhibitors, which prevent the formation of new blood vessels that surround and "feed" cancer cells.

Source:

Bevacizumab is supplied by Genentech as a clear to slightly opalescent, sterile liquid ready for parenteral administration. Each 5-cc (100 mg, 25 mg/mL) glass vial contains sodium phosphate trehalose, polysorbate 20, and sterile water for injection (SWFI), USP. The vials contain no preservative and are for single use only.

For further details and molecule characterization, see the Bevacizumab Investigator Brochure.

How Supplied:

Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration. Each 100mg (25mg/ml – 4 ml fill) glass vial contains Bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP. The previous formulation distributed by NCI was a 10mg/ml concentration available in a 100mg /10ml vial.

Storage and Stability:

Upon receipt of the study drug, vials are to be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE. Vials should be protected from light.

Opened vials must be used within 8 hours. VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 subject may not be used for any other subject. Once study drug has been added to a bag of sterile saline, the solution must be administered within 8 hours.

Administration:

Bevacizumab will be administered as per MSKCC guidelines.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

6.1.1 Patient > 18 years of age.

6.1.2 History of histologically confirmed colorectal adenocarcinoma metastatic to the liver with no clinical or radiographic evidence of extrahepatic disease. Confirmation of diagnosis must be performed at MSKCC

6.1.3 Potentially completely resectable hepatic metastases without current evidence of other metastatic disease.

6.1.4 Abdominal and pelvic CT scans and chest CT or x-ray within 6 weeks prior to registration. (MRI of abdomen may be substituted for CT of abdomen.)

6.1.5 Lab values within 14 days prior to registration:
WBC $\geq$ 3.0 K/uL
ANC > 1.5 K/uL
Platelets $\geq$ 75 K/uL
Total bilirubin < 1.5 mg/dL
INR < 1.5
Creatinine < 2.0 mg/dL
HGB $\geq$ 9 gm/dL

6.1.6 Prior chemotherapy is acceptable if last dose given $\geq$ 3 weeks prior to registration to this study. [Note: no chemotherapy to be given after resection of liver lesions prior to treatment on this study.]

6.1.7 KPS $\geq$ 70%

6.1.8 Signed informed consent

6.2 Subject Exclusion Criteria

6.2.1 Prior radiation to the liver (Prior radiation therapy to the pelvis is acceptable if completed at least 4 weeks prior to registration.)

6.2.2 Active infection, ascites, hepatic encephalopathy

6.2.3 Prior treatment with HAI FUDR

6.2.4 Female patients who are pregnant or lactating

6.2.5 Subjects discovered to have $\geq$ 1+ proteinuria at baseline will undergo a 24-hour urine collection, which must be an adequate collection and must demonstrate <1 g of protein/24 hr to allow participation in this study.

6.2.6 Patients may not be receiving any other investigational agents (Note: exception will be made for patients who have received the glycoprotein A33).

6.2.7 Patients with known brain metastases that would confound the evaluation of neurologic and other adverse events will be excluded. Patients with history of primary CNS tumors, seizures not well-controlled with standard medical therapy, or history of stroke will also be excluded.

6.2.8 History of allergic reactions attributed to compounds of similar chemical or biologic composition to Bevacizumab.

6.2.9 Serious or non-healing active wound, ulcer, or bone fracture

6.2.10 Major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to Day 1 of protocol treatment (Surgery performed to resect metastatic lesions and

place pump will not exclude patient from protocol; Day 1 of protocol treatment will take place no sooner than 28 days after surgery.)

6.2.11 Current or recent use of a thrombolytic agent

6.2.12 Chronic daily treatment with aspirin (> 325 mg/d) or nonsteroidal anti-inflammatory medications known to inhibit the platelet function.

6.2.13 Presence of bleeding diathesis or coagulopathy.

6.2.14 History of serious systemic disease, including myocardial infarction within the last 12 months, uncontrolled hypertension (blood pressure of > 160/110 mmHg on medication), unstable angina within the last 12 months, New York Heart Association (NYHA) Grade II or greater congestive heart failure (see Appendix C), unstable symptomatic arrhythmia requiring medication (subjects with chronic atrial arrhythmia, i. e. atrial fibrillation or paroxysmal supraventricular tachycardia are eligible), or peripheral vascular disease (Grade II or greater, see Appendix C).

6.2.15 Patients with a history of stroke or transient ischemic attack.

6.2.16 Presence of central nervous system or brain metastases.

6.2.17 Patients who have a diagnosis of Gilbert's disease.

7.0 RECRUITMENT PLAN

We will make every effort to include women and minorities. We will go through the appropriate informed consent process and register subjects accordingly.

8.0 PRETREATMENT EVALUATION

Prior to treatment start, patients will undergo the following procedures, in order:

CT angiogram to determine arterial structures
Surgery to resect liver metastases, perform a cholecystectomy, and to place hepatic arterial infusion pump
Perfusion flow scan (TcMAA)
Baseline CT scan of the chest, abdomen and pelvis

The following tests are required within 6 weeks prior to registration: CT abdomen*, CT pelvis, and CT chest.

	Within 14 days prior to registration	*Post surgery, within 3 weeks prior to Cycle 1*	*Within 48 hours prior to Cycle 1*
CT Chest/ Abdomen/Pelvis*		X	
EKG	X		
HX, PE, BP	X		
Pregnancy test (females of child-bearing potential)	X		
KPS	X		X
Ht / Wt	X		
PT	X		
CBC with diff/plts	X		X
Albumin	X		X
Total bilirubin	X		X
BUN, creatinine	X		X
Alk Phos, SGOT, LDH	X		X

CEA	X		X
Urinalysis	X		X
Serum electrolytes			X
CT angio or Celiac axis & SMA angio**			
Mediport placement***			

* MRI may be obtained instead of CT if patient's disease is not visible on CT
** This may be obtained at any time prior to surgery
***This must take place no less than seven (7) days prior to treatment start

9.0 TREATMENT/INTERVENTION PLAN

9.1.1 Chemotherapy will be administered on a 5-week cycle basis. Pump therapy with FUDR and Dex will be administered on Day 1 of each cycle. The pump will be emptied and filled with heparin and normal saline on Days 15 and 29. Systemic chemotherapy will be administered on Days 15 and Day 29 of each cycle. Treatment recycles on Day 36.

On Days 15 and 29, patients will receive systemic chemotherapy. For patients receiving Oxaliplatin + 5FU/LV, Oxali/LV will be administered concurrently via a Y-line over a 120-minute infusion. 5FU will follow by a 48-hour infusion. For patients receiving CPT-11 + 5FU/LV, CPT-11/LV will be administered concurrently via a Y-line over a 30 minute infusion, and 5FU will follow by a 48-hour infusion. Those patients on the Bevacizumab arm will receive the drug over a 10 minute infusion on Days 15 and 29.

- Hypertension will be monitored through routine evaluation of blood pressure prior to each bevacizumab treatment. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.
- Proteinuria will be monitored by urine protein: creatinine (UPC) ratio or dipstick at least every 6 weeks.
- If patients on treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4-8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin/restart bevacizumab until 4 weeks after that procedure (in the case of high risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 wk and bevacizumab no earlier than 8 wk after surgery).

9.1.2 For the first cycle, doses of FUDR and Dex will be calculated based on the predetermined flow rate provided by the pump manufacturer. Thereafter, doses will be adjusted (lowered, if necessary, but never increased, even if the patient gains weight). The pump will be filled with FUDR, Dexamethasone, heparin and saline.

Dose calculation:

FUDR: $\frac{0.12 \text{ mg/kg X pump volume}}{\text{pump flow rate}}$

Dexamethasone: $\frac{1 \text{ mg/day X pump volume}}{\text{pump flow rate}}$

Overweight patients:

If a patient is 25% above ideal weight, dose of FUDR and systemic chemotherapy will be calculated as follows:

Ideal Body weight (kg):

Males: 50kg + (2.3 x height in inches above 5 ft)
(ie: for a patient who is 5'10", use 10)
Females: 45.5 kg + (2.3 x height in inches above 5 ft)
Example: Male who is 100 kg and 5'10"
Ideal Body Weight is: 50 + (2.3 x 10) = 73 kg
Therefore, 100 + 73 = 173 ÷ 2 = 86.5 would be the Ideal Average Weight to use.

Heparin: 30,000 units total dose

Normal saline: quantity sufficient to make total reservoir volume of 30 ml.

If no dose modification due to toxicity is required, the dosages given above will be repeated on Day 1 of Cycle 2 and all subsequent cycles.

9.1.3 On Days 15 and 29 of each cycle, the pump will be emptied and then filled with 30,000 units of heparin in normal saline (q.s. 30cc) for 14 days.

9.1.4 Patients must meet all hematologic and blood chemistry criteria outlined in Section 6.0 before beginning the first cycle of therapy. For subsequent systemic treatments, patients must meet the following criteria:

ANC	> 1000 μL
Platelet count	≥ 75,000 μL
Creatinine	≤ 1.8 mg/dL

If counts are outside these levels on date of scheduled systemic treatment, therapy will be delayed one week.

If patient's liver function tests (Alkaline Phosphatase, SGOT, Bilirubin) show continued increase from baseline, the attending physician may choose to hold systemic treatment, and only resume once liver function tests either stabilize or decrease. Parameters for treatment with FUDR via intrahepatic pump are outlined in Section 12.6.

9.1.5 All reasonable efforts will be made to adhere to treatment and evaluation schedules, however minor infrequent variations to accommodate holidays, transportation issues, or patient's personal schedule will be permitted if these do not, in the opinion of the investigator, constitute a major safety or compliance issue. Such variations, assuming they do not occur with unreasonable frequency or regularity, will not be considered protocol violations.

9.1.6 Allowance will be made for those patients randomized to receive Avastin who live at a significant distance from the Center to receive local systemic treatment. Avastin will not be supplied free of charge to the patient in these cases. The patients and their local physicians will be monitored closely to ensure adherence to protocol requirements for treatment.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

	Before surgery	*At time of surgery*	*Day 1* each Cycle*	*q2 weeks*	*q12 weeks*
HX,PE, BP			X	X	
Tox assessment Neurotox assessment			X	X	
Weight			X		
KPS			X		
CBC, Plts			X	X	
BUN, Creat			X	X	
Bili, SGOT			X	X	
Alk phos, LDH			X	X	
Electrolytes			X		
CEA			X		
Urinalysis			X		
EKG**					X
CT chest/ abdomen/pelvis***					X ‡
Plasma levels/VEGF			**X**		
Tumor tissue levels VEGF		**X**			

***** *Or within 48 hours prior to Day 1*

*** EKGs will be performed every 12 weeks for only those patients randomized to receive Bevacizumab; other EKGs performed as deemed clinically necessary, at the discretion of the attending MD*

**** MRI may be obtained instead of CT if patient's disease is not visible on CT*

‡ CT scans to be performed every 12 weeks, allowing for scheduling conflicts; a slight variance in the timing will not be considered a protocol deviation.

10.1 While being treated with protocol therapy, patients will be seen at or prior to the first day of each cycle by their medical oncologist.

Title of Table (bold)										
Test Type	**Time 1**	**Non-Billable Research Charges**	**Time 2**	**Non-Billable Research Charges**	**Time 3**	**Non-Billable Research Charges**	**Time 4**	**Non-Billable Research Charges**	**Time 5**	**Non-Billable Research Charges**
N/A		N/A		N/A		N/A		N/A		N/A

11.0 TOXICITIES/SIDE EFFECTS

All toxicities will be rated as per the NCI Common Toxicity Criteria except neurosensory and hepatic enzyme toxicities related to intrahepatic pump therapy (see section 12.5, FUDR Dose Modifications and Table I).

11.1 Toxicity Related to Chemotherapy

11.1.1 FUDR: gastritis, gastroduodenal ulcers, chemical hepatitis, sclerosing cholangitis with jaundice, pruritus, diarrhea.

11.1.2 Dex: sodium retention, fluid retention, hypertension, development of cushingoid state, secondary adrenocortical and pituitary hypo-responsiveness, decreased carbohydrate tolerance, manifestations of latent diabetes.

11.1.3 Systemic Chemotherapy (Oxaliplatin*, CPT-11, 5FU/LV): diarrhea, myelosuppression, nausea, vomiting, stomatitis, neurotoxicity; neutropenia, thrombocytopenia, cumulative asthenia (CPT-11).

*Neurosensory Toxicity Guidelines:
Prior to each oxaliplatin dose, the patient should be questioned for symptoms of neurosensory toxicity. The table below presents the scale, which should be used instead of the NCI Common Toxicity Criteria for assessing neurosensory toxicity,

Specific Neurosensory Toxicity Scale

Grade 0	No symptoms
Grade 1	Paresthesias/dysesthesias of short duration with complete resolution prior to the next cycle. Does not interfere with function.
Grade 2	Paresthesias/dysesthesias persisting between two cycles without functional impairment.
Grade 3	Paresthesias/dysesthesias with pain/functional impairment that also interfere with ADL.

(See Section 12.2 for Oxaliplatin dose modification due to neurosensory toxicity.)

11.2 Toxicity Related to Bevacizumab:

Hypertension: Seen at a rate of approximately 10-15% and may be dose-related. In one study, at the 5 mg dose, two out of 35 patients receiving 5mg of Bevacizumab, and nine out of 32 patients receiving 10mg of Bevacizumab had hypertensive events. Hypertension was generally well managed.

Bleeding: In a lung cancer trial, there were six life-threatening bleeding events among 66 subjects. There were no life-threatening hemorrhagic events in completed Phase III trials in breast and colorectal cancers. Minor mucocutaneous bleeding (epistaxis) has also been seen in all Bevacizumab clinical trials at a rate of approximately 20-30%.

Thrombosis: In a large Phase III trial, 76 subjects (19.4%) receiving bolus IFL in combination with Bevacizumab had thromboembolic events compared with 64 subjects (16.2%) in the bolus IFL alone arm. Most of these events were venous (i.e., 65 subjects or 16.6% in the combination arm versus 60 subjects or 15.2% in the chemotherapy alone arm). The number of arterial events was 13 (3.3%) in the Bevacizumab + bolus IFL arm versus 4 (1.0%) in the bolus IFL alone arm.

Proteinuria: Proteinuria has been seen in all Bevacizumab clinical trials to date. In a large Phase II trial of colorectal cancer the incidence of proteinuria was similar between the Bevacizumab + bolus

IFL arm compared with IFL alone. However, based on a Phase III trial in breast cancer and a previous Phase II trial in colon cancer, proteinuria may be a Bevacizumab -related safety signal. However, no clinical sequelae resulted from proteinuria such as renal dysfunction or edema. The results also suggested that proteinuria may be dose-related.

Leukopenia: A modest increase in the incidence of Grade 3 and 4 leukopenia in subjects treated with Bevacizumab (37.0%) versus placebo (31.1%) was noted in a Phase III colorectal trial.

Neutropenia: When combined with chemotherapy, Bevacizumab increased the risk of neutropenia compared to chemotherapy alone. In a phase III trial with IFL +/- Bevacizumab in colorectal cancer, grade 3-4 neutropenia was 21% in the Bevacizumab + IFL arm vs. 14% in the IFL arm (grade 4 neutropenia was 3% vs. 2%).

Gastrointestinal Perforation: In the Phase III colorectal trial, the addition of Bevacizumab to bolus-IFL chemotherapy appeared to increase the risk of gastrointestinal perforation. There were 0 cases in the placebo arm, and 6 cases in the Bevacizumab plus bolus IFL arm.

CHF: There are no data to support that Bevacizumab increases the risk of CHF in subjects without exposure to anthracyclines.

Wound Healing: Partial delay in wound healing has been demonstrated in animal models treated with anti-VEGF antibodies. In one study, 173 subjects in the Bevacizumab-containing arm who underwent surgery within 28-60 days prior to beginning the study experienced no increase in post-operative bleeding or wound healing complications. In this same study, 5 of 55 subjects in the Bevacizumab-containing arms who underwent major surgery (requiring anesthesia) while on-study experienced post-operative bleeding or wound healing complications within 60 days since surgery. In the control arm, 25 subjects underwent surgery and none had bleeding or wound healing complications. It is possible, therefore, that Bevacizumab may delay or compromise wound healing in some subjects that undergo major surgery while on study.

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

11.3 Toxicity Related to the Pump and Catheters

Infection, hepatic artery thrombosis, pump malfunction, catheter occlusion, intra-abdominal bleed.

12.0 DOSE MODIFICATIONS

12.1 Oxaliplatin / 5FU:

12.1.1 Patients who experience grade 3 or 4 toxicity may, at the discretion of the investigator, continue treatment at a lower dosage level once toxicities have fully resolved.

12.1.2 Guidelines for re-starting medication are listed in table below:

Oxaliplatin + 5FU/Dose Reduction for Hematologic Toxicities (mg/m^2/day)

GRADE	Toxicity	5FU Infusion	Oxaliplatin
3	Neutropenia	20% reduction	20% reduction
4	Neutropenia	30% decrease	30% decrease
3	Febrile neutropenia[a]	20% decrease	20% decrease
3	Thrombocytopenia	20% decrease	20% decrease
4	Febrile neutropenia	40% decrease	20% decrease
4	Thrombocytopenia	40% decrease	20% decrease

[a]Febrile Neutropenia = ANC $< 1.0 \times 10^9$/L with fever $\geq 38.5^{\circ}$ C

Oxaliplatin + 5FU/LV Dose reductions for Non-Hematologic Toxicities (mg/m^2/day)

GRADE	Toxicity	5FU Infusion	Oxaliplatin
3	Nausea and/or vomiting despite premedication with an effective antiemetic therapy	20% decrease	20% decrease
4	Nausea and/or vomiting despite premedication with an effective antiemetic therapy	40% decrease	20% decrease
3	Diarrhea despite premedication with an effective antidiarrheal therapy	20% decrease	20% decrease
4	Diarrhea despite premedication with an effective antidiarrheal therapy	40% decrease	20% decrease
3	Stomatitis	20% decrease	No dose reduction
4	Stomatitis	30% decrease	20% decrease
≥ 2	Cardiac toxicity	Stop treatment	Stop 5FU, continue Oxaliplatin treatment (no dose reduction)
3 or 4	Hand/Foot Skin reaction	20% decrease	No dose reduction

Oxaliplatin Dose Modifications for Neurosensory Toxicity

	< 7 Days	**Persistent Between Cycles**
Dysesthesias with cold	No change	No change
Paresthesias	No change	↓ 25%
Paresthesias with functional impairment	n/a	Stop

Note: If pseudo laryngopharyngeal dysesthesia occurs, the next dose of Oxaliplatin should be administered as a three-hour infusion. Subsequent Oxaliplatin infusions should be administered as three-hour infusions, or shorter as tolerated.

12.2 CPT-11 Dose Modifications for Hematologic Toxicity and Diarrhea:

GRADE	Toxicity	CPT-11	5FU
3	Neutropenia, thrombocytopenia, diarrhea	20% decrease	20% decrease
4	Neutropenia, thrombocytopenia, diarrhea	40% decrease	40% decrease

12.6 FUDR Dose Modifications

"Reference value" is defined as the value obtained on the first day of the most recent FUDR dose.

To determine if a FUDR dose modification is necessary, compare reference value to the either the value obtained on the day pump was emptied (e.g. day 14) or the value obtained on the day of planned pump filling (e.g. day 28), whichever is higher.

Percentages listed under "FUDR Dose" refer to percentage of last dose of FUDR administered.

TABLE I: FUDR DOSE MODIFICATION SCHEMA:

	Reference Value*	**% FUDR dose**
SGOT *(at pump emptying or day of planned retreatment, whichever is higher)*	0 to < 2 x reference value	100%
	2 to < 3 x reference value	80%
	3 to < 4 x reference value	50%
	> 4 x reference value	Hold
ALK PHOS *(at pump emptying or day of planned retreatment, whichever is higher)*	0 to < 1.2 x reference value	100%
	1.2 to < 1.5 x reference value	50%
	> 1.5 x reference value	Hold
TOT BILI *(at pump emptying or day of planned retreatment, whichever is higher)*	0 to < 1.2 x reference value	100%
	1.2 to < 1.5 x reference value	50%
	> 1.5 x reference value	Hold
If SGOT > 4X reference value, alkaline phosphatase > 1.5X reference value, total bilirubin > 1.5X reference value, then treatment will be held and will not be reinstituted until values come down to more normal levels, as indicated in section "Recommencing FUDR Treatment After Hold".		

*** If patient's Alkaline Phosphatase or T Bili shows a continual rise from Day 1 of treatment, then the Day 1 value will be used as the reference value for that patient when determining whether to hold treatment, and time of re-treatment after hold.**

RECOMMENCING TREATMENT AFTER HOLD

REASON FOR TREATMENT DELAY	**Chemotherapy resumed when value has returned to:**	**% FUDR dose**
SGOT elevation	3 X reference value	25% of last dose

Alkaline Phosphatase elevation	1.2 X reference value	25% of last dose
Total bilirubin elevation	1.2 X reference value	25% of last dose

12.5.1 If patient develops a total bilirubin $\geq$ 3.0 mg/dl, the pump should be emptied and Dex 25 mg plus heparin 30,000 u and saline 30 cc placed in the pump q 14 days. Once there is no longer evidence of toxicity, Dex dose should be tapered in increments of 5 mg every 14 days. Tapering will continue unless enzymes increase. FUDR should be permanently discontinued unless there is evidence of disease progression (increasing CEA, worsening CT scan, worsening clinical status) AND bilirubin has returned to $\leq$ 1.5 mg/dl. In this case, FUDR can be restarted as follows: Use 25% of the last FUDR dose given with Dex, heparin and saline in the pump for 7 days. Pump should be emptied after 7 days, and patients given a 3-week rest period. This treatment and treatment schedule should continue as long as bilirubin remains $\leq$ 1.5 mg/dl and liver enzyme values do not increase.

12.5.2 Epigastric pain unresponsive to oral H_2 blocker use is suggestive of gastroduodenal irritation or ulcer. Severe pain should prompt workup with an upper gastrointestinal endoscopy. Serum amylase should be checked along with the routine blood (screening profile, creatinine, and CBC) in patients with abdominal pain. If an ulcer or gastroduodenitis is documented, therapy should be held for one month to allow healing. If abdominal pain is severe, the pump should be emptied of FUDR until results of workup are available.

12.7 Bevacizumab Dose Modifications

Drug treatment will be modified in the event of certain adverse events (as shown in the following table). There are no reductions in the Bevacizumab dose. If adverse event occur that require holding Bevacizumab, the dose will remain the same once treatment resumes. Regardless of the reason for holding the drug treatment, the maximum allowable length of treatment interruption is 2 months (2 cycles).

Bevacizumab should be held in patients with symptoms/signs suggestive of RPLS, pending workup and management, including control of blood pressure. Bevacizumab should be discontinued upon diagnosis of RPLS. Resumption of Bevacizumab may be considered in patients who have documented benefit from the agent, provided that RPLS was mild and has completely resolved clinically and radiographically within 2-4 weeks. The decision to resume Bevacizumab in these patients must be discussed with the study chair and approved by the sponsor.

Infusion-Related Adverse Events

Infusion of Bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. Subjects who experience a NCI CTCAE v. 3.0 Grade 3 or 4 allergic reaction/hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from Bevacizumab treatment.

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

Bevacizumab Dose Modification Table:

Event	Action to be Taken
Hypertension Grade 3 Grade 4	If not controlled with medication, discontinue from the study Discontinue the patient from the study
Hemorrhage Grade 3 Grade 4	Hold drug treatment until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable • There is no bleeding diathesis that would increase the risk of therapy • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence Patients who experience a repeat Grade 3 hemorrhagic event will be discontinued from treatment Discontinue the patient from the study
Venous Thrombosis Grade 3/Asymptomatic Grade 4 Symptomatic Grade 4	Hold study drug treatment. If the planned duration of full-dose anticoagulation is < 2 weeks, drug should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is > 2 weeks, drug may be resumed during the period of full-dose anticoagulation if all of the following criteria are met: • The patient must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin (or other anticoagulant) prior to restarting study drug treatment • The patient must not have had a Grade 3 or 4 hemorrhagic event while on study • The patient must not have had evidence of tumor involving major blood vessels on any prior CT scan Discontinue the patient from the study
Arterial Thromboembolic Event (angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event) Any Grade	Discontinue Bevacizumab
Proteinuria ≥ 2 g/24 hours	

Grade 4 (nephrotic syndrome)	Hold drug until proteinuria improves to < 2 g of protein in a 24-hour urine collection. If the 24-hour urine does not improve to < 2 g within 2 months, discontinue the patient from the study. Discontinue the patient from the study
Congestive Heart Failure (Left ventricular systolic dysfunction) No dose modifications for grade 1/2 events Grade 3 Grade 4	 Discontinue Bevacizumab Discontinue Bevacizumab

13.0 CORRELATIVE STUDIES

13.1 Liver Biopsy

Permission from patients entering the study will be obtained to take normal and tumor liver biopsies at the time of surgery. These will be sent to Dr. David Solit's lab at Memorial Sloan Kettering, Genitourinary Oncology Service.

Rationale/Objective: This study is based on the hypothesis that the growth and progression of metastatic liver lesions are dependent on the factors that support angiogenesis and lymphangiogenesis. As signaling molecules regulating these two processes are driven by three different tyrosine kinase receptors, namely VEGFR1 (hemangiogenesis), VEGFR2 (Angiogenesis), and VEGFR3 (lymphangiogenesis), we propose to assess the expression pattern of these receptors and their cognate ligands including VEGF-A, VEGF-C, and VEGF-D in the metastatic lesions. Since Bevacizumab selectively blocks the activity of VEGF-A, but not VEGF-C and VEGF-D, these studies will provide important information as to whether inhibition of VEGF-A/VEGFR2 signaling pathway is sufficient to block tumor angiogenesis and lymphangiogenesis within the liver lesions.

We anticipate that tumors that primarily overexpress VEGF-A/VEGFR2 are going to be more responsive to Bevacizumab (anti-VEGF-A) therapy. On the other hand, tumors that overexpress both VEGF-A/VEGFR2 and VEGF-C, -D/VEGFR3 signaling pathways may be less sensitive to Bevacizumab (anti-VEGF-A) therapy, as VEGFR3 activation may promote lymphangiogenesis and neo-angiogenesis. Therefore, by evaluating a number of different VEGF receptors we can see if certain receptors are seen more often and may therefore be more predictive of TTP and overall survival.
In parallel to these studies, plasma circulating levels of VEGF-A, -B, and -C will be assessed. In addition, the number of circulating CD133+VEGFR2+ and CD34+VEGFR2+ endothelial progenitors will be quantified. These data provide important information as to whether these surrogate markers could be used to evaluate progression and survival in patients treated with Bevacizumab.

13.2 Planned Experiments

Determination of angiogenesis:

a. The angiogenic index will be determined on the biopsy sample by staining with vWF, VE-cadherin, CD31 (PECAM) and VEGF receptors, including VEGFR1, VEGFR2, and VEGFR3.
b. Plasma levels of VEGF-A and PlGF will be performed by evaluation of ELISA assay. Extreme care will be used to eliminate the contribution of these factors by activated platelets.
c. Quantification of the number of circulating CD133(AC133)+VEGFR2+ and CD34+ VEGFR2+ endothelial progenitors and VEGFR1+ Pro-angiogenic hematopoietic cells. Flow cytometry will be used to quantitate the number of circulating cells.
d. The stability of the newly formed vessels will be determined on the biopsy sample by staining with smooth muscle alpha-actin collagen type IC, and integrins. The levels of metalloproteinases which are induced by VEGFR1, VEGFR2 and VEGFR3 activation, including MMP-9 and MMP-2 will also be assessed.

Determination of lymphangiogenesis:

a. VEGFR3, podoplanin-A, Lyve-1 expression to determine the level of lymphangiogenic activity/vessels will be performed on the biopsy sample.
b. Plasma VEGF-C and VEGF-D levels. Both pro-VEGF-C and active VEGF-C will be quantified.
c. The number of circulating CD133+VEGFR3+ circulating lymphangiogenic progenitor cells will be determined.

Frozen and paraffin cut section of the tumor tissue/biopsy sample will be analyzed for the expression of VEGFR1, VEGFR2, and VEGFR3 using standard immunohistochemical techniques. Acetone-fixed frozen sections will be incubated with FITC-conjugated monoclonal antibodies to VEGFR1, VEGFR2 and VEGFR3, and the stained slides will be analyzed by standard fluorescent microscopy. Co-staining with CD31 and smooth muscle alpha actin, collagen Type-IC and integrins on the paraffin-fixed section will determine the number of pericyte-coated stabilized capillaries.

The apoptotic status of tumor cells and endothelial cells will be examined on the biopsy sample by TUNEL assay using commercially available kits. The identity of the endothelial cells will be established by co-immunostaining with endothelial specific markers including cWF and VE-cadherin. The level of endothelial activation will be examined by determination of ICAM1, VCAM1 and E-selectin expression.

RNA extraction, complementary DNA synthesis, and RT-PCR:

Peripheral blood mononuclear cells will be analyzed for VEGF-A, VEGF-B, VEGF-C, and VEGF-D expression by reverse transcriptase-polymerase chain reaction (RT-PCR) and Western analysis. Extreme care will be used to eliminate the contribution of activated platelets to the expression of VEGF or VEGF receptor levels. For PCR, total RNA will be extracted from circulating cells by using TRI reagent following the manufacturer's instructions. As control cells we will use RNA from human umbilical endothelial cells (HUVECs) and leukemic cells. Complementary DNA will be subsequently synthesized from total cellular RNA using First Strand Synthesis Kit, and PCR will be performed using a PCR thermal cycler. The PCR program used to amplify the VEGFs will consist of a precycle of 5 minutes at 94° C, 45 seconds at 60° C, and 45 seconds at 72° C. Following this initial cycle, the reaction will be continued for 35 cycles of 1 minute at 94° C, 45 seconds at 65° C, and 2 minutes at 72° Cm and conclude with 7 minutes at 72° C. The primer sequences will be as follows: -actin forward primer: TCATGTTTGAGACCTTCAA; -actin reverse primer: GTCTTTGCGGATGTCCACG (-actin PCR product: 513 base pairs [bp]); VEGF-C forward

primer: GTGACCAACATGGAGTCGTG; VEGF-C reverse primer: CCAGAGATTCCATGCCACTT (VEGF-C PCR product: 660 bp); VEGFR3 forward primer: ATTTGTGATTTTGGCCTTGC; FLT-4 reverse primer: CAGGCTCATGAACTTGAAAGC (VEGFR3 PCR product: 550 bp); VEGFR2 (KDR) forward primer: GTGACCAACATGGAGTCGTG; and VEGFR2 reverse primer: CCAGAGATTCCATGCCACTT (VEGFR2 PCR product: 660 bp).

Protein extraction and Western blotting:

Western blotting will be used to detect and validate the expression of VEGFs and VEGFRs on the peripheral blood mononuclear cells and late outgrowth colonies (CFU-EC) from CD133+VEGFR2+ endothelial progenitors isolated from the peripheral blood cells. Endothelial colonies (CFU-EC) will be generated by incubation with VEGF-A or VEGF-C with the peripheral blood mononuclear cells. Outgrowth endothelial colonies and other hematopoietic mononuclear cells will be lysed in cold RIPA buffer (50 mM/L Tris, 5 mM/L ethylenediaminetetraacetic acid, 1% Triton X-114, o.4% sodium cacodylate, and 150 mM NaCl) in the presence of protease inhibitors (1 mg/mL aprotinin, 10 mg/mL leupeptin, 1 mmol/L-glycerophosphate, 1 mM sodium orthovanadate, and 1 mM/L phenylmethysulfonyl fluoride). As controls, protein will also be extracted from human umbilical endothelial (HUVEC) and leukemic cells. HUVECs will be used as positive controls for the expression of VEGFR1, VEGFR2, and VEGFR3. Leukemia cells will be used as control for the expression of VEGF-C, VEGF-D, and VEGF-A. After centrifugation to remove cell debris, supernatants (a total protein minimum of 500 ng) will be immunoprecipitated overnight at 4° C with protein G-agarose beads and an antiphosphotyrosine antibody (Santa Cruz, Biotechnology) to precipitate phosphorylated proteins or with a mouse antihuman VEGFs or VEGF receptors. Precipitated proteins/antibody/beads are then washed twice, re-suspended in loading buffer, and then subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis (7.5% gels) under reducing conditions (in the presence of mercaptoethanol). Proteins are subsequently blotted onto a nitrocellulose membrane following conventional protocols. Finally, blots will be blocked in 1% bovine serum albumin/phosphate-buffered salin-0.1%. Tween 20 for 1 hour at room temperature followed by incubation with primary and secondary antibodies. Antibodies used will include the mouse antihuman VEGFs or VEGF receptors, and a secondary peroxidase-labeled goat antimouse antibody. The ECL chemiluminescence detection system and ECL film will be used to visualize the presence of proteins on the nitrocellulose blots.

14.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

14.1 Tumor assessments while on treatment will not be necessary since tumor is resected.

14.2 After treatment is completed, patient should be seen every 3 months.

14.3 CT scan of the chest, abdomen and pelvis, and CEA every 3 months for the first 2 years after the completion of treatment.

14.4 Colonoscopy within the first 2 years after completion of treatment.

14.5 CT scan of the chest, abdomen and pelvis and CEA every 4 months between 2 and 4 years after completion of the treatment.

14.6 CT scan of the chest, abdomen and pelvis and CEA every 6 months between 4 to 5 years, and yearly thereafter until patient expires.*

*Follow up schedule is subject to MD discretion.

15.0 CRITERIA FOR REMOVAL FROM STUDY

15.1 Development of clear-cut evidence of recurrent colorectal cancer in the liver compared to the baseline postoperative CT scan.

15.2 Development of clear-cut evidence of extrahepatic recurrence via clinical exam or imaging studies.

15.3 Patient is unable to resume hepatic arterial FUDR due to hepatic toxicity.

15.4 Unacceptable toxicity that does not respond to the dosage modification.

15.5 Patient elects to discontinue treatment.

15.6 Changes in a patient's condition which render the patient unacceptable for further treatment in the judgment of the investigator.

Patients who have an ongoing bevacizumab-related Grade 4 or serious adverse event at the time of discontinuation from study treatment will continue to be followed until resolution of the event or until the event is considered irreversible (see Section 12.7).

16.0 BIOSTATISTICS

This study will 1:1 randomize 80 patients to two treatment arms: hepatic arterial infusion of FUDR and dexamethasone with systemic chemotherapy, +/- systemic Bevacizumab (anti VEGF-A). The primary endpoint of the study is disease-free survival. This sample is chosen to provide an estimate of the median time-to progression in each arm, to within +/- six months, assuming exponentially distributed survival times, and a one-year progression-free survival probability of 70%. All progression and survival probabilities will be estimated using the Kaplan-Meier method. If the one-year progression-free survival probability in the Bevacizumab arm is 80% or higher we will consider this a sign of potentially improved efficacy and an encouragement for a larger comparative study. The decision to initiate such a study will depend on many factors, including tolerability of the regimen.

The systemic chemotherapy will be either CPT-11 + 5FU/LV or Oxaliplatin + 5FU/LV, depending on whether the patient has received any chemotherapy before, and if so, whether the previous regimen utilized Oxaliplatin (see section **3.3** for further details). The assignment of systemic chemotherapy, therefore, is not subject to randomization. To ensure that the distribution of previous chemotherapy status is relatively balanced between the two treatment arms, randomization will be stratified using two variables: prior chemotherapy status, and clinical risk score (CRS). CRS utilizes a system of points, awarding one point for each of the following factors: node-positive primary, disease-free interval of < 12 months, more than 1 tumor, tumor size > 5cm, and CEA > 200 ng/ml. Patients will be stratified by CRS: 0-2 points vs. 3 or more. The randomization will take place after surgery for complete resection of liver metastases.

As for the correlative studies, tissue and plasma expression levels for markers in the VEGF family (VEGF-A, VEGF-B, VEGF-C, VEGF-D, PlGF, TF, PTEN, PAR-1, PAR-2, p53) will be expressed as "+"

or "-" for each marker, and compared with McNemar's test, separately for each arm and marker. Baseline and follow-up plasma levels will also be analyzed in the same way. With 40 patients, we will have approximately 80% power to detect a difference of 45% in the proportion of patients over-expressing a given marker (e.g., 70% + at baseline, and 25%+ at follow-up) for each arm. A similar analysis is planned for comparing baseline levels with interim and post-treatment levels.

Baseline tissue levels will also be compared with time-to-progression, again separately for each arm and marker, using the log-rank test. We will have sufficient power to detect large differences only in this relatively small study. Specifically, we will have approximately 80% chance of finding a significant result if the median TTP of those patients who are marker "-" at baseline is approximately 2.8 times of those who are "+" (Type I error of 5%, log-rank test, assuming 50% prevalence for the marker).

Statistical considerations TF –

Immunohistochemistry
About 45% of colon cancer patients are expected to be KRAS and BRAF mutated. Therefore among 100 patients, 45 are expected to carry either KRAS or BRAF mutations while and 55 would be wild-type. With 45 patients we can estimate the proportion of positive TF staining within +/- 15% error for the KRAS or BRAF mutated patients. With 55 patients we can estimate the proportion of positive TF staining within +/- 14% error for the wild type patients.

Serum analysis
As no reference values in patients with metastatic colorectal cancer are known, the statistical analysis will be performed post-hoc. The sample size of the blood replicates is however based on guidlines elaborated by a consensus paper regarding exploration of new biomarkers (Pintilie M et al 2009).

Approximate accrual rate for this study is 4 patients per month.

17.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

17.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. .

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

17.2 Randomization

Patients will be randomized after surgery for complete resection of liver metastases. Two stratification variables will be used: prior chemotherapy status and clinical risk score (0-2 vs. 3 or more) [See Appendix A, Fong Score].

18.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

18.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

18.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://mskweb2.mskcc.org/irb/indexx.htm.

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e. g. protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institution Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g. NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

19.0 PROTECTION OF HUMAN SUBJECTS

19.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research

Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

Serious Adverse Event (SAE) Reporting

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

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - o An explanation of how the AE was handled
    - o A description of the participant's condition
    - o Indication if the participant remains on the study

- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

For IND/IDE protocols: The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office .

All SAE reports must also be forwarded <u>as soon as possible</u> to:
Genentech Drug Safety
Fax: (650) 225-4682 or (650) 225-4683

For questions related to safety reporting, contact:

Genentech Drug Safety
Tel: 1-888-835-2555

Genentech may contact the reporter for additional information, clarification, or current status of the subject for whom and adverse event was reported.

19.2 Genentech Adverse Events Reporting Definitions

A serious treatment emergent adverse event (STEAE) is any sign, symptom or medical condition that emerges during Bevacizumab treatment or during a post-treatment follow-up period that (1) was not present at the start of Bevacizumab treatment and it is not a chronic condition that is part of the patient's medical history, OR (2) was present at the start of Bevacizumab treatment or as part of the patient's medical history but worsened in severity and/or frequency during therapy, AND that meets any of the following regulatory serious criteria:

- Results in death
- Is life-threatening
- Requires or prolongs inpatient hospitalization
- Is disabling
- Is a congenital anomaly/birth defect
- Is medically significant or requires medical or surgical intervention to prevent one of the outcomes listed above.

Assessing Causality:

The event should be assessed to decide whether there is a reasonable possibility that bevacizumab caused or contributed to an adverse event. The following general guidance may be used.

Yes: if the temporal relationship of the clinical event to bevacizumab administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No: if the temporal relationship of the clinical event to bevacizumab administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

For Investigator Sponsored IND Exempt Studies, there are some reporting requirements for the FDA in accordance with the guidance set forth in 21 CFR 314.80.

All Postmarketing 15-Day "Alert Reports" submitted to the FDA by the Sponsor-Investigator must also be faxed to: Genentech Drug Safety, Fax: (650) 225-4682 or (650) 225-5288.

For questions related to safety reporting, contact:

Genentech Adverse Events
Tel: Penny Wilkins, Drug Safety Scientist
(650) 225-4846
OR
Ron Magana, Clinical Safety Associate
(650) 225-4926
Fax: (650) 225-4682 or (650) 225-4683

20.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

21.0 REFERENCES

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APPENDIX A

Clinical Risk Score for Tumor Recurrence*

	Survival (%)					
Score	**1-yr**	**2-yr**	**3-yr**	**4-yr**	**5-yr**	**Median (mo)**
0	93	79	72	60	60	74
1	91	76	66	54	44	51
2	89	73	60	51	40	47
3	86	67	42	25	20	33
4	70	45	38	29	25	20
5	71	45	27	14	14	22

Each risk factor is one point: node-positive primary, disease-free interval < 12 months, > 1 tumor, size > 5cm, CEA > 200 ng/ml. Adding all risk factors yields score between 0 – 5.

*Fong Y, Fortner J, Sun RL, Brennan M, Blumgart L. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer. Ann Surg 1999; 230: 309-321.