A Randomized Phase II Study of Irinotecan and Cetuximab with or without the Anti-Angiogenic Antibody, Ramucirumab (IMC-1121B), in Advanced, K-ras Wild-type Colorectal Cancer Following Progression on Bevacizumab-Containing Chemotherapy

STUDY CHAIR: Howard S. Hochster, MD
STUDY CO-CHAIR: Deirdre Cohen, MD
Peter O’Dwyer, MD
STUDY STATISTICIAN: Paul Catalano, Sc D
GI COMMITTEE CHAIR: Al B. Benson III, MD
SWOG CO-CHAIR: Howard S. Hochster, MD

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Irinotecan (NSC #616348) Commercially available for this study
Cetuximab (NSC #714692) Commercially available for this study
Ramucirumab (NSC #749128) (IND 109448) Supplied by ImClone Systems for this study

STUDY PARTICIPANTS
US Sites Only
ALLIANCE / Alliance for Clinical Trials in Oncology
NRG / NRG Oncology Foundation, Inc
SWOG / SWOG Cancer Trials Support Unit (CTSU)*

*NOTE: This study is supported by the NCI Cancer Trials Support Unit (CTSU). Institutions not aligned with ECOG-ACRIN will participate through the CTSU mechanism as outlined in the protocol.

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Addendum #5 – 6/14
Addendum #6 – 6/14
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STUDY CHAIR
Howard S. Hochster, MD
Yale Cancer Center
333 Cedar Street, Box 208028
New Haven, CT 06520
Telephone: 203-785-2360 (work hours)
203-200-4422 (evenings and weekends)
Email: howard.hochster@yale.edu

STUDY CO-CHAIR
Peter O'Dwyer, MD
University of Pennsylvania Cancer Center
1223 Penn Tower
3400 Spruce Street
Philadelphia, PA 19104
Phone: (215) 662-7268
Fax: (215) 243-3268
Email: peter.odwyer@uphs.upenn.edu
# CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

<table>
<thead>
<tr>
<th>To submit site registration documents:</th>
<th>For patient enrollments:</th>
<th>Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:</th>
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</thead>
<tbody>
<tr>
<td>CTSU Regulatory Office</td>
<td>Please refer to the patient enrollment section for instructions on using the OPEN system.</td>
<td>ECOG-ACRIN Operations Office – Boston, FSTRF, 900 Commonwealth Avenue Boston, MA 02215 (ATTN: DATA). Phone # 617-632-3610 Fax # 617-632-2990 Data should be sent via postal mail (preferred), however fax is accepted. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.</td>
</tr>
<tr>
<td>1818 Market Street, Suite 1100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Philadelphia, PA 19103</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phone – 1-866-651-CTSU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fax – 215-569-0206</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at [https://www.ctsu.org](https://www.ctsu.org). Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol. CTSU sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.

**For patient eligibility or treatment-related questions** Contact the Study PI of the Coordinating Group.

**For questions unrelated to patient eligibility, treatment, or data submission** contact the CTSU Help Desk by phone or e-mail:

CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

**For detailed information on the regulatory and monitoring procedures for CTSU sites** please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members’ website [https://www.ctsu.org](https://www.ctsu.org)

The CTSU Web site is located at [https://www.ctsu.org](https://www.ctsu.org)
Eligibility: metastatic or advanced CRC, K-ras wild-type, first line therapy with oxaliplatin-containing chemotherapy and bevacizumab, now progressing.

Stratify:

1) PS (0 vs. 1)

2) Discontinuation of oxaliplatin first-line therapy prior to progression (yes vs. No)

3) Progression ≤ 6 months of last treatment vs. > 6 months

Primary endpoint: PFS; 90% power to detect difference between 4.5 months for control vs. 7.65 months for experimental arm (\(\alpha = 0.10, \beta = 0.10\))

* Treatment should not be started until at least 28 days after last bevacizumab dose.

** Arm B closed to accrual in Addendum #5. New patients are randomized to Arm A or Arm C.

Accrual Goal = 135
1. Introduction

1.1 Colon Cancer

1.1.1 Background

Colorectal cancer (CRC) is a significant cause of cancer mortality. The worldwide incidence of CRC in 2000 was estimated as 944,700 cases (males: 498,000; females: 446,000 cases) (1). In the United States (US) colorectal cancer accounts for approximately 11% of all cancer deaths (2). At diagnosis, 40% of the world’s CRC population have metastatic or “synchronous metastases.” In the US, approximately 20% of newly diagnosed patients with CRC will have synchronous metastatic cancer (3). Approximately 25% of patients with localized disease at diagnosis will ultimately develop metastatic disease. Unfortunately only a small number of patients with stage IV cancer can be cured with multimodality therapy. The majority of patients with metastatic, stage IV CRC will ultimately die of their disease (4).

Newly developed, and now standard, therapies for patients with stage IV CRC have dramatically improved survival and enhanced quality of life. Thus, in the U.S., initial therapy with combinations of 5-fluorouracil (5FU) and oxaliplatin (FOLFOX) or 5FU and irinotecan (FOLFIRI) have increased response rates to approximately 45 percent (5). The addition of bevacizumab to either FOLFOX or FOLFIRI has produced response rates of 60%. Indeed, for approximately eight percent of patients with stage IV CRC, the addition of surgery to successful chemotherapy will produce a cure (6). Upon progression after so-called “first-line therapy,” approximately 20% of patients will respond to a second systemic treatment combination. Most important, median survival for patients with stage IV CRC is now approaching 2.5 years (7). It is likely that with a better understanding of how to incorporate intratumoral molecular parameters such as mutations in the k-ras gene and/or quantitation of a tumor's repair genes such ERCC-1 or XRCC-1 and/or targets such as thymidylate synthase into treatment strategies, complete responses and cure rates will continue to improve.

1.1.2 First Line therapy

A series of clinical trials in the first line therapy of metastatic CRC have improved survival from a median of 12 months to nearly 24 months. A series of trial showed that combination therapy using oxaliplatin (FOLFOX4) or irinotecan (IFL or FOLFIRI) gave improved RR, OS and PFS compared with FU and LV bolus or infusion therapy. This was confirmed in the N971 US Intergroup trial showing improved RR, OS and PFS for FOLFOX compared with the control arm of IFL (5). Shortly thereafter a randomized trial of IFL with or without bevacizumab showed and improved HR for PFS and OS for the addition of the anti-VEGF antibody. This has been adopted into standard practice with all 5FU based first line therapies, including FOLFIRI or FOLFOX. A more recent study (NO16966) demonstrated
improved PFS with the addition of bevacizumab to either FOLFOX or CapeOX therapy, though of a smaller benefit due to early stopping of chemotherapy (7). As FOLFOX has become the standard first-line chemotherapy platform, particularly in the US, second line therapy has relied on irinotecan based programs.

1.1.3 Second Line Therapy

A study performed by the GERCOR demonstrated that the sequence FOLFOX followed by FOLFIRI was equivalent to the reverse sequence (8). As a result, US practice has evolved to use irinotecan based regimens as second-line therapy. Either FOLFIRI or irinotecan seem equally useful in this situation and either may be used as there is no study showing a synergistic effect of fluoropyrimidines with irinotecan. In the GERCOR multi-center study, patients with advanced CRC were treated with FOLFOX followed by FOLFIRI at the time of progression or the reverse sequence. In the FOLFOX first arm, the response rate for second line FOLFIRI was 4% and PFS was 2.5 months. A larger second line study was performed to examine the role of the anti-EGF antibody, cetuximab as second line therapy on patients progressing on FOLFOX. In this 1300 patient study, the subjects were randomized to irinotecan alone or irinotecan plus cetuximab (9). The patient populations were not selected for Kras status. Again the response rate for second line irinotecan was 4.2% and PFS was 2.6 months (n = 650).

Recent reports of the predictive value of K-ras gene mutation (36,37) have demonstrated convincingly that patients with mutations in codon 12 and 13 (as determined by RT-PCR from FFPET) do not benefit from the use of anti-EGFR antibodies, either as single agent or in combination with chemotherapy programs (10). As such, two treatment tracks exist for second-line therapy, based on cetuximab use in the K-ras wild-type group and irinotecan based therapy alone in those with Kras mutations. In this study, the patient population will be limited to those with Kras wild-type status, as both arms will receive cetuximab and irinotecan.

1.1.4 Biweekly Dosing of Cetuximab

Cetuximab is approved for previously treated colon cancer with non-mutated K-ras ("wild type"). The standard dose and schedule is 400 mg/m² loading dose x 1, then weekly 250 mg/m². Because of the long half-life of therapeutic monoclonal antibodies, such as cetuximab, many such agents have alternate dosing schedules of q2 weeks or even q3 weeks. In this study we have chosen the dose of 500 mg/m² every two weeks, for the reasons detailed below, and also to facilitate co-administration with the irinotecan (180 mg/m²) biweekly schedule.

Data supporting the biweekly dose of cetuximab 500 mg/m² have been presented and published. Tabernero, et al (Tabernero, Cervantes, Martinelli, et. Al, J Clin Oncol, 24 (18 Suppl), 142s) performed a phase I/PK study demonstrating equivalent pharmacokinetic parameters for the drug on the q2w schedule. 10 patients treated on the standard dose/schedule were used in
comparison. No significant differences were seen with respect to AUC, half-life, or steady-state clearance between the two schedules (Table 1). In addition, the Phase I portion of the study escalated cetuximab dose to achieve a gr 2-3 skin rash, reaching doses of 700 mg/m² q2w safely. The study was continuing at the time of presentation.

Table 1

<table>
<thead>
<tr>
<th>Schedule</th>
<th>C_{min} (µg/mL)</th>
<th>AUC (µg/mL*h)</th>
<th>t_{1/2} (h)</th>
<th>CL_{ss} (L/h/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400/250 mg/m² q1w</td>
<td>47.0 (37.3)</td>
<td>17278 (5205)</td>
<td>110 (24)</td>
<td>0.016 (0.004)</td>
</tr>
<tr>
<td>400 mg/m² q2w</td>
<td>25.6 (11.8)</td>
<td>27655 (6965)</td>
<td>124 (25)</td>
<td>0.015 (0.004)</td>
</tr>
<tr>
<td>500 mg/m² q2w</td>
<td>35.2 (13.8)</td>
<td>34953 (6275)</td>
<td>134 (33)</td>
<td>0.015 (0.003)</td>
</tr>
</tbody>
</table>

This combination of irinotecan 180 mg/m² and cetuximab 500 mg/m² q2w has also been reported in a Spanish phase II study (Martin-Martorell, et.al. Br J Ca 99: 455-458, 2008). Forty patients were treated and a response rate of 23% was reported (compared with 20% in the EPIC trial, N =1147), with a Disease Control Rate of 60%. Median time to progression was 3.4 months and overall survival was 8 months. This also is approximately equivalent to the cetuximab arm of the EPIC trial. Toxicity of grade 3-4 severity was reported as diarrhea = 10%, neutropenia = 7.5% and skin toxicity = 7.5%, which are all somewhat lower than similarly reported toxicity rates in the EPIC trial. In short, this phase II study suggests the activity and toxicity is not substantially different using irinotecan and cetuximab q2w compared with irinotecan every 3 weeks with weekly cetuximab. This biweekly schedule has been widely adopted in practice by US oncologists.

1.2 **Vascular Endothelial Growth Factor and Angiogenesis**

Angiogenesis, the formation of new capillaries and blood vessels, is a tightly-controlled, multistep process that is a component of normal physiology (including development of the embryonic vasculature, wound healing, ovulation, and menstruation). Pathologic angiogenesis contributes to tumor growth and metastasis, as well as other human diseases such as diabetic retinopathy, rheumatoid arthritis, and psoriasis (11-13). A number of growth factors have been identified as positive regulators of angiogenesis, including members of the vascular endothelial growth factor (VEGF) family, basic fibroblast growth factor, transforming growth factor alpha, transforming growth factor beta, tumor necrosis factor, platelet-derived endothelial growth factor, hepatocyte growth factor, angiogenin, interleukin-8, and placental growth factor (14,15). VEGF-A is one of several related cytokines; it is distinct in that it acts as an endothelial cell-specific mitogen and is the growth factor most consistently found in conditions associated with angiogenesis (16-19). The biological activity of VEGF-A (hereafter VEGF) is principally mediated by two structurally-related, high affinity tyrosine kinase receptors: the 180 kDa fms-like tyrosine kinase (VEGFR-1 or Flt-1) (20,21); and the 200 kDa receptor (VEGFR-2 or kinase insert domain-containing receptor [KDR]), or its murine homologue, fetal liver kinase-1 (Flk-1)(20,21). Targeted deletion of genes encoding VEGF, VEGFR-1, or VEGFR-2 in mice is lethal to the
embryo, demonstrating the physiological importance of the VEGF pathway in blood vessel formation. Mice lacking even a single VEGF allele die prior to birth due to vascular abnormalities (24,25). VEGFR-2-deficient mice have impaired blood island formation and lack mature endothelial cells (26), whereas VEGFR-1 null embryos have abundant endothelial cell-like cells, but fail to develop normal vasculature (27).

1.3 The Role of VEGF and VEGFR-2 in Angiogenesis and Tumor Growth

The importance of VEGF and VEGFR-2 in angiogenesis and tumor growth has been demonstrated in several animal models. VEGFR-2 expression is associated with activated endothelium and is strongly upregulated in tumor endothelium (16,28). Inhibiting the function of the VEGF/VEGFR-2 pathway via a number of approaches, including anti-VEGF antibodies, anti-VEGFR-2 antibodies, anti-VEGF antisense ribonucleic acid expression, VEGF-based immunotoxins, soluble VEGF receptors, ribozymes to VEGF receptors, and small molecule VEGFR-2 tyrosine kinase inhibitors, has been shown to inhibit new blood vessel formation and tumor growth in a variety of animal models (29-32).

VEGF and VEGFR-2 are overexpressed in the great majority of human cancers, including carcinomas of the gastrointestinal tract, pancreas, breast, cervix, bladder, ovary, uterus, endometrium, and kidney; Kaposi’s sarcoma; glioblastoma multiforme; and hemangioblastomas. In addition, messenger ribonucleic acid for both VEGFR-1 and VEGFR-2 is greatly upregulated in tumor-associated endothelial cells, but not in the vasculature of the surrounding normal tissue. A correlation between VEGFR-2 expression and tumor microvessel density has been associated with poor prognosis, advanced disease, increased risk of metastasis and recurrence, and lower relapse-free survival in patients with a variety of cancers (13,32).

Accumulating evidence suggests that the dual autocrine/paracrine mechanism also may play an important role in the growth and metastasis of certain solid tumors. For example, a VEGF/VEGFR autocrine loop was proposed as a mediator of growth and metastasis of several types of tumors, including carcinomas of prostate, ovary, pancreas, and breast; malignant pleural mesothelioma; and melanoma (32). These observations suggest that anti-VEGFR-2 antibodies may have potential as antiangiogenic and antitumor agents.

1.4 IMC-1121B (Ramucirumab)

Ramucirumab is a recombinant human monoclonal antibody (MAb) of the immunoglobulin G, subclass 1 (IgG1) that specifically binds to the extracellular domain of VEGFR-2 with high affinity. This antibody potently blocks the binding of the VEGF ligand to VEGFR-2, inhibits VEGF-stimulated activation of both VEGFR-2 and p44/p42 MAP kinases, and neutralizes VEGF-induced mitogenesis of human endothelial cells.

Ramucirumab has been shown to block the interaction of VEGF and VEGFR-2 (with a concentration that inhibits binding by 50% of approximately 1 nM), and to inhibit VEGF-stimulated proliferation of endothelial cells and VEGF-induced migration of human leukemia cells (33,34).

Preclinical pharmacodynamic data demonstrate that Ramucirumab binds specifically and with high affinity to the VEGFR-2, and is capable of inhibiting certain in vitro biological processes. These include VEGF/VEGFR-2 interaction,
VEGF-stimulated VEGFR-2 activation, proliferation of human endothelial cells, VEGF-induced migration of human leukemia cells, and VEGF-induced phosphorylation of VEGFR-2 in both human umbilical vein endothelial cells and porcine aortic endothelial cells engineered to overexpress VEGFR-2 (34). These processes are likely involved in tumor angiogenesis. Potent angiogenic and antitumor effects are observed when DC101, an antibody to murine VEGFR-2, is administered to mice bearing syngeneic tumors or human tumor xenografts. The results of these preclinical pharmacodynamic studies support the investigation of Ramucirumab in the treatment of solid tumors.

Two repeat-dose toxicology studies (5 weeks and 39 weeks) were conducted in cynomolgus monkeys. In the 5-week repeat-dose study, Ramucirumab was administered intravenously at doses of 0, 4, 12, or 40 mg/kg. There were no Ramucirumab-related effects seen in clinical signs, body weights, food consumption, urinalysis, blood pressure, hematology, coagulation, and serum chemistry. There were also no Ramucirumab-related effects found at gross pathology evaluation. Histopathology evaluation revealed focal muscle fiber degeneration and mononuclear cell infiltration in skeletal muscle (quadriceps femoris) in test article-treated animals only. These effects were concluded to be not treatment-related due to the focal nature of the lesions and the low incidence in females. The Ramucirumab injection sites had mild reactions consisting of mononuclear cells or mononuclear and polymorphonuclear cells in perivascular areas. Based on the results of this study, intravenous administration of Ramucirumab was well tolerated at dose levels from 4 to 40 mg/kg for four doses and the no-observable-effect level (NOEL) in this study was ≥ 40 mg/kg, the highest dose administered.

In the 39-week repeat-dose study, Ramucirumab was administered via intravenous infusion at dose levels of 5, 16, and 50 mg/kg to cynomolgus monkeys for 11 weekly doses over 12 weeks (females only) or weekly for 39 weeks (males and females) of study. There were no Ramucirumab-related effects noted in animals treated at up to 50 mg/kg for 12 weeks of study. Thickening and osteochondropathy of the epiphyseal growth plate was noted at 5 mg/kg and above in animals treated for 39 weeks. This was an anticipated mechanism-related effect. Treatment with Ramucirumab resulted in renal toxicity at the 16- and 50-mg/kg dose levels after 39 weeks. In addition, clinical chemistry and urinalysis parameters indicated that the renal toxicity had manifested at 16 mg/kg and 50 mg/kg after 26 weeks. A NOEL of Ramucirumab could not be established when administered intravenously once a week for 39 weeks in male or female cynomolgus monkeys.

1.4.1 Clinical Studies

Two Phase 1 studies are being conducted to evaluate the safety and antitumor effects of Ramucirumab administered either weekly (CP12-0401) or every other week or every third week (CP12-0402) at doses ranging from 2 mg/kg through 20 mg/kg in patients with advanced cancer. Two mechanism-based, dose-limiting toxicities were observed at the weekly schedule of 16 mg/kg, symptomatic hypertension and deep vein thrombosis, both of which occurred after several cycles of Ramucirumab infusion. Thus, the maximum tolerated dose for the weekly study was determined as 13 mg/kg.
administered on a weekly schedule. The MTD has not been reached for the every other week or the every third week schedules.

A total of 37 patients have been enrolled in study CP12-0401 (Ramucirumab administered weekly) at doses of 2 to 16 mg/kg; this patient population includes 23 males and 14 females, ranging in age from 36 to 76 years. Adverse events ≥ grade 3 considered to be at least possibly-related to Ramucirumab were reported in 10 patients and include hypertension, deep vein thrombosis, headache, vomiting, anemia, increased amylase, hyperphosphatemia, and proteinuria. To date, four confirmed partial responses (in melanoma, gastric and neuroendocrine tumors, and uterine leiomyosarcoma) have been reported, and at least nine patients have experienced prolonged stable disease (> 6 months). At least one of these patients had been treated previously with the anti-VEGF agent bevacizumab. Importantly, other evidence of clinical benefit has also been noted. In particular, several patients (melanoma [1 patient], gastric cancer [1 patient], and thyroid cancer [2 patients]) experienced significant pain relief along with reductions in analgesic requirements, and a patient with refractory pleural effusions experienced significant reductions in fluid retention and a lower frequency of thoracenteses.

A total of 25 patients have been enrolled in study CP12-0402 (Ramucirumab administered every other week or every 3 weeks), of whom 24 have received treatment at doses ranging from 6 mg/kg to 20 mg/kg. The MTD has not been reached for the every-other-week or the every-third-week schedules; the study is ongoing but currently closed to enrollment.

A total of 13 of 24 (54.2%) patients to date have experienced events that were considered possibly, probably, or definitely related (related) to treatment with Ramucirumab. The most common (> 10%) treatment-related events were proteinuria (16.7%), diarrhea (12.5%), and hypertension (12.5%). Adverse events ≥ Grade 3 considered to be at least possibly related to Ramucirumab were reported in three patients and include duodenal ulcer hemorrhage (Grade 4), hypertension, and fatigue.

As of 1 September 2008, 19 patients were evaluable for response; of these patients, 12 have experienced a best overall response of stable disease, including five with SD ≥ 6 months. These five patients had cancers of the colon (2 patients), liver (2 patients), and kidney (1 patient). Three of these patients have had ongoing SD for > 10 months duration. Six patients remain on study (two patients in the 10-mg/kg every other week cohort, two patients in the 15-mg/kg every three week cohort, and two patients in the 20-mg/kg every three week cohort).

As of January 18, 2010, at least 454 patients had received at least one dose of IMC-1121B on ImClone sponsored phase 1-2 studies and at least 83 patients had received at least one dose of blinded IMC-1121B/placebo on ImClone sponsored randomized phase III studies. Data safety monitoring committee reviews have been performed regularly on phase 2 studies in melanoma (involving combination with
dacarbazine), prostate cancer (involving combination with mitoxantrone/prednisone), ovarian cancer (monotherapy), colorectal cancer (involving combination with mFOLFOX-6) and breast cancer (involving combination with docetaxel).

Some of the published data include:

a) The Phase 1 Monotherapy Study (Spratlin et al. J Clin Oncol 2010; 28: e-published 4 Jan 2010). 37 patients treated with advanced, refractory solid tumors. Ramucirumab was given weekly as monotherapy. Reported results included PR in 4/27 (15%) patients with measurable disease and PR or SD ≥ 6 months in 11/37 (30%) of patients.

b) Initial Phase 2 Presentation for metastatic, TKI-refractory Renal Cancer (Garcia et al. ESMO/ECCO Berlin 2009. 40 patients were given ramucirumab 8mg/kg q 2 wk. Of these, 50% had prior sunitinib, 35% prior sunitinib and sorafenib and15% prior sorafenib. The preliminary median PFS is 6 months and 3/40 (7%) had confirmed PR. The drug was well-tolerated.

Additional phase II studies are underway in RCC, HCC, melanoma, prostate cancer, NSCLC, ovarian cancer, GBM, colorectal, breast and bladder cancer. Phase 3 studies are underway in breast cancer, with others planned in HCC, colorectal cancer. Further phase 2 results will be presented at GU ASCO (RCC update), ASCO (melanoma, HCC, NSCLC) in 2010.

Additional toxicities (observed in preliminary phase 2 studies) and potential toxicities (based on the known toxicity profiles of agents which inhibit the VEGF or VEGF-receptor pathway) are presented in the most recent Investigator Brochure. No additional safety patterns have been demonstrated conclusively beyond those observed, discussed and reported in the most recent Investigator Brochure.

1.4.2 Dose Rationale

Nonclinical data obtained from a murine BxPC-3 xenograft model have demonstrated that the efficacy of DC101, a murine analogue to Ramucirumab, was evident in vivo at trough concentrations of 20 µg/mL. The target serum concentration for Ramucirumab is hypothesized to be one that maintains Ramucirumab at trough plasma concentrations ≥ 20 µg/mL. Preliminary pharmacokinetic (PK) data from studies CP12-0401 and CP12-0402 indicate that the minimum 20 µg/mL target trough concentrations are attainable. In the every-other-week protocol, following the initial dose of 6 mg/kg, mean serum trough concentrations (immediately prior to the next dose) of Ramucirumab were 31 µg/mL (range: 18–64 µg/mL [n=7]). Analysis of the initial 8-mg/kg dose at the same time point yielded a mean serum trough concentration of 115 µg/mL (range: 18 - 205 µg/mL [n=3]). To provide a suitable margin above the 20 µg/mL Ramucirumab target concentration, the proposed dose and regimen for this Phase 3 study will be 8 mg/kg Ramucirumab given every other week. At this dose and regimen, the half-life following the initial infusion of IMC-Ramucirumab is approximately 155 hours; following
later infusions during the first cycle, the half-life is approximately 300 hours, suggesting that steady state is being approached. Supporting this observation is the finding that as the dose of IMC-Ramucirumab was increased from 6 to 13 mg/kg, clearance decreased from 0.237 mL/hr/kg to a plateau of 0.06 mL/hr/kg (clearance at 8 mg/kg was approximately 0.113 mL/hr/kg).

1.5 Summary and Study Rationale

First line therapy of CRC at this time generally includes bevacizumab plus combination chemotherapy, which most commonly in the US includes oxaliplatin, leucovorin and 5FU (a modified FOLFOX regimen). Whether continuing anti-angiogenic therapy after first line therapy is beneficial remains an open question. Studies to date have shown benefit for addition of bevacizumab in first line therapy and in second line therapy in bevacizumab-naïve patients. In the case of patients with Kras wild-type cancers, standard second line therapy would generally include irinotecan with cetuximab, based on the EPIC trial which demonstrated a doubling in PFS (9). We have chosen this regimen as the control arm for this study, which will compare addition of the anti-VEGFR antibody, Ramucirumab. The goal of this study is to show improved PFS with the addition of a novel second line anti-angiogenic antibody.
Summary of Toxicity Review

The study was closed to accrual on June 14, 2012 after 35 registrations were accrued as per pre-planned toxicity review. 18 patients (17 treated; one case never started assigned therapy) were accrued to Arm A (IC) and 17 (16 treated; one case was a duplicate registration) to Arm B (ICR). AdEERS Reporting was reviewed and real time data were obtained on all treated patients. It was clear that more toxicity was seen in Arm B. Worst toxicity per patient is seen in the figure below. The overall grade 3-5 toxicity rates were 17% for Arm A and 75% for Arm B. There were 2 toxic deaths in Arm B. Toxicities of higher incidence in Arm B included neutropenia, mucositis, diarrhea and GI perforation (including peri-anal abscess). In addition mean dose given in Arm B (mean % RDI) was considerably lower in Arm B: 65% for irinotecan, 85% for cetuximab and 92% for ramucirumab (even though no dose reductions were allowed in the protocol). This compares to 99% irinotecan and 98% cetuximab average %RDI in Arm A. Furthermore, only 3/17 patients in Arm A required dose reduction, compared to 15/16 in Arm B. On the other hand with a median of 8 cycles preliminary analysis showed that fewer patients in Arm B went off treatment for progression compared with Arm A, and more remained on treatment at the time of the analysis. Of the 17 treated in Arm A, 8 out of 9 patients off study had progression (PD), while in Arm B, of the 16 treated, only 1 out of 5 who went off study, went off for PD. These findings suggest potential benefit for the addition of ramucirumab among patients who can tolerate therapy. Therefore, we propose a reduced dose regimen in Arm C (modified ICR) with irinotecan 150 mg/m², cetuximab 400 mg/m² and ramucirumab 6 mg/m² as starting doses, more strict eligibility criteria, and more aggressive dose modifications for toxicity. Because those patients on protocol who did tolerate the ICR regimen at the reduced doses seemed to stay on study longer, we believe the study should be continued as modified at those lower doses. The Arm C starting doses are equal to the actual “percent recommended dose intensity” received by patients in Arm B.
2. Objectives

2.1 Progression Free Survival
To evaluate the Progression Free Survival (PFS) for the addition of the anti-angiogenic antibody, Ramucirumab, in combination with irinotecan and cetuximab as second line therapy for patients with K-ras wild-type colorectal cancer, as compared to the patients without the antibody.

2.2 Response Rate
To evaluate the Response Rate for irinotecan, cetuximab and Ramucirumab in this patient population.

2.3 Toxicity Rates
To evaluate the Grade 3-4 toxicity rates for the combination in this patient population.

2.4 Overall Survival
To evaluate Overall Survival for irinotecan, cetuximab, and ramucirumab in this patient population.
3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient’s eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient’s chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____________________________
Patient’s Initials (L, F, M) _____________________________
Physician Signature and Date _____________________________

NOTE: All questions regarding eligibility should be directed to the study chair or study chair liaison.

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

3.1 Eligibility Criteria

_____ 3.1.1 Age ≥ 18 years.

_____ 3.1.2 Women must not be pregnant or breast-feeding due to potential danger to the fetus, by therapy including Ramucirumab. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy.

Female of child bearing potential? (Yes or No) ______
If yes: Date of blood test or urine study: _______________
If no, reason: Post menopausal, date of LMP ______
Status post TAH: Date of surgery ______
Status post tubal ligation: Date of surgery ______

_____ 3.1.3 Women of childbearing potential and sexually active males must use an accepted and effective method of contraception or agree to abstain from sexual intercourse during their participation in the study and for 3 months following completion of their participation.

_____ 3.1.4 Patients must have measurable disease as defined in Section 6.1.2.

_____ 3.1.5 Histologically documented adenocarcinoma (including the histologic variants of adenocarcinoma) of the colon or rectum.

_____ 3.1.6 Patients K-ras status must be wild type (not mutated). K-ras status determination may be based on either primary or metastatic tumor.

NOTE: The assay must be performed by a Clinical Laboratory Improvement Amendments (CLIA) approved laboratory.

_____ 3.1.7 Patients must have had prior first-line therapy with oxaliplatin-based fluoropyrimidine-containing chemotherapy and bevacizumab for metastatic colorectal cancer.
3.1.8 Registration within 42 days of evidence of disease progression.

3.1.8.1 Current date ______________

3.1.8.2 Date of progression _______________

3.1.8.3 Date of last chemotherapy ______________

3.1.8.4 Date of last bevacizumab ______________

3.1.9 [Deleted in Addendum #3]

3.1.10 Was oxaliplatin discontinued before date of progression?

3.1.10.1 Yes _____________ No ______________

3.1.11 Performance Status 0-1.

3.1.11.1 PS 0 _________ 1 ___________

3.1.12 Adequate Organ Function ≤ 4 weeks prior to registration.

3.1.12.1 Hematologic: Absolute neutrophil count (ANC) ≥ 1500/µL, hemoglobin ≥ 9 g/dL, and platelets ≥ 75,000/µL.

ANC: ______ Date: _______

Hemoglobin: ______ Date: _______

Platelets: ______ Date: _______

3.1.12.2 Renal: Serum creatinine ≤ 1.5 x the ULN, or creatinine clearance (measured via 24-hour urine collection) ≥ 40 mL/minute.

Serum creatinine: ______ Date: _______

Creatinine clearance: ______ Date: _______

3.1.12.3 Proteinuria: Urinary protein ≤ 1+ on dipstick or routine urinalysis (UA); if urine dipstick or routine analysis is ≥ 2+, a 24-hour urine collection for protein must demonstrate < 1000 mg of protein in 24 hours to allow participation in the study.

Urinary protein ≤ 1+ (Yes / No) ______ Date: _______

If no, is the 24-hour collection < 1000 mg protein? ______

3.1.12.4 Hepatic: Total bilirubin ≤ 2.0 mg/dL, and aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 x the institutional upper limit of normal (ULN) [or 5.0 x the ULN in the setting of liver metastases]. Albumin within institutional normal range.

Total bilirubin: ______

AST: ______ Date: _______

ALT: ______ Date: _______

Albumin: __________ Date: _______

Liver metastases? (Yes / No): ______ Date: _______

3.1.12.5 Coagulation: International Normalized Ratio (INR) ≤ 1.6 (unless receiving anticoagulation therapy). Patients on full-
dose anticoagulation must be on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin. If receiving warfarin, the patient must have an INR ≤ 3.0 and no active bleeding (i.e., no bleeding within 14 days prior to first dose of study therapy).

INR: __________ Date: __________

Is patient receiving warfarin? (Yes / No): ______

3.1.13 No prior therapy with drugs other than oxaliplatin and a fluoropyrimidine plus bevacizumab for this disease. Chemotherapy drugs and bevacizumab may be stopped and started as long as no prior disease progression requiring change in chemotherapy agents occurred.

3.1.14 No clinically significant (equivalent to NCI CTCAE grade 3-4) bleeding episodes within the prior 3 months.

3.1.15 No active infection, symptomatic congestive heart failure, unstable angina pectoris, symptomatic or poorly controlled cardiac arrhythmia, uncontrolled thrombotic or hemorrhagic disorder.

3.1.16 No uncontrolled or poorly-controlled hypertension despite standard medical management (e.g. consistently SBP > 160 and DBP > 90 mmHg).

3.1.17 No major surgery within 28 days prior to randomization, or subcutaneous venous access device placement within 7 days prior to randomization.

3.1.18 No history of acute arterial thrombotic events within 6 months (including CVA, TIA, MI or unstable angina).

3.1.19 No brain or CNS metastases.

3.1.20 No other cancer requiring therapy within last three years (except in situ carcinoma or non-melanoma skin cancer).

3.1.21 Patients must not have an acute or subacute intestinal obstruction. No history of bowel obstruction, GI perforation, major abdominal surgery with bowel resection, or peri-rectal/peri-anal abscess within 6 months prior to randomization.

3.1.22 Patient must not have a history of inflammatory bowel disease requiring pharmacological and/or surgical intervention within the 12 months prior to randomization.

3.1.23 Patient must not have a known allergy to any of the treatment components.
4. Registration and Randomization Procedures

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

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) or by calling the PMB at 240-276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for E7208 site registration:

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

Submitting Regulatory Documents

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

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

Required Protocol Specific Regulatory Documents

1. CTSU Regulatory Transmittal Form.

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

3. A. CTSU IRB Certification Form.
   Or

   B. Signed OMB No. 0990-0263
   Or

   C. IRB Approval Letter
NOTE: The above submissions must include the following details:

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

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

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

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

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member.
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

NOTE: The OPEN system will provide the site with a printable confirmation of randomization. Please print this confirmation for your records.
Further instructional information is provided on the OPEN tab of the CTSU members’ side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Patients must not start protocol treatment prior to registration.

Treatment should start within 7 working days after registration but not less than 28 days after last dose of bevacizumab.

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

4.1 Protocol Number

4.2 Investigator Identification
- Institution and affiliate name
- Investigator’s name

4.3 Patient Identification
- Patient’s initials and chart number
- Patient’s Social Security number
- Patient demographics
  - Sex
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment

4.4 Eligibility Verification
Patients must meet all of the eligibility requirements listed in Section 3.0. An eligibility checklist has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG-ACRIN Operations Office – Boston.

STRATIFICATION FACTORS:
- Performance Status 0 vs. 1
- Discontinuation of oxaliplatin before disease progression: Yes vs. No
- Time since treatment with chemotherapy or bevacizumab ≤ 6 months vs. > 6 months.

4.5 Additional Requirements
- Patients must provide a signed and dated, written informed consent form.
4.5.2 Specimens are to be submitted as outlined in Section 10.

4.6 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted according to the instructions in the E7208 Forms Packet. Document the reason for not starting protocol treatment on the off-treatment form. Also report the date and type of the first non-protocol treatment that the patient receives on the Non-Protocol Therapy Form.

4.7 EKG, UPC and Pregnancy Test Reimbursement Guidelines

ImClone has agreed to provide reimbursement towards the non-standard of care pregnancy, UPC and EKG time points while patients are on protocol treatment. These tests should not be submitted to the patient’s insurance for reimbursement. Institutions should submit these costs to the ECOG-ACRIN Operations Office – Boston using the E7208 EKG/UPC/Pregnancy Test Reimbursement Invoice (Appendix VI).

Baseline pregnancy test is considered standard of care and should be submitted to the patient’s insurance for reimbursement. All additional pregnancy tests, all UPC and all EKG time points as outlined in Section 7 of the protocol are considered non-standard of care.

Please refer to the table below for reimbursable time points:

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Every Six Weeks</th>
<th>End of Treatment</th>
<th>30 Days After End of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>EKG</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test*</td>
<td>X*</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>UPC</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Baseline pregnancy test is standard of care and should be submitted to patient’s insurance for reimbursement.

In order to authorize reimbursement, the results of the EKG, UPC and Pregnancy test must accompany the E7208 Reimbursement Invoice (Appendix VI) as well as the Substitute W-9 Tax Form (Appendix VII). These items should be sent to the ECOG-ACRIN Operations Office – Boston, Attn: Drug Orders (fax: 617-632-2063). The ECOG-ACRIN Operations Office – Boston will review/approve the invoices and submit for payment on a quarterly basis.

If you have any questions about this process, please contact a member of the ECOG-ACRIN Industry Team at the ECOG-ACRIN Operations Office – Boston (617-632-3610).
5. Treatment Plan

NOTE: Patients must not start treatment until at least 28 days from last dose of bevacizumab.

5.1 Administration Schedule

5.1.1 Treatment/ARM A – (IC)

5.1.1.1 Cetuximab 500 mg/m^2 IV q 14 days
- The first infusion is to be administered over 120 minutes with subsequent infusions over 60 minutes

5.1.1.2 Irinotecan 180 mg/m^2 IV over 60-90 minutes q 14 days
Cetuximab should be given prior to irinotecan.
Repeat cycles every 14 days until progression.

NOTE: It is recommended that 50mg of diphenhydramine be administered prior to the initial 3 doses of ramucirumab, and may or may not be continued for subsequent doses per the investigator’s discretion.

NOTE: Irinotecan pre-medication should be given per standard institutional practice.

5.1.2 Treatment/ARM B – (ICR)
CLOSED to accrual in Addendum #5

5.1.3 Treatment/ARM C – (mICR)

5.1.3.1 Ramucirumab 6 mg/kg IV over 60 minutes q 14 days
- The dose of ramucirumab is to be recalculated should the patients weight change by 10% or more.

5.1.3.2 Cetuximab 400 mg/m^2 IV q 14 days
- The first infusion is to be administered over 120 minutes with subsequent infusions over 60 minutes.

5.1.3.3 Irinotecan 150 mg/m^2 IV over 60-90 minutes q 14 days
Ramucirumab should be given first, followed by cetuximab and then irinotecan.
Repeat cycles every 14 days until progression.

NOTE: It is recommended that 50mg of diphenhydramine be administered prior to the initial 3 doses of ramucirumab, and may or may not be continued for subsequent doses per the investigator’s discretion.

NOTE: Irinotecan pre-medication should be given per standard institutional practice.
Adverse Event Reporting Requirements

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

- **Routine reporting:** Adverse events are reported in a routine manner at scheduled times during a trial (please refer to the E7208 Forms Packet for the list of forms with directions and timeframes for routine adverse event reporting).

- **Expedited reporting:** In addition to routine reporting, certain adverse events must be reported in an expedited manner via CTEP-AERS for timelier monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

5.2.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be **ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.**

- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

<table>
<thead>
<tr>
<th>ATTRIBUTION</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated</td>
<td>The AE is <strong>clearly NOT related</strong> to treatment</td>
</tr>
<tr>
<td>Unlikely</td>
<td>The AE is <strong>doubtfully related</strong> to treatment</td>
</tr>
<tr>
<td>Possible</td>
<td>The AE <strong>may be related</strong> to treatment</td>
</tr>
<tr>
<td>Probable</td>
<td>The AE is <strong>likely related</strong> to treatment</td>
</tr>
<tr>
<td>Definite</td>
<td>The AE is <strong>clearly related</strong> to treatment</td>
</tr>
</tbody>
</table>

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator’s Brochure, the Package Insert, as well as company safety reports.

- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.

- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
• **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.

• **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:
  - Death
  - A life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours).
  - 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 a serious adverse event when it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

### 5.2.3 Reporting Procedure


In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (617-632-3610) for Arms A, B and C and
- the FDA (1-800-332-1088) for Arm A

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

**Supporting and follow up data:** Any supporting or follow up documentation must be faxed to ECOG-ACRIN (617-632-2990), Attention: AE within 48-72 hours. In addition, supporting or follow up documentation must be faxed to

- the FDA (800-332-0178), for Arm A, in the same timeframe.

**NCI Technical Help Desk:** For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at [ncitelphelp@ctep.nci.nih.gov](mailto:ncitelphelp@ctep.nci.nih.gov).

### 5.2.4 Determination of Reporting Requirements

Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- the phase (0, 1, 2, or 3) of the trial
• whether the patient has received an investigational or commercial agent or both
• the seriousness of the event
• the Common Terminology Criteria for Adverse Events (CTCAE) grade
• whether or not hospitalization or prolongation of hospitalization was associated with the event
• when the adverse event occurred (within 30 days of the last administration of investigational agent vs. > 30 days after the last administration of investigational agent)
• the relationship to the study treatment (attribution)

Using these factors, the instructions and tables in the following sections have been customized for protocol E7208 and outline the specific expedited adverse event reporting requirements for study E7208.
5.2.5 **Steps to Determine if an Adverse Event is to be Reported in an Expedited Manner for Arm A**

1. **Identify** the type and grade of the event using CTCAE v4.0
2. **Determine** if the event is related to the protocol treatment (attribution)
3. **Determine** the expectedness of the event. An unexpected event is defined as one where the type of severity of the event is not listed in the investigator’s brochure, package insert or protocol.
4. With this information, review the chart in Section 5.2.6 to determine if event is reportable via CTEP-AERS
5. **Is the event reportable?**
   - **No**
   - **Yes**
     - Report the event via CTEP-AERS

Refer to footnote b in Section 5.2.6 to determine if the event meets the protocol specific reporting requirements for this study. If so, report the event via CTEP-AERS.
### 5.2.6 Expedited Reporting Requirements for Arm A on Protocol E7208

#### Commercial Agents: Irinotecan and Cetuximab

Expedited reporting requirements for adverse events experienced by patients on arms with commercial agents only

<table>
<thead>
<tr>
<th>Attribution</th>
<th>Grade 4 Unexpected</th>
<th>Grade 4 Expected</th>
<th>Grade 5 Unexpected</th>
<th>Grade 5 Expected</th>
<th>ECOG-ACRIN and Protocol-Specific Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated or Unlikely</td>
<td></td>
<td></td>
<td>7 calendar days</td>
<td>7 calendar days</td>
<td>See footnote (b) for special requirements.</td>
</tr>
<tr>
<td>Possible, Probable, Definite</td>
<td>7 calendar days</td>
<td></td>
<td>7 calendar days</td>
<td>7 calendar days</td>
<td></td>
</tr>
</tbody>
</table>

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

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

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

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

5.2.7.1 Guidelines for adverse events **OCCURRING WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS** of the last administration of the investigational agent(s).

Determine if the event meets the definition of a **Serious Adverse Event** (SAE) as outlined by the six criteria in the top portion of the table below in Section 5.2.8.

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

**Identify the type and grade** of the event using CTCAE v4.0

Determine if the patient was **hospitalized** for ≥ 24 hours for the event

With this information, review the chart in Section 5.2.8 to determine if event is reportable via CTEP-AERS

**Is the event reportable?**

Yes

Report the event via CTEP-AERS

No

Refer to Section 5.2.9 to determine if the event meets the protocol specific reporting requirements for this study. If so, report the event via CTEP-AERS

Refer to Section 5.2.9 to determine if the event meets the protocol specific reporting requirements for this study. If so, report the event via CTEP-AERS
5.2.7.2 Guidelines for adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational agent(s).

If the adverse event meets the definition of a **Serious Adverse Event** (SAE) as outlined by the six criteria in the top portion of the table below in Section 5.2.8, AND has an attribution of possible, probably or definite, the following events require reporting as follows:

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

**NOTE:** Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported via CTEP-AERS even if the patient is off study

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

---

5.2.8 Expedited Reporting Requirements for Arms B and C on protocol E7208

Investigational Agents: Ramucirumab (IMC-1121B)

Commercial Agents: Irinotecan and Cetuximab

*When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events follow the guidelines for investigational agents.*

**Late Phase 2 and Phase 3 Studies**

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND **within 30 Days of the Last Administration of the Investigational Agent/Intervention**

**NOTE:** Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.
FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

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

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

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

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

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

Expeditied AE reporting timelines are defined as:

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

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

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

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

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5.2.9 Additional instructions, requirements and exceptions for Arms B and C on protocol E7208

**Additional Instructions:**

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD.
Medical Help Desk at 301-897-7497 or aemd@tech-res.com. This will need to be discussed on a case by case basis.

**E7208 specific expedited reporting requirements:**

**GI Events:** All grade 2 or higher GI perforations and peri-rectal abscess events, regardless of grade or whether or not the patient was hospitalized, must be reported via CTEP-AERS within the timeframes specified in the table in Section 5.2.8.

5.2.10 **Other recipients of adverse event reports and supplemental data**

ECOG-ACRIN will forward CTEP-AERS reports to the appropriate regulatory agencies and pharmaceutical company, if applicable.

The drug supporter is obliged to forward reported AEs to the FDA. A drug supporter representative may call a site for additional or supplemental information regarding a serious adverse event. Any additional written AE information requested by the drug supporter MUST be submitted to BOTH ECOG-ACRIN and the drug supporter.

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

5.2.11 **Second Primary Cancer Reporting Requirements**

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

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

  1. Submit a completed Second Primary Form within 30 days to ECOG-ACRIN at
     ECOG-ACRIN Operations Office – Boston
     FSTRF
     900 Commonwealth Avenue
     Boston, MA 02215
  2. Submit a copy of the pathology report to ECOG-ACRIN confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, submit a copy of the cytogenetics report (if available) to ECOG-ACRIN

- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol).** Secondary malignancies require both routine and expedited reporting as follows:
1. Submit a completed Second Primary Form within 30 days to ECOG-ACRIN at
   
   ECOG-ACRIN Operations Office – Boston
   FSTRF
   900 Commonwealth Avenue
   Boston, MA 02215

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

3. Submit a copy of the pathology report to ECOG-ACRIN and NCI/CTEP confirming the diagnosis.

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

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

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

**NOTE:** Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.
5.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Cetuximab (NSC 714692)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. They are developed and continuously monitored by the CTEP Investigational Drug Branch (IDB). The information listed in the CAEPR(s) below, as well as the other resources described in the 'Determination of reporting requirements' part of the Adverse Event Reporting section in this protocol, can be used to determine expectedness of an event when evaluating if the event is reportable via CTEP-AERS Arm A. Frequency is provided based on 2282 patients. Below is the CAEPR for Cetuximab.

### Version 2.1, March 31, 2010

<table>
<thead>
<tr>
<th>Likely (&gt;20%)</th>
<th>Less Likely (&lt;=20%)</th>
<th>Rare but Serious (&lt;3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLOOD AND LYMPHATIC SYSTEM DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EAR AND LABYRINTH DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>External ear inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinnitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EYE DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry eye</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uveitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watering eyes</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheilitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucositis oral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema limbs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flu like symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cardiac chest pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IMMUNE SYSTEM DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>Anaphylaxis</td>
<td></td>
</tr>
</tbody>
</table>
### INFECTIONS AND INFESTATIONS

| Infection 2 | Infections and infestations – Other (aseptic meningitis) |

### INVESTIGATIONS

| Neutrophil count decreased |
| Weight loss |
| White blood cell decreased |

### METABOLISM AND NUTRITION DISORDERS

| Anorexia |
| Dehydration |
| Hypocalcemia |
| Hypomagnesemia |

### MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS

| Arthralgia |
| Back pain |
| Myalgia |

### NERVOUS SYSTEM DISORDERS

| Headache |
| Syncope |

### RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS

| Allergic rhinitis |
| Bronchospasm |
| Cough |
| Dyspnea |
| Hoarseness |
| Pneumonitis |
| Respiratory, thoracic, and mediastinal disorders - Other (non-cardiogenic pulmonary edema) |

### SKIN AND SUBCUTANEOUS TISSUE DISORDERS

| Dry skin |
| Alopecia |
| Nail loss |
| Palmar-plantar erythrodysesthesia syndrome |
| Photosensitivity |
| Pruritus |
| Purpura |
| Rash acneiform |
| Rash maculo-papular |
| Skin ulceration |
| Urticaria |

### VASCULAR DISORDERS

| Hypotension |
| Thromboembolic event |

---

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

2. Infection could include all 75 sites of infections under the INFECTIONS AND INFESTATIONS SOC.
Also reported on cetuximab trials but with the relationship to cetuximab still undetermined:

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Disseminated intravascular coagulation; Hemolysis

**CARDIAC DISORDERS** - Atrial fibrillation; Atrial flutter; Chest pain - cardiac; Left ventricular systolic dysfunction; Myocardial infarction; Paroxysmal atrial tachycardia; Pericardial effusion; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia

**EAR AND LABYRINTH DISORDERS** - Hearing impaired

**EYE DISORDERS** - Blurred vision; Extraocular muscle paresis; Eyelid function disorder; Keratitis; Photophobia; Vitreous hemorrhage

**GASTROINTESTINAL DISORDERS** - Colitis; Dysphagia; Esophagitis; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal hemorrhage (including Colonic or Gastric hemorrhage or hemorrhage in other sites under the GASTROINTESTINAL DISORDERS SOC); Gastrointestinal perforation (Colonic perforation, Duodenal perforation, or perforation in other sites under the GASTROINTESTINAL DISORDERS SOC); Gastrointestinal ulcer (ulcer includes Duodenal ulcer, Rectal ulcer, or ulcer in other sites under the GASTROINTESTINAL DISORDERS SOC); Ileus; Pancreatitis; Rectal fistula

**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Edema face; Sudden death NOS

**HEPATOBILIARY DISORDERS** - Cholecystitis; Hepatic failure

**INJURY, POISONING AND PROCEDURAL COMPLICATIONS** - Bruising; Wound dehiscence

**INVESTIGATIONS** - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Creatinine increased; Platelet count decreased; Serum amylase increased

**METABOLISM AND NUTRITION DISORDERS** - Hyperkalemia; Hyperuricemia; Hypokalemia; Hyponatremia; Hypophosphatemia

**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (myasthenia); Musculoskeletal and connective tissue disorder - Other (Sudeck's Atrophy)

**NERVOUS SYSTEM DISORDERS** - Ataxia; Dizziness; Dysgeusia; Extrapyramidal disorder; Intracranial hemorrhage; Nervous system disorders - Other (cholinergic syndrome); Neuralgia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Tremor

**PSYCHIATRIC DISORDERS** - Agitation; Depression

**REPRODUCTIVE SYSTEM AND BREAST DISORDERS** - Reproductive system and breast disorders - Other (balanitis); Vaginal inflammation

**REPRODUCTIVE SYSTEM AND BREAST DISORDERS** - Adult respiratory distress syndrome; Atelectasis; Bronchopulmonary hemorrhage; Epistaxis; Pleural effusion; Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans-organized pneumonia [BOOP])

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Hirsutism; Skin hypopigmentation; Skin and subcutaneous tissue disorders - Other (skin fissures)

**VASCULAR DISORDERS** - Flushing; Hypertension; Lymphedema; Vasculitis

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

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

Version 4.0 of the CTCAE is identified and located on the CTEP website at [http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All appropriate treatment areas should have access to a copy of version 4.0 of CTCAE.

5.4.1 General Considerations

a. A new cycle of treatment may begin when the ANC is ≥ 1,500/mcl, the platelet count is ≥ 75,000/mcl, and any treatment-related GI toxicity is resolved to ≤ Grade 1.

b. If the initiation of a new cycle, or treatment during a cycle is delayed for ≥ 4 weeks, the patient should be removed from protocol treatment.

c. Held doses are not to be made up.

d. If one therapeutic agent is permanently discontinued secondary to toxicity, then therapy with the other study agents should continue and the patient should remain on-study with full adherence to all protocol-related requirements.

e. In the event of serious or life-threatening conditions, hold the offending agent. If the patient is to continue on therapy, all agents should be held until the toxicity resolves to grade < 2.

f. Dose reductions for all agents are as follows:

<table>
<thead>
<tr>
<th>ARM</th>
<th>AGENT</th>
<th>INITIAL DOSE</th>
<th>LEVEL -1</th>
<th>LEVEL -2</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (IC)</td>
<td>Cetuximab</td>
<td>500 mg/m²</td>
<td>400 mg/m²</td>
<td>250 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Irinotecan</td>
<td>180 mg/m²</td>
<td>150 mg/m²</td>
<td>120 mg/m²</td>
</tr>
<tr>
<td>B (ICR)</td>
<td>Ramucirumab</td>
<td>8 mg/kg</td>
<td>6 mg/kg</td>
<td>5 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Cetuximab</td>
<td>500 mg/m²</td>
<td>400 mg/m²</td>
<td>250 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Irinotecan</td>
<td>180 mg/m²</td>
<td>150 mg/m²</td>
<td>120 mg/m²</td>
</tr>
<tr>
<td>C (mICR)</td>
<td>Ramucirumab</td>
<td>6 mg/kg</td>
<td>5 mg/kg</td>
<td>4 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Cetuximab</td>
<td>400 mg/m²</td>
<td>250 mg/m²</td>
<td>200 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Irinotecan</td>
<td>150 mg/m²</td>
<td>120 mg/m²</td>
<td>90 mg/m²</td>
</tr>
</tbody>
</table>

**NOTE:** In the event that an agent is given at dose level (-2) and dose modification rules call for further reduction, the agent should be discontinued.
5.4.2 Hematologic toxicities

No Ramucirumab or cetuximab dose modifications (or delays) will be made for hematologic toxicity. Continue Ramucirumab or cetuximab when irinotecan is held for hematologic toxicities.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Reduce irinotecan one dose level at the next cycle. For subsequent cycles, resume at the previous dose levels, provided ANC ≥ 1,500/mcl and platelets ≥ 75,000/mcl.</td>
</tr>
<tr>
<td>3-4</td>
<td>Hold irinotecan. If counts recover to ANC ≥ 1,500/mcl and platelets ≥ 75,000/mcl, irinotecan may be resumed at one lower dose level at next cycle. For subsequent cycles, continue at the reduced dose levels from the previous cycle.</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>Hold irinotecan. If fever resolves and counts recover to ANC ≥ 1,500/mcl and platelets ≥ 75,000/mcl, irinotecan may be resumed at one lower dose level at next cycle. For subsequent cycles, continue at the reduced dose levels from the previous cycle.</td>
</tr>
</tbody>
</table>

5.4.3 Diarrhea

No Ramucirumab dose delay will be made for diarrhea. Continue Ramucirumab when other agents are held. Dose modifications should be made for toxicity only when patient is receiving intensive loperamide therapy.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Be sure intensive loperamide is being taken. For subsequent cycles, resume all agents at the previous dose levels, provided diarrhea has fully resolved before restarting treatment.</td>
</tr>
<tr>
<td>3</td>
<td>Be sure intensive loperamide is being taken. If so, and grade 3 diarrhea lasts longer than 48 hours, reduce irinotecan one dose level. Do not treat again until the diarrhea resolves to ≤ grade 2.</td>
</tr>
<tr>
<td>4</td>
<td>Be sure intensive loperamide is being taken. Hold irinotecan. If diarrhea resolves to ≤ grade 2, irinotecan and cetuximab should be resumed at one lower dose level for subsequent cycles. For subsequent cycles, continue both agents at the reduced dose levels from the previous cycle.</td>
</tr>
</tbody>
</table>

5.4.4 Nausea and/or vomiting

These dose modifications for nausea and/or vomiting should be made only if they persist/occur despite two treatments with adequate (combination) antiemetics therapy.

No Ramucirumab or cetuximab dose modifications (or delays) will be made for nausea/vomiting. Continue Ramucirumab or cetuximab when irinotecan is held.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4</td>
<td>Reduce <em>irinotecan</em> one dose level. For subsequent cycles, continue irinotecan at the reduced dose level from the previous cycle.</td>
</tr>
</tbody>
</table>
5.4.5 Mucositis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Reduce irinotecan one dose level for subsequent cycles. No modifications (or delays) will be made for Ramucirumab or cetuximab.</td>
</tr>
<tr>
<td>3</td>
<td>Hold irinotecan. If mucositis resolves to ≤ Grade 2, resume both irinotecan and cetuximab at one lower dose level for subsequent cycles. No modifications (or delays) will be made for Ramucirumab.</td>
</tr>
<tr>
<td>4</td>
<td>Hold ALL protocol treatment. If mucositis resolves to ≤ Grade 2, reduce all agents one dose level for all subsequent cycles.</td>
</tr>
</tbody>
</table>

5.4.6 Pulmonary Toxicity

5.4.6.1 For Grade 2 or worsening pulmonary symptoms unrelated to underlying cancer, cetuximab treatment should be stopped and symptoms investigated. Cetuximab treatment may resume at one lower dose level when symptoms resolve to ≤ Grade 1 and cetuximab-related pneumonitis is ruled out.

5.4.6.2 For ≥ Grade 3 cough, dyspnea, hypoxia, pneumonitis, or pulmonary infiltrates, hold cetuximab until interstitial lung disease is ruled out. Continue Ramucirumab and irinotecan. Discontinue all protocol treatment if interstitial lung disease is confirmed.

5.4.7 Hypomagnesemia has been seen with cetuximab. For Grade 3-4 hypomagnesemia, hold cetuximab until hypomagnesemia resolves to ≤ Grade 2. Then restart cetuximab at the -1 dose. For any grade of hypomagnesemia, magnesium supplementation should be provided.

5.4.8 Hypertension (Dose delays for Ramucirumab only)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Consider increased BP monitoring; start anti-hypertensive medication if appropriate</td>
</tr>
<tr>
<td>(SBP 120-139 mmHg or DBP 80-89 mm Hg)</td>
<td></td>
</tr>
<tr>
<td>Grade 2 asymptomatic</td>
<td>Begin anti-hypertensive therapy and continue agent</td>
</tr>
<tr>
<td>(SBP 140-159 mmHg or DBP 90-99 mm Hg)</td>
<td></td>
</tr>
<tr>
<td>Grade 2 symptomatic</td>
<td>Start or adjust anti-hypertensive medication</td>
</tr>
<tr>
<td>(SBP 140-160 mmHg or DBP 90-100 mm Hg)</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>Hold agent until symptoms resolve AND BP &lt; 160/90mmHg</td>
</tr>
<tr>
<td>(≥ SBP 160 mmHg or ≥ DBP 100 mmHg)</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>Discontinue agent</td>
</tr>
<tr>
<td>(Hypertensive crisis or malignant hypertension)</td>
<td></td>
</tr>
</tbody>
</table>

Patients who hold or discontinue Ramucirumab due to hypertension may continue other protocol treatment.

5.4.9 Venous Thrombotic Events

Patients should be carefully monitored for evidence of thromboembolic disease during treatment.
5.4.9.1 Grade 3 venous thrombosis or asymptomatic pulmonary embolism: Hold Ramucirumab. Ramucirumab 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 be on stable dose of low molecular weight heparin prior to restarting Ramucirumab treatment;
- The patient must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels);
- The patient must not have had hemorrhagic events while on study.

5.4.9.2 Grade 4 or for recurrent/worsening venous thromboembolic events after resumption of Ramucirumab: Discontinue Ramucirumab.

5.4.9.3 For symptomatic pulmonary embolism, patients will discontinue all protocol treatment.

5.4.10 Arterial Thrombotic Events

5.4.10.1 For Grade 2 arterial thrombotic events not present at baseline or worsened since the initiation of protocol therapy, discontinue Ramucirumab. Patients may continue other protocol treatment.

5.4.10.2 For Grade 3 cerebrovascular ischemia, and/or peripheral or visceral arterial ischemia, discontinue Ramucirumab. Patients may continue other protocol treatment.

5.4.10.3 For Grade 3 cardiac ischemia/infarction, discontinue Ramucirumab. Patients may continue other protocol treatment.

5.4.10.4 For any Grade 4 arterial thrombotic event, including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia, discontinue all protocol treatment.

5.4.11 Left Ventricular Dysfunction

5.4.11.1 Grade 3 LV dysfunction: Symptomatic CHF responsive to intervention.
- Discontinue cetuximab (for patients on the control arm) or cetuximab and ramucirumab (for patients on the experimental arm). Patients may continue other protocol treatment.

5.4.11.2 Grade 4 LV dysfunction: Poorly controlled refractory CHF; intervention such as ventricular assist device or heart transplant is indicated.
- Discontinue all protocol treatment.
5.4.12 Hemorrhage/bleeding

5.4.12.1 For Grade 3 hemorrhage/bleeding, permanently discontinue Ramucirumab and hold other protocol treatment; once hemorrhage or bleeding resolves, other protocol treatment may be continued at the treating physician’s discretion.

5.4.12.2 For Grade 4 hemorrhage/bleeding, discontinue all protocol treatment.

5.4.13 Proteinuria (Dose delays for Ramucirumab only)

5.4.13.1 For proteinuria ≥ 2+ or UPC (urinary protein: creatinine ratio) > 1.0: Confirm total urine protein with a 24-hour urine collection. For 2+ proteinuria, the scheduled dose of Ramucirumab may be given while awaiting the results of the 24-hour collection. For > 2+ proteinuria, hold Ramucirumab while awaiting results of the 24-hour urine collection. Other protocol treatment may be continued. If proteinuria is 2-3 g/24 hours, hold Ramucirumab until urine protein recovers to < 2 g/24 hours, then resume at the -1 dose level. Continue other protocol treatment. A second dose reduction (to 5 mg/kg every other week) is permitted if the protein level > 2g/24 hours recurs. Ramucirumab will be discontinued permanently if the protein level is > 3g/24 hours, if there is a third occurrence of proteinuria > 2 g/24 hours, or if the protein level does not return to < 2g/24 hours within 2 weeks.

5.4.13.2 If nephrotic syndrome (Grade 4 proteinuria) occurs, discontinue Ramucirumab.

5.4.14 Cutaneous toxicity (Dose modifications for cetuximab only)

<table>
<thead>
<tr>
<th>Grade 3 Rash</th>
<th>Cetuximab</th>
<th>Outcome</th>
<th>Cetuximab Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st occurrence</td>
<td>Hold infusion 1 to 2 wks</td>
<td>If improvement: Continue at current dose&lt;br&gt; If no improvement: Discontinue cetuximab</td>
<td></td>
</tr>
<tr>
<td>2nd occurrence</td>
<td>Hold infusion 1 to 2 wks</td>
<td>If improvement: Reduce one dose level&lt;br&gt; If no improvement: Discontinue cetuximab</td>
<td></td>
</tr>
<tr>
<td>3rd occurrence</td>
<td>Hold infusion 1 to 2 wks</td>
<td>If improvement: Reduce two dose levels&lt;br&gt; If no improvement: Discontinue cetuximab</td>
<td></td>
</tr>
<tr>
<td>4th occurrence</td>
<td>Discontinue cetuximab</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Grade 4 Rash | Discontinue cetuximab |
5.4.15 Infusion Reactions

<table>
<thead>
<tr>
<th>Grade</th>
<th>Reaction Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Slow the infusion rate by 50%. Monitor the patient for worsening of the condition. For subsequent infusions, premedicate with diphenhydramine 50mg IV (or equivalent); additional premedication may be administered at the investigator’s discretion.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Stop the infusion. Administer diphenhydramine 50mg IV (or equivalent), acetaminophen 650 mg orally for fever, and oxygen. Resume the infusion at 50% of the prior rate once the infusion reaction has resolved or decreased to grade 1; the infusion duration should not exceed 2 hours. For subsequent infusions, premedicate with diphenhydramine 50mg IV (or equivalent); additional premedication may be administered at the investigator’s discretion.</td>
</tr>
<tr>
<td>Grade 3 and Grade 4</td>
<td>Immediately and permanently discontinue the offending agent. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms.</td>
</tr>
</tbody>
</table>

For grade 1 or 2 reactions manifesting only as delayed drug fever, see Section 5.4.16.

For grade 4 or allergy related edema and angioedema and hypotension, permanently discontinue all medications.

For a second Grade 1 or 2 infusion reaction, administer dexamethasone 10mg IV (or equivalent); then, for subsequent infusions, premedicate with diphenhydramine 50mg IV (or equivalent), acetaminophen 650 mg orally, and dexamethasone 10mg IV (or equivalent).

5.4.16 Drug Fever

In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the study drug or to an infectious etiology. If a patient experiences isolated drug fever, for the next dose, pre-treat with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion); repeat antipyretic dose 6 and 12 hours after cetuximab infusion. The infusion rate will remain unchanged for future doses.

If a patient experiences recurrent isolated drug fever following premedication and post-dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be 50% of previous rate. If fever recurs following infusion rate change, the investigator should assess the patient’s level of discomfort with the event and use clinical judgment to determine if the patient should receive further cetuximab.
5.4.17 Other Grade 3 and 4 Toxicities

For grade 3 events hold the offending agents until the toxicity resolves to grade ≤ 1. If grade 4, please discuss with the study chair.

5.5 Supportive Care

5.5.1 All supportive measures consistent with optimal patient care will be given throughout the study.

5.5.2 Diarrhea Management

For symptoms of diarrhea and/or abdominal cramping that occur at any time during a treatment cycle with irinotecan, patients will be instructed to begin taking loperamide. Loperamide should be started at the earliest sign of (1) a poorly formed or loose stool or (2) the occurrence of 1 to 2 more bowel movements than usual in 1 day or (3) an increase in stool volume or liquidity. Loperamide should be taken in the following manner: 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around the clock until diarrhea-free for at least 12 hours. Patients may take loperamide 4 mg every 4 hours during the night. Loperamide should not be used for more than 48 hours. Patients should be provided with loperamide at the initial treatment visit so that they have sufficient supply on hand in case antidiarrheal support is required. Additional antidiarrheal measures may be used at the discretion of the treating physician. Patients should be instructed to increase fluid intake to help maintain fluid and electrolyte balance during episodes of diarrhea.

5.5.3 Antibiotics

Oral fluoroquinolone treatment should be initiated for any of the following:
- Diarrhea persisting for more than 24 hours despite loperamide
- ANC < 500/mcl (even in the absence of diarrhea or fever)
- Fever with diarrhea (even in the absence of neutropenia)
- Antibiotic therapy should also be initiated in patients who are hospitalized with prolonged diarrhea (even in the absence of neutropenia).

5.5.4 Lacrimation, rhinorrhea, miosis, diaphoresis, hot flashes, flushing, abdominal cramping, diarrhea, or other symptoms of early cholinergic syndrome may occur during or shortly after receiving irinotecan. Atropine, 0.25-1.0 mg IV or SC may be used to treat these symptoms. In patients with troublesome or recurrent symptoms, prophylactic administration of atropine shortly before irinotecan therapy may be considered. Additional antidiarrheal measures may be used at the discretion of the treating physician. Combination anticholinergic medications containing barbiturates or other agents (e.g., Donnatal®) should not be used because these may affect irinotecan metabolism. Anticholinergics should be used with caution in patients with potential contraindications (e.g., obstructive uropathy, glaucoma, tachycardia, etc.).
Late diarrhea (e.g., developing more than 24 hours after irinotecan) should be managed with loperamide as described above.

5.5.5 Pegfilgrastim, epoetin and darbepoetin alfa may be administered at the treating investigator's discretion.

5.5.6 Dermatology Management

Suggested algorithm for management of cutaneous toxicity and paronychia:

In this protocol, acneiform rash and paronychia will be graded according to version 4.0 of the NCI-CTCAE definitions of rash/desquamation and nail changes. The patient should be followed until resolution of these toxicities.

Acneiform rash and paronychia should be managed according to the algorithms in Table 1-1 and Table 1-2. Cetuximab therapy treatment adjustments should be made according to Tables 1-3. Cetuximab dose reductions will be permanent (i.e., no dose re-escalations).
### Table 1-1: Algorithm for Management of Acneiform Rash

<table>
<thead>
<tr>
<th>Dermatological Evaluation</th>
<th>Mild (Grade 1)</th>
<th>Moderate or Severe (Grades 2+3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STCN 50 mg BID and Topicals BID</td>
<td>Reassess in 2 weeks</td>
<td>STCN 100 mg BID and Topicals BID</td>
</tr>
<tr>
<td>Reassess in 2 weeks</td>
<td>Increase STCN and Topical or Oral Antibiotics</td>
<td>Reassess in 2 weeks</td>
</tr>
<tr>
<td>2 Weeks STCN and Continue Topicals</td>
<td>2 Weeks STCN and Continue Topicals</td>
<td>Oral Steroids and STCN and Continue Topicals</td>
</tr>
<tr>
<td>Reassess in 2 weeks</td>
<td>Consider: Dose Modification or Oral Isotretinoin</td>
<td></td>
</tr>
</tbody>
</table>

**Key:**
- **Improvement**
- **Worse/No Change**

**STCN:** Semisynthetic tetracyclines (doxycycline or minocycline)

**Topicals:** Hydrocortisone 2.5% cream or alclomethasone 0.05% cream

**Oral Steroids:** Methylprednisolone dose pack

**Isotretinoin:** Low doses (10-20 mg a day) or isotretinoin as a single agent
Table 1-2: Algorithm for Management of Paronychia

<table>
<thead>
<tr>
<th>Dermatological Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (Grade 1)</td>
</tr>
<tr>
<td>Emollients and/or</td>
</tr>
<tr>
<td>Topical Corticosteroids</td>
</tr>
<tr>
<td>Reassess in 2 weeks</td>
</tr>
<tr>
<td>Emollients and/or</td>
</tr>
<tr>
<td>Topical Corticosteroids</td>
</tr>
<tr>
<td>Reassess in 2 weeks</td>
</tr>
<tr>
<td>Culture and Sensitivity,</td>
</tr>
<tr>
<td>then (appropriate)</td>
</tr>
<tr>
<td>Topical or Oral</td>
</tr>
<tr>
<td>Antibiotics</td>
</tr>
<tr>
<td>Reassess in 2 weeks</td>
</tr>
<tr>
<td>Culture and Sensitivity,</td>
</tr>
<tr>
<td>then (appropriate)</td>
</tr>
<tr>
<td>Topical or Oral</td>
</tr>
<tr>
<td>Antibiotics</td>
</tr>
<tr>
<td>Partial or Total Nail</td>
</tr>
<tr>
<td>Avulsion</td>
</tr>
<tr>
<td>Reassess in 2 weeks</td>
</tr>
<tr>
<td>Consider: Dose</td>
</tr>
<tr>
<td>Modification or Partial</td>
</tr>
<tr>
<td>or Total Nail Avulsion</td>
</tr>
</tbody>
</table>

Key:
- Improvement
- Worse/No Change

STCN: Semisynthetic tetracyclines (doxycycline or minocycline)
Topicals: Hydrocortisone 2.5% cream or alclomethasone 0.05% cream
Oral Steroids: Methylprednisolone dose pack
Isotretinoin: Low doses (10-20 mg a day) or isotretinoin as a single agent
5.6 Duration of Therapy

Patients will receive protocol therapy unless:

5.6.1 Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the E7208 Forms Packet.

5.6.2 Patient withdraws consent.

5.6.3 Patients should be treated on study with medications as assigned until discontinuation for toxicity or disease progression by RECIST criteria.

5.7 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 5 years from the date of registration. All patients must also be followed through completion of all protocol therapy.
6. Measurement of Effect

6.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every eight weeks.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in RECIST.

- The following general principles must be followed:
  1. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before registration.
  2. Measurable disease is defined by the presence of at least one measurable lesion.
  3. All measurements should be recorded in metric notation by use of a ruler or calipers.
  4. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

6.1.1 Definitions

Evaluable for Objective Response

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

(NOTE: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response

Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target lesion assessment. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.1.2 Disease Parameters

Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm
with calipers by clinical exam. All tumor measurements must be recorded in millimeters.

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq 15$ mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter $<10$ mm or pathological lymph nodes with $\geq 10$ to $< 15$ mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. Non-measurable also includes lesions that are $< 20$ mm by chest x-ray.

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum of the diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.
Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of unequivocal progression of each should be noted throughout follow-up.

6.1.3 Methods 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 registration.

The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (e.g., skin nodules). 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

This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up must be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image
acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

**PET-CT**

At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

**Ultrasound**

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

**Endoscopy, Laparoscopy**

The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

**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 guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

**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.

FDG-PET

FDG-PET may not be used as a response assessment in this study.

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression, See Section 6.1.4.3).

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. (Note: a change of 20% or less that does not increase the sum of the diameters by 5 mm or more is coded as stable disease)

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of eight weeks.

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis)

NOTE: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Non-CR/Non-PD
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 (see Section 6.1.4.3). Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest “increase” in the size of one or more on-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from “trace” to “large”, an increase in nodal disease from “localized” to “widespread”, or an increase sufficient to require a change in therapy.

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

6.1.4.3 Evaluation of New Lesions
The appearance of new lesions constitutes Progressive Disease (PD).

6.1.4.4 Evaluation of Best Overall Response
The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence or non-protocol therapy (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.
For Patients with Measurable Disease (i.e., Target Disease)

<table>
<thead>
<tr>
<th>Target Lesions</th>
<th>Non-Target Lesions</th>
<th>New Lesions*</th>
<th>Best Overall Response</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>CR Non-CR/Non-PD</td>
<td>No</td>
<td>PR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR Not evaluated</td>
<td>No</td>
<td>PR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR Non-PD/not evaluated</td>
<td>No</td>
<td>PR</td>
<td>Documented at least once ≥ 8 wks. from study entry</td>
<td></td>
</tr>
<tr>
<td>SD Non-PD/not evaluated</td>
<td>No</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD Any</td>
<td>Yes or No</td>
<td>PD</td>
<td></td>
<td>No prior SD, PR or CR</td>
</tr>
<tr>
<td>Any PD**</td>
<td>Yes or No</td>
<td>PD</td>
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</tr>
<tr>
<td>Any Any</td>
<td>Yes</td>
<td>PD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
**In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

NOTE: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment.

Duration of Response

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 progressive disease is objectively documented.

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, including the baseline measurements.

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of eight weeks.
7. Study Parameters

7.1 Therapeutic Parameters

1. Prestudy scans and x-rays used to assess all measurable or non-measurable sites of disease must be done within 4 weeks prior to randomization/registration.

2. Prestudy CBC (with differential and platelet count) should be done ≤ 4 weeks before randomization/registration.

3. All required prestudy chemistries, as outlined in Section 3, should be done ≤ 4 weeks before randomization/registration – unless specifically required on Day 1 as per protocol.

<table>
<thead>
<tr>
<th>Test / Assessment</th>
<th>Pre-Study</th>
<th>Every 2 weeks</th>
<th>Every 4 weeks</th>
<th>Every 6 weeks until progression</th>
<th>Follow-up1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History and Physical</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Weight and Performance Status</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Pressure7</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity Assessment</td>
<td>X</td>
<td>X</td>
<td>X6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease Assessment</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EKG</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X6</td>
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<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC/diff/plts</td>
<td>X²</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry Panel (chem. 6 including creatinine)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td>CT scans (chest/abd/pelvis)</td>
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<td>X4</td>
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</tr>
</tbody>
</table>

1. Every 3 months if patient is < 2 years from study entry, every 6 months if patient is 2-5 years from study entry. No specific requirements if patient is more than 5 years from study entry.
2. CBCs (with differential and platelet count) which includes WBC, ANC, Platelets, Hbg, and Hct required for protocol therapy must be done < 24 hours prior to the treatment cycle.
3. Within 2 weeks prior to registration for women of childbearing potential; and every 6 weeks during treatment or per institutional guidelines, whichever is shorter.
4. CT scans every 4 cycles until progression.
5. At the end of treatment. Repeat as clinically indicated.
6. Toxicity Assessment every 2 cycles for the first 4 cycles on study and then every 2 cycles thereafter. An assessment is also required at the end of treatment and 30 days after the end of treatment.
7. Blood pressure should be monitored twice per week for the first 4 weeks and then every 2 weeks thereafter.
8. Urine dipstick may be used. However, in the occurrence of 2+ urine, UPC must be used.
9. At the end of treatment with a 30 day safety followup. Repeat as clinically indicated.
10. Submit from patients who consent "Yes" to "May your coded samples and related coded information be kept for use in research to learn about, prevent, find or treat cancer?" See Section 10.
8. **Drug Formulation and Procurement**

8.1 **Irinotecan (CPT-11) (NSC-616348)**

*Other Names* Irinotecan hydrochloride trihydrate [CPT-11, (4S)-4, 1 1- diethyl-4-hydroxy-9-[(4-piperidinopiperidino) carbonyloxy] -IHpyrano [3',4':6, 7l indolzino [1,2-bl quino line-3, 14(4H, I2H)dione hydrochloride trihydrate] is a topoisomerase I inhibitor.

8.1.1 Classification

Topoisomerase I inhibitor

8.1.2 Toxicology

**Human Toxicity**: Virtually all Phase I and II studies of irinotecan 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 include nausea and vomiting, anorexia, abdominal cramping, cumulative asthenia, thrombocytopenia, renal insufficiency, increase in transaminase level and hair loss. Sporadic cases of pulmonary toxicity, manifested as shortness of breath and nonproductive cough, have also been reported.

8.1.3 Mode of Action

Causes single stranded DNA breakage by inhibition of the intranuclear enzyme topoisomerase-1. Leads to apoptotic cell death via defects in DNA repair.

8.1.4 Pharmacology

**Pharmacokinetics**: Several studies describing the pharmacokinetic characteristics of irinotecan (CPT-11) and its active metabolite, SN-38, when administered alone or in combination with other agents (including cisplatin) in patients with small cell or non-small cell lung cancer have been reported in published literature. CPT-11 is converted by carboxylesterases to its more active metabolite, SN-38. In vitro, SN-38 is 250 to 1,000 fold more potent than CPT-11 in the inhibition of topoisomerase I activity. A reversible, pH-dependent hydrolysis converts the closed lactone E ring form of both CPT-11 and SN-38 to the open, carboxylate form of each compound. Only the closed ring (lactone) forms of CPT-11 and SN-38 are effective topoisomerase I inhibitors. The mean terminal half-life of SN-38 in plasma is slightly longer than that for CPT-11; 11.5 ± 3.8 hours versus 6.3 ± 2.2 hours for the lactone forms. Peak plasma concentrations for CPT-11 occur at the end of the infusion. The time to peak for SN-38 is highly inter-patient dependent occurring at variable times points 30 to 90 minutes after the end of infusion. Murine studies suggest that the liver may concentrate, convert CPT-11 to SN-38, and eliminate both compounds as well as the glucuronide conjugate of SN-38 (SN-38G) via biliary secretion. In rats, 55% of radiolabeled CPT-11 was excreted unchanged in the bile within 24 hours, while 21.7% was transformed to SN-38. It recently was demonstrated that plasma
concentrations of SN-38G in patients occur 0.5 to 3 hr after the SN38 peak and plasma levels generally exceeded that of SN-38. Overall, 73% of the radioactivity could be recovered from the feces of rats and 25% from the urine. Bile concentrations of CPT-11 were 10 to 60 fold higher than plasma concentrations in one patient during the first 6 hours following administration, while bile concentrations of SN-38 were 2 to 9 fold higher. Renal clearance has not been reported to be a major route of elimination for these compounds in humans.

8.1.5 Formulation

The drug is supplied in two forms: 2 ml vials containing 40 mg of drug and 5 ml vials containing 100 mg of drug. The drug is supplied in brown vials and appears as a pale-yellow-to-yellow crystalline powder and pale yellow transparent solution when reconstituted.

8.1.6 Storage and Stability

Irinotecan vials must be stored in a cool, dry place, protected from light in a locked cabinet accessible only to authorized individuals. It is stable for at least three years at room temperature. Irinotecan is stable for 24 hours in glass bottles or plastic bags after reconstitution with D5W.

8.1.7 Dose Specifics

8.1.7.1 rms A (IC) and B (ICR)

Irinotecan will be given at a dose of 180 mg/m² intravenously over 60-90 minutes every 2 weeks.

8.1.7.2 Arm C (mICR)

Irinotecan will be given at a dose of 150 mg/m² intravenously over 60-90 minutes every 2 weeks.

8.1.8 Preparation

Irinotecan will be diluted with D5W to a total volume of 500 ml and infused intravenously over 60-90 minutes. Nothing else should be added to the bag.

8.1.9 Route of Administration

Intravenous administration only.

8.1.10 Incompatibilities

Do not mix with any other compound.

8.1.11 Availability

This drug is commercially available for purchase by a third party. This drug will not be supplied by the NCI.

8.1.12 Side Effects

Hematologic: Leukopenia, neutropenia, anemia, thrombocytopenia, neutropenic fever, hemorrhage
Gastrointestinal: Diarrhea (early and late – see administration above), nausea and vomiting, anorexia, abdominal pain, flatulence, stomatitis, dyspepsia, dehydration

Hepatic: Elevated transaminases.

Cardiovascular: Vasodilation, hypotension, myocardial infarction, stroke, edema

CNS: Dizziness, confusion, somnolence, insomnia, back pain

Respiratory: Pulmonary embolism,

Dermatologic: Alopecia, rash

Other: Asthenia, thrombophlebitis, sweating, weight loss, chills

8.1.13 Nursing/Patient Implications

Premedicate with antiemetics in anticipation of mild to moderate nausea and vomiting. When used in combination with 5-fluroruracil and leucovorin the nausea and vomiting will likely be worse.

Fatalities have been reported with thromboembolic events and neutropenic sepsis in patients receiving 5-fluorouracil, leucovorin and irinotecan.

Monitor for diarrhea. Diarrhea occurring within one hour of irinotecan has been treated with atropine 0.25 to 1mg IV or SC. Loperamide has been effective in treating later diarrhea and the patient should be instructed on its immediate use at the first loose stool following the irinotecan (see Section 5.5.2).

Monitor CBC, platelets, and liver function tests.

Dose modifications per the protocol or the package insert should be followed for hematologic and gastrointestinal toxicity.

Advise patient of likely post-treatment neutropenia and instruct in appropriate neutropenic precautions.

Administration of an oral quinolone antibiotic may decrease the risk of neutropenic sepsis in patients receiving 5-fluorouracil/leucovorin and irinotecan.

8.2 Cetuximab

8.2.1 IMC-C225, Erbitux®, NSC-714692

8.2.2 Classification

Anti-EGF Receptor antibody

8.2.3 Mode of Action

Cetuximab, a chimerized antibody of the IgG1 subclass, was originally derived from a mouse myeloma cell line. Cetuximab was genetically engineered by cloning the heavy and light chains of cetuximab and adapting them for expression together with the constant regions of the human kappa light chain and human gamma 1 heavy chain. The chimerization resulted in an antibody with binding affinity to epidermal
growth factor receptors (EGFR) greater than the natural ligand epidermal growth factor (EGF). Cetuximab blocks binding of EGF and transforming growth factor alpha (TGFα) to EGFR and inhibits ligand-induced activation of this tyrosine kinase receptor. Cetuximab also stimulates EGFR internalization, effectively removing the receptor from the cell surface for interaction with ligand.

8.2.4 Storage and Stability

Cetuximab is an anti-EGFR human-to-murine chimeric antibody. Cetuximab is expressed in SP2/0 myeloma cell line, grown in large scale cell culture bioreactors and purified to a high level purity using several purification steps including protein A chromatography, ion exchange chromatography, low pH treatment and nanofiltration. Cetuximab is not known to be a vesicant.

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F). DO NOT FREEZE. Increased particulate formation may occur at temperatures at or below 0°C. This product contains no preservatives. Preparations of cetuximab in infusion containers are chemically and physically stable for up to 12 hours at 2°C to 8°C (36°F to 46°F) and up to 8 hours at controlled room temperature (20°C to 25°C; 68°F to 77°F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2°C to 8°C. Discard any unused portion of the vial.

8.2.5 Dose Specifics

8.2.5.1 Arms A (IC) and B (ICR)
Cetuximab will be given as a 500 mg/m² dose every 2 weeks.

8.2.5.2 Arm C (mICR)
Cetuximab will be given as a 400 mg/m² dose every 2 weeks.

8.2.6 Preparation

The product is formulated to 2 mg protein/mL with phosphate buffered saline, pH 7.2 ± 0.2 and aseptically filled into sterile glass vials, 100 mg per 50 cc vial, and stored as a liquid at 2 to 8°C. Each vial contains the following active and inactive ingredients per 1.0 mL: 2 mg of cetuximab, 145 nmol/L sodium chloride, and 10 mmol/L sodium phosphate.

Preparation and Administration: Cetuximab is supplied as a 50-mL, single-use vial containing 100 mg of cetuximab at a concentration of 2 mg/mL in phosphate buffered saline. The solution should be clear and colorless and may contain a small amount of easily visible white amorphous cetuximab particulates. DO NOT SHAKE OR DILUTE.

- Cetuximab must not be administered as an IV push or bolus.
- Cetuximab must be administered with the use of a low protein binding 0.22-micrometer in-line filter.
8.2.7 Route of Administration

**Administration of Cetuximab:** In an effort to prevent a hypersensitivity reaction, all patients should be premedicated with diphenhydramine hydrochloride 50 mg (or an equivalent antihistamine) by IV given 30-60 minutes prior to the first dose of cetuximab. Premedication may be administered prior to subsequent doses, but at the Investigator's discretion, the dose of diphenhydramine (or a similar agent) may be reduced.

The initial dose of cetuximab is 500 mg/m² intravenously administered over AT LEAST 120 minutes, followed by ONE HOUR infusions every 2 weeks. **Cetuximab should not be given at a rate faster than 5 ml/min for the first dose.** Patients must be continuously observed during the infusion for signs of anaphylaxis.

Patients will be closely monitored for treatment-related adverse events, especially hypersensitivity reactions, during the infusion and the post-infusion observation hour. For the duration that patients are on study therapy, adverse event monitoring will be done continuously. Patients will be evaluated for adverse events at each visit and are to be instructed to call their physician to report any clinically significant adverse events between visits.

Severe infusion reactions occurred with the administration of cetuximab in approximately 3% (17/633) of patients, rarely with fatal outcome (< 1 in 1,000). Approximately 90% of severe infusion reactions were associated with the first infusion of cetuximab despite the use of prophylactic antihistamines. These reactions were characterized by the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria and/or hypotension. Caution must be exercised with every cetuximab infusion, as there were patients who experienced their first severe infusion reaction during later infusions.

Cetuximab can be administered via infusion pump or syringe pump.

**Infusion Pump:**

1. Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike or other appropriate transfer device may be used).
2. Fill cetuximab into a sterile evacuated container or bag such as glass containers, polyolefin bags (e.g., Baxter Intravia), ethylene vinyl acetate bags (e.g., Baxter Clintec), DEHP plasticized PVC bags (e.g., Abbott Lifecare), or PVC bags.
3. Repeat procedure until the calculated volume has been put in to the container. Use a new needle for each vial.
4. Administer through a low protein binding 0.22-micrometer in-line filter (placed as proximal to the patient as practical).
5. Affix the infusion line and prime it with cetuximab before starting the infusion.
6. Maximum infusion rate should not exceed 5 mL/min.
7. Use 0.9% saline solution to flush line at the end of infusion.

Cetuximab should be piggybacked to the patient’s infusion line. Following the cetuximab infusion, a 1-hour observation period is recommended.

8.2.8 Incompatibilities

Cetuximab should not be mixed with any other drug.

8.2.9 Availability

Cetuximab is approved for this indication and is commercially available. Please refer to the commercial package insert for complete prescribing and toxicity information.

8.2.10 Anticipated Adverse Events

Except where indicated, the data described below reflect exposure to cetuximab in 633 patients with advanced metastatic colorectal cancer. Cetuximab was studied in combination with irinotecan (n=354) or as monotherapy (n=279). Patients receiving cetuximab plus irinotecan received a median of 12 doses (with 88/354 [25%] treated for over 6 months), and patients receiving cetuximab monotherapy received a median of 7 doses (with 26/279 [9%] treated for over 6 months). The population had a median age of 59 and was 60% male and 91% Caucasian. The range of dosing for patients receiving cetuximab plus irinotecan was 1-84 infusions, and the range of dosing for patients receiving cetuximab monotherapy was 1-63 infusions.

The most serious adverse reactions associated with cetuximab were:

- Infusion reaction (3%);
- Dermatologic toxicity (1%);
- Interstitial lung disease (0.5%);
- Fever (5%);
- Sepsis (3%);
- Kidney failure (2%);
- Pulmonary embolus (1%);
- Dehydration (5%) in patients receiving cetuximab plus irinotecan, 2% in patients receiving cetuximab monotherapy;
- Diarrhea (6%) in patients receiving cetuximab plus irinotecan, 0% in patients receiving cetuximab monotherapy.

Thirty-seven (10%) patients receiving cetuximab plus irinotecan and 14 (5%) patients receiving cetuximab monotherapy discontinued treatment primarily because of adverse events.

The most common adverse events seen in 354 patients receiving cetuximab plus irinotecan were acneiform rash (88%),
asthenia/malaise (73%), diarrhea (72%), nausea (55%), abdominal pain (45%), and vomiting (41%).

The most common adverse events seen in 279 patients receiving ERBITUX monotherapy were acneiform rash (90%), asthenia/malaise (49%), fever (33%), nausea (29%), constipation (28%), and diarrhea (28%).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Data in patients with advanced colorectal carcinoma in the following table are based on the experience of 354 patients treated with cetuximab plus irinotecan and 279 patients treated with cetuximab monotherapy. [ERBITUX™ (Cetuximab) package insert. ImClone Systems Incorporated and Bristol-Myers Squibb Company. 2004 ER-B00001-02-04].

NOTE: There have been reports of hypomagnesemia during cetuximab therapy. The majority of the cases have been documented as decreased serum magnesium levels observed in routine electrolyte monitoring, and not as a result of clinical symptoms.
Incidence of Adverse Events (≥ 10%) in Patients with Advanced Colorectal Carcinoma

<table>
<thead>
<tr>
<th>Body System</th>
<th>Preferred Term</th>
<th>ERBITUX plus Irinotecan (n=354)</th>
<th>ERBITUX Monotherapy (n=279)</th>
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<tr>
<td></td>
<td></td>
<td>Grades 1 - 4</td>
<td>Grades 3 and 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grades 1 - 4</td>
<td>Grades 3 and 4</td>
</tr>
<tr>
<td>% of Patients</td>
<td></td>
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<tr>
<td><strong>Body as a Whole</strong></td>
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<tr>
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<td>Infection</td>
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<tr>
<td>Back Pain</td>
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<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Headache</td>
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<tr>
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<td>29</td>
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<td>Vomiting</td>
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<tr>
<td>Conjunctivitis</td>
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</table>

1 Adverse events that occurred (toxicity Grades 1 through 4) in ≥10% of patients with refractory colorectal carcinoma treated with ERBITUX plus irinotecan or in ≥10% of patients with refractory colorectal carcinoma treated with ERBITUX monotherapy.

2 Asthenia/malaise is defined as any event described as “asthenia”, “malaise”, or “somnolence”.

3 Includes cases reported as infusion reaction.

4 Infusion reaction is defined as any event described at any time during the clinical study as “allergic reaction” or “anaphylactoid reaction”, or any event occurring on the first day of dosing described as “allergic reaction”, “anaphylactoid reaction”, “fever”, “chills”, “chills and fever” or “dyspnea”.

5 Acneiform rash is defined as any event described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis”.

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1 Adverse events that occurred (toxicity Grades 1 through 4) in ≥10% of patients with refractory colorectal carcinoma treated with ERBITUX plus irinotecan or in ≥10% of patients with refractory colorectal carcinoma treated with ERBITUX monotherapy.

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5 Acneiform rash is defined as any event described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis”.

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8.2.11 Nursing/Patient Implications

Resuscitation equipment and medications to treat hypersensitivity reactions should be available during and for one hour following each cetuximab infusion.

Blood pressure, pulse and temperature should be taken pre-infusion, at midpoint, end of infusion and one hour post-infusion.

Patients should be observed for 1 hour following the initial dose and 30 minutes following the weekly doses.

Patients should be observed for signs of hypersensitivity/anaphylaxis.

Safety Precautions

Appropriate mask, protective clothing, eye protection, gloves, and Class II vertical-laminar-airflow safety cabinets are recommended during preparation and handling. Opened vials must be disposed of at the investigational center as chemotherapy or biohazardous waste provided documented procedures for destruction are in place. Otherwise, opened vials must be returned to BMS for disposal. For questions regarding cetuximab destruction please contact BMS at 866 339-4267 or 203 677-7017.

Cetuximab therapy should be used with caution in patients with known hypersensitivity to cetuximab, murine proteins, or any component of this product.

It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving cetuximab as sunlight can exacerbate any skin reactions that may occur.

8.3 IMC 1121B

8.3.1 Other Names

Ramucirumab, 1121B

8.3.2 Classification:

Recombinant anti-VEGF human monoclonal antibody

8.3.3 Mode of Action:

IMC-1121B is a recombinant human monoclonal antibody of the IgG1 subclass that specifically binds to the extracellular domain of the VEGFR-2. This antibody effectively blocks VEGF/VEGFR-2 interaction, inhibits VEGF-stimulated activation of VEGFR-2 and p44/p42 mitogen-activated protein kinases, and neutralizes VEGF-induced mitogenesis of human endothelial cells.

8.3.4 Storage and Stability

Chemical and physical in-use stability has been demonstrated for up to 24 hours below 25°C (77°F). DO NOT FREEZE OR SHAKE IMC-1121B. From a microbiological point of view, the prepared product should be used immediately. If not used immediately, in-use storage time and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C (36°F - 46°F). IMC-
1121B should be protected from light when being stored. In the event of a temperature excursion, please complete the E7208 Temperature Excursion Form (Appendix VIII) and email to TempExcursions@Imclone.com.

8.3.5 Dose Specifics

8.3.5.1 Arm B (ICR):

Patients will receive 8 mg/kg of IMC-1121B every 2 weeks, administered as an I.V. infusion over 1 hour. The dose of IMC-1121B will be dependent upon the patient’s baseline body weight in kilograms. This dose will be recalculated if there is a 10% change in body weight from baseline. IMC 1121B is formulated at 10 mg/mL (with a dose of 8 mg/kg).

Premedication

Premedication is recommended but not required prior to infusion of ramucirumab. Recommended premedication agents include histamine H1 antagonists such as diphenhydramine hydrochloride 50 mg I.V. (or equivalent). Additional premedication may be provided at investigator discretion.

8.3.5.2 Arm C (mICR):

Patients will receive 6 mg/kg of IMC-1121B every 2 weeks, administered as an I.V. infusion over 1 hour. The dose of IMC-1121B will be dependent upon the patient’s baseline body weight in kilograms. This dose will be recalculated if there is a 10% change in body weight from baseline. IMC 1121B is formulated at 10 mg/mL (with a dose of 8 mg/kg).

Premedication

Premedication is recommended but not required prior to infusion of ramucirumab. Recommended premedication agents include histamine H1 antagonists such as diphenhydramine hydrochloride 50 mg I.V. (or equivalent). Additional premedication may be provided at investigator discretion.

8.3.6 Preparation

IMC-1121B drug product are sterile, preservative-free, injectable liquids in single-use 50-mL vials containing 500 mg/50 mL IMC-1121B in a histidine-buffered formulation at a final concentration of 10 mg/mL. Each vial is packaged and labeled in accordance with local regulations.

The dose of IMC-1121B should be aseptically withdrawn from the vial and transferred to a sterile AVIVA, ethylene vinyl acetate, polyolefin, or polyvinyl chloride I.V. bag, or an evacuated United States Pharmacopeia Type II (or local equivalent) glass I.V. container. For dose volumes < 250 mL, a sufficient quantity of sterile normal saline (0.9% weight/volume) solution must be added to the container (or
removed in the case of a prefilled bag such as AVIVA) to make the total volume 250 mL. For dose volumes > 250 mL, the addition of sterile normal saline is not required.

The container should be gently inverted to ensure adequate mixing. Different drug product lots or formulations must not be mixed in a single infusion.

Chemical and physical in-use stability has been demonstrated for up to 24 hours below 25°C (77°F). **DO NOT FREEZE OR SHAKE IMC-1121B.** From a microbiological point of view, the prepared product should be used immediately. If not used immediately, in-use storage time and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C (36°F - 46°F). IMC-1121B should be protected from light when being stored.

8.3.7 Route of Administration

The infusion should be delivered over 60 minutes. The infusion rate should not exceed 25 mg/minute. An infusion set (non-vented for plastic or vented for glass container) equipped with a downstream in-line, 0.2-µm or 0.22-µm protein-sparing filter is required for administration of IMC-1121B or placebo. The infusion tubing must be flushed with normal saline to ensure delivery of the calculated dose.

8.3.8 Incompatibilities

No formal drug interaction studies have been performed with IMC-1121B in humans.

8.3.9 Availability

Ramucirumab is an investigational agent (IND 109448), available free of charge and distributed by ImClone Systems. Ramucirumab is available as an injectable solution, in single-use, 50-ml vials containing 500 mg at a concentration of 10mg/ml. The histidine buffer contains 10mM histidine, 75mM sodium chloride, 133mM glycine and 0.01% Tween® -80.

**Starter Supply**

Following submission and approval of the required regulatory documents as outlined in Section 4 a five cycle starter supply (ten 50-ml vials containing 500 mg at a concentration of 10mg/ml) of Ramucirumab may be ordered from ImClone Systems.

Investigators must fax a completed E7208 Drug Request Form (See **Appendix IV**) to ImClone Systems at 908-218-0963. **When completing the E7208 Drug Request Form indicate “Starter Supply” under number of vials.**

Ramucirumab will be shipped to a responsible person (e.g., a pharmacist) at the investigator’s institution. Vials are shipped in refrigerated shippers to maintain temperature between 2°C - 8°C. Vials must be kept refrigerated between 2°C - 8°C at all times. IMC-1121B should be protected from light when being stored. **DO NOT FREEZE OR SHAKE IMC-1121B.**
Institutions should allow 7 business days (excluding Fridays) for shipment of drug from ImClone Systems from receipt of the E7208 Drug Request Form. Shipments will be made from ImClone Systems on Monday through Thursday for delivery on site Tuesday through Friday. There will be no weekend or holiday delivery of drugs. The E7208 Drug Request Form can be downloaded from the ECOG website in WORD format.

**Initial Drug Orders for Each Patient**

Following submission and approval of the required regulatory documents and patient registration, a supply of Ramucirumab may be ordered from ImClone Systems. Investigators must fax a completed E7208 Drug Request Form (See Appendix IV) to ImClone Systems at 908-218-0963.

Ramucirumab will be shipped to a responsible person (e.g., a pharmacist) at the investigator’s institution. Vials are shipped in refrigerated shippers to maintain temperature between 2°C - 8°C. Vials must be kept refrigerated between 2°C - 8°C at all times. IMC-1121B should be protected from light when being stored. DO NOT FREEZE OR SHAKE IMC-1121B.

The initial request will be for a sufficient number of vials to complete three cycles (i.e. six week supply at 8mg/kg IV every two weeks) based on the patient’s weight in “kg” at the time of patient registration.

Institutions should allow 7 business days (excluding Fridays) for shipment of drug from ImClone Systems from receipt of the E7208 Drug Request Form. Shipments will be made from ImClone Systems on Monday through Thursday for delivery on site Tuesday through Friday. There will be no weekend or holiday delivery of drugs. The E7208 Drug Request Form can be downloaded from the ECOG website in WORD format.

**Important Reorder Instructions**

Once it is determined that the patient will continue treatment, please reorder study drug immediately. Reorders should be a sufficient number of vials to complete three cycles (i.e. six week supply at 8mg/kg IV every two weeks) based on the patient’s weight in “kg” at the time of patient registration. Dose and volume of the drug are dependent upon the patient’s baseline body weight in kilograms. The dose should be recalculated if there is a 10% change in body weight from baseline.

Institutions should allow 7 business days (excluding Fridays) for shipment of drug from ImClone Systems from receipt of the E7208 Drug Request Form. Shipments will be made from ImClone Systems on Monday through Thursday for delivery on site Tuesday through Friday. There will be no weekend or holiday delivery of drugs. The E7208 Drug Request Form can be downloaded from the ECOG website in WORD format.
Drug Destruction and Return

When all patients have completed treatment at your institution, all unused, partially used, expired or empty containers must be destroyed at the site according to the institution’s policy for drug destruction. Please maintain appropriate records of the disposal, including dates and quantities. Sites are required to complete the Investigational Agent Disposition Form located in Appendix V. A copy of this form should be sent to Lisa Kennedy at lisa.kennedy@imclone.com.

Drug Inventory Records

Investigational Product Records at Investigational Site(s): It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried.

Please note that expiration dates are not listed on the vials. Lot numbers and related expiration dates are listed on the Drug Product Request Shipment Form which is shipped with the vials. Sites should keep a copy of this form as part of their drug inventory records.

8.3.10 Side Effects

Adverse events of concern, which may or may not be associated with IMC-1121B therapy, include infusion reactions, hypertension, arterial or venous thrombotic events, proteinuria, bleeding, headache and fatigue.

8.3.11 Nursing/Patient Implications

1. Monitor patient closely during infusion, for infusion related events.
2. Monitor blood pressure prior to each dose to assess for development of hypertension.
3. Instruct patient to monitor and report signs/symptoms of: bleeding (nose bleeds, blood in sputum), wound healing problems, abdominal pain, thromboembolic problems (chest or leg pain, dyspnea, vision changes, severe headache, cough, swelling)
4. Baseline urine protein must be performed and repeated every six weeks. If elevated, 24 hour urine collection must be performed.
5. Treat pain, arthralgias, etc. with acetaminophen, or other pain relief strategies that do not interfere with the clotting cascade.

Safety Precautions

Appropriate mask, protective clothing, eye protection, gloves, and Class II vertical-laminar-airflow safety cabinets are recommended during preparation and handling. Opened vials must be disposed of at the investigational center as chemotherapy or biohazardous waste provided documented procedures for destruction are in place. Otherwise, opened vials must be returned to Imclone for disposal. For questions regarding IMC-1121B destruction please contact Imclone at 866 339-4267 or 203 677-7017.
IMC-1121B therapy should be used with caution in patients with known hypersensitivity to cetuximab, murine proteins, or any component of this product.

It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving IMC-1121B as sunlight can exacerbate any skin reactions that may occur.
9. Statistical Considerations

9.1 Revised Statistical Design - Arms A (IC) and C (mICR)

Safety Monitoring

The revised investigational regimen (that is, Arm C (mICR), a revision of the previous investigational Arm B) will be examined among the first 16 patients enrolled to Arm C post the re-activation of the randomized trial. Randomization will commence to Arms A and C and for purposes of adverse event evaluation, close monitoring of the study will occur until 16 patients have been enrolled to Arm C and followed through 2 cycles of therapy. During this safety evaluation period all patients will be followed closely with monthly conference calls of the study team and independent toxicity monitor to review all real-time CTEP-AERS reports and any case report form reported treatment-related adverse events. At the time of suspension of this study prior to reactivation, the accrual rate was about 3-4 patients per month. Given this expected recruitment pattern upon initially re-opening the study, it appears reasonable to have calls on a monthly basis. Once fully reactivated, the accrual rate should be 10 patients per month. If the accrual pattern is substantially higher during the first few months after reactivation, the study team will convene calls every two weeks.

The toxic death rate on Arm B (ICR) prior to study suspension was 2/16 patients or 12.5%. With 16 patients on Arm C (mICR) evaluated under the new regimen the probability of observing 1 or more toxic deaths is 81.5% if the true toxic death rate is 10% and 88.2% under a true toxic death rate of 12.5%. No toxic deaths were observed in Arm A prior to suspension among 17 treated patients. Under the revised design with 16 patients evaluated on Arm C (mICR) the probability of observing one or more toxic deaths under a true toxic death rate of 0.77% is 11.6%. If one or more toxic deaths occur at any point during the 16 patient evaluation of Arm C, the study will close to accrual and the regimen will be abandoned.

The safety evaluation will also closely assess all treatment-related toxicities other than those of grade 5 with a particular emphasis on evaluating grade 3 and 4 events. Prior to suspension the grade 3 or higher treatment-related adverse event rate on Arm A was 16.7%. With 16 patients on Arm C there is 81% power to detect a true grade 3 or higher toxicity rate of 39% (versus a null of 16.7%) and 90% power to detect a true rate of 44% using a one-sided exact binomial test at the 11% significance level (evaluating Arm C separately as the power for the two-group comparison is limited). The observed grade 3 or higher toxicity rate on Arm B was 87.5%. If the grade 3 or higher toxicity test is significant after 16 patients on Arm C, the study will suspend accrual and the feasibility of the revised regimen will be evaluated by the study team and independent toxicity monitor, including a detailed review of all grade 3 or higher treatment related events. In addition to the above safety monitoring plan, the study will suspend upon the report of any colonic perforation event, regardless of treatment attribution or grade. A detailed review of the circumstances surrounding the event will be conducted and, in the case of the event occurring on Arm C, the feasibility of the revised regimen will be evaluated by the study team and toxicity monitor. The colonic perforation rate on Arm B (ICR) prior to study suspension was 2/16 patients or 12.5%. With 16 patients on Arm C (mICR) evaluated under the new
regimen the probability of observing 1 or more colonic perforations is 81.5% if the true rate is 10% and 88.2% under a rate of 12.5%. No toxic deaths were observed in Arm A prior to suspension among 17 treated patients.

In addition, the evaluation of 16 patients randomized to Arm C will allow estimation of any given toxicity with a 90% confidence interval that is no wider than 44.3 percentage points and there is 56.0% probability of observing any given event (1 or more out of 16 patients) with a true frequency of 5% and 81.5% probability observing 1 or more events with true frequency of 10%.

Primary Efficacy Design

Patients will be randomized equally between the two treatment arms A (IC) and C (mICR) with stratification based on performance status (0 vs. 1), discontinuation of oxaliplatin before disease progression (Yes vs. No), and time frame of progression (within 6 months of last treatment vs. > 6 months since last treatment). Patients previously randomized to arms A and B before the redesign of the experimental regimen will not be part of the formal efficacy evaluation and will be reported separately.

With 48 eligible patients per arm followed for progression-free survival (disease progression or death without evidence of progression), this study has over 85% power to detect a difference of 4.5 months median PFS in the control arm A (40% PFS at 6 months assuming exponential failure) versus 7.65 months median PFS (58% PFS at 6 months) in the experimental arm (Arm C) using a one-sided stratified log rank test conducted with 15% type 1 error. The study will require approximately 10 months of accrual at 10 patients per month and 6 additional months of follow-up to achieve the events required (67 PFS events) to provide at least 85% power for the stated alternative of a 48% increase in median PFS. Response, overall survival, and toxicity are secondary endpoints and will be reported at the time of primary PFS analysis. With 48 eligible patients per arm, the width of any 90% confidence interval on a binomial proportion will be no wider than 26 percentage points. In addition, the probability of observing a rare (2% probability) toxicity in either arm is greater than 62% at full accrual. Allowing for roughly 5% ineligibility and including the 35 patients who were previously randomized to Arms A and B of the study prior to its redesign, this study will require a total of 135 patients and 100 patients will be accrued to the revised study (Arm A versus Arm C).

This study will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC) for early stopping due to efficacy and futility. One interim stratified log rank test for efficacy will be performed at 60% PFS information (40 PFS events), expected to occur roughly at the time accrual completes and six months before full information is achieved. Type I error control will be accomplished using an O'Brien-Fleming type boundary, with Lan-Demets use function methodology to adjust the boundary for the exact information time achieved at the interim analysis. If the study is positive, the DSMC may recommend early reporting; there is at least 55% probability of rejecting the null at the interim analysis if the alternative hypothesis is true. At the interim analysis time, the PFS hazard ratio will also be computed from a stratified proportional hazards regression model. If the HR exceeds 1 (that is, evidence that PFS is worse in the experimental Arm C), the DSMC may recommend abandoning the regimen and early reporting of negative results. The effect of the interim analysis
on the operating characteristics of the trial is fairly small (less than 1% absolute effect on significance level and power).

Additional Safety Monitoring

In addition to the safety monitoring that will occur in the first 16 patients randomized to Arm C (described above), interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 5.2 and ECOG-ACRIN Operations Office – Boston’s real-time monitoring of events through CTEP-AERS report notifications will be in place for this trial. This system provides monthly notifications to the study chair, study statistician and independent toxicity monitor of certain reportable grade 4 or higher events and all grade 5 events.

Original Statistical Design (Arms A and B)

Patients will be randomized equally between the two treatment arms with stratification based on performance status (0 vs. 1), discontinuation of oxaliplatin before disease progression (Yes vs. No), and time frame of progression (within 6 months of last treatment vs. > 6 months since last treatment). With 70 eligible patients per arm followed for progression-free survival (disease progression or death without evidence of progression), this study has 90% power to detect a difference of 4.5 months median PFS in the control arm (40% PFS at 6 months assuming exponential failure) versus 7.65 months median PFS (58% PFS at 6 months) in the experimental arm using a one-sided log rank test conducted with 10% type 1 error. The study will require approximately 7 months of accrual at 20 patients per month and 7 additional months of follow-up to achieve the events required (100 PFS events) to provide 90% power for the stated alternative of a 70% increase in median PFS. Response, overall survival, and toxicity are secondary endpoints and will be reported at the time of primary PFS analysis. With 70 eligible patients per arm, the width of any 90% confidence interval on a binomial proportion will be no wider than 21 percentage points. In addition, the probability of observing a rare (1% probability) toxicity in either arm is greater than 50% at full accrual. Allowing for 5% ineligibility, this study will require a total of 147 patients.

Safety Monitoring

Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 5.2 and ECOG-ACRIN Operations Office – Boston’s real-time monitoring of events through CTEP-AERS report notifications will be in place for this trial. This system provides monthly notifications to the study chair, study statistician and independent toxicity monitor of certain reportable grade 4 or higher events and all grade 5 events.

In addition to ECOG-ACRIN’s routine semi-annual reporting of case report form toxicities through interim study reports and real-time monitoring of adverse events through CTEP-AERS, this study will include a detailed toxicity review of both treatment arms after 20 patients on each arm have been treated with at least two cycles of therapy. After 20 patients have been randomized per arm, the
study will suspend accrual. After the first 20 patients have been treated with at least 2 cycles of therapy, there will be a formal toxicity review once all cycle 2 treatment forms and associated adverse event forms through this treatment period have been submitted to the ECOG-ACRIN Operations Office – Boston. The study statistician will prepare a report of all case report form and CTEP-AERS reportable events for review by the study team and independent toxicity monitor. The study will remain suspended until the review is complete.

With 20 patients per arm, there is greater than 55% probability of observing one or more rare (true probability of 4%) toxicities on either arm and greater than 87% chance of observing one or more toxicities with true rate in excess of 10%. If 4 or more patients experience grade 4 or worse treatment-related events in an arm, consideration will be given to closing the trial or modifying the treatment regimens. Under this monitoring rule, there is less than 2% probability of meeting the monitoring boundary if the true grade 4 or higher toxicity probability is 5% but 89% chance of meeting the boundary if the true probability is 30%. For other true grade 4 probabilities of 10%, 20% and 25%, the corresponding probabilities of reaching the boundary are 13%, 59% and 77%, respectively. Toxicity analyses will be conducted separately in each arm. In addition to grade 4 toxicities, differences between the treatment arms with respect to all grade toxicities, grade 3-4 toxicities, and non-hematologic toxicities will be assessed. If it is deemed necessary by the study team/independent toxicity monitors, an additional interim safety assessment will be conducted.

Grade 5 events will also be separately monitored and reported. The recently reported EPIC trial (Sobrero et al., 2008) observed a toxic death rate of 0.77% in the cetuximab plus irinotecan arm (5 deaths among 650 patients). Taking 0.77% as the null toxic death rate for either arm in this trial and 5% or higher as an unacceptable alternative toxic death rate, we will consider modifying or closing the trial if in either arm 1 or more treatment-related toxic deaths are observed among the first 20 treated patients. Under the null hypothesis there is a 14% probability of observing one or more grade 5 events in the first 20 patients and 64% probability under the alternative. If the true grade 5 event rate is as high as 10%, there is 88% probability of observing 1 or more toxic deaths in the first 20 patients treated on an arm. In addition to the toxicity analysis at suspension, grade 5 events will be continuously monitored, reported and reviewed as indicated above. At full accrual, the probability of observing 2 or more grade 5 events out of 70 patients in an arm is 10% under the null hypothesis and 87% under the alternative hypothesis.

9.3 Study Monitoring

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

9.4 Gender and Ethnicity

Based on previous data from E3200 the anticipated accrual in subgroups defined by gender and race is:

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Gender</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
<td>Total</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>50</td>
<td>81</td>
<td>131</td>
</tr>
<tr>
<td>Ethnic Category: Total of all subjects</td>
<td>50</td>
<td>85</td>
<td>135</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Category</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Black or African American</td>
<td>5</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>45</td>
<td>78</td>
<td>123</td>
</tr>
<tr>
<td>Racial Category: Total of all subjects</td>
<td>50</td>
<td>85</td>
<td>135</td>
</tr>
</tbody>
</table>

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.
10. Pathology Review

Paraffin-embedded tumor and normal mucosa tissue specimens are to be submitted for research from patients who consent “Yes” to “May your coded samples and related coded information be kept for use in research to learn about, prevent, find or treat cancer?” Paraffin blocks are being collected from this study for the purpose of tissue banking for use in future research and will be retained indefinitely at the ECOG-ACRIN Central Repository for use in future studies.

Appendix II, Pathology Submission Guidelines, is available for distribution to the pathologist, outlining the submission requirements.

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

10.1 Materials Required For This Protocol

10.1.1 Forms – Must be sent with each submission

- Pathology Material Submission Form (#638 v04.2), Parts A & B completed. Please identify the clinical status of the submitted material (i.e., pretreatment as opposed to remission and relapse).
- A copy of the surgical pathology report
- Immunologic studies, if available
- Sample Tracking System Shipping Manifest

10.1.2 Biological Material

- One H & E stained slide of the tumor
- One paraffin block from representative sections of primary tumor
- One paraffin block from normal colon tissue

NOTE: If tissue blocks are not available, please contact the ECOG-ACRIN Pathology Coordinating Office – Reference Laboratory (PCORL) at 312-503-3384 to discuss alternative submission requirements. If pathology materials cannot be submitted, please indicate the reason on the Pathology Material Submission Form (#638 v04.2) and include a letter of explanation.

10.2 Shipping Procedures

Tissue specimens and the required forms and reports are to be submitted within 1 month of patient registration to:

ECOG-ACRIN Pathology Coordinating Office
Robert H. Lurie Comprehensive Cancer Center
of Northwestern University Medical School
Olson Pavilion - Room 8421
710 North Fairbanks Court
Chicago, IL 60611
10.3 **ECOG-ACRIN Sample Tracking System**

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

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

**Important:** Any case reimbursements associated with specimen submissions may not be captured if specimens are not logged into STS. Additionally, please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: [http://www.ecog.org/general/stsinfo.html](http://www.ecog.org/general/stsinfo.html). Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest should be shipped with all specimen submissions.

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

**Study Specific Notes**

If STS is unavailable at time of sample submission, submit the specimens with the required documentation and retroactively enter the information when STS is available. Notify the PCORL the day of shipment either by phone or e-mail (ecogpcorl@jimmy.harvard.edu).

10.4 **Banking**

Specimens submitted will be retained at the ECOG-ACRIN Central Repository for possible use in future ECOG-ACRIN approved studies. Residual blocks will be available for purposes of individual patient management on specific written request. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

10.5 **Sample Inventory Submission Guidelines**

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

Please refer to the E7208 Forms Packet for the forms submission schedule and copies of all forms. The E7208 Forms Packet may be downloaded by accessing the ECOG World Wide Web Home Page (http://www.ecog.org). Forms must be submitted to the ECOG-ACRIN Operations Office – Boston, FSTRF, 900 Commonwealth Avenue, Boston, MA 02215 (ATTN: DATA).

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

11.1 **Records Retention**

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study is being conducted under an IND. All records pertaining to the trial (including source documents) must be maintained for:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

Please contact the ECOG-ACRIN Operations Office – Boston prior to destroying any source documents.

12. **Patient Consent and Peer Judgment**

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

13. **References**


36. Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, Simes RJ, Chalchal H, Shapiro JD, Robitaille S, Price TJ, Shepherd L, Au HJ,

A Randomized Phase II Study of Irinotecan and Cetuximab with or without the Anti-Angiogenic Antibody, Ramucirumab, in Advanced, K-ras Wild-type Colorectal Cancer Following Progression on Bevacizumab-Containing Chemotherapy

Appendix I

Informed Consent Template for Cancer Treatment Trials (English Language)
[Deleted in Addendum #5]

INFORMED CONSENT INTENTIONALLY REMOVED FROM PROTOCOL DOCUMENT

Appendix I was removed from the protocol document in Addendum #5 and is posted as a separate document on the ECOG website. This was removed from the protocol to comply with NCI formatting guidelines.
A Randomized Phase II Study of Irinotecan and Cetuximab with or without the Anti-Angiogenic Antibody, Ramucirumab, in Advanced, K-ras Wild-type Colorectal Cancer Following Progression on Bevacizumab-Containing Chemotherapy

Appendix II

Pathology Submission Guidelines

The following items are included in Appendix II:

2. Instructional memo to submitting pathologists
3. List of Required Materials for E7208
4. Pathology Submission Form (#638 v04.2)
Guidelines for Submission of Pathology Materials

The following items should always be included when submitting pathology materials to the ECOG-ACRIN Pathology Coordinating Office:

- Institutional Surgical Pathology Report
- Pathology materials (see attached List of Required Material)
- Pathology Material Submission Form (#638 v04.2)

Instructions:

1. Place the Patient ID label provided by the ECOG-ACRIN Operations Office – Boston in Part A of the Pathology Material Submission Form.

   If a label is not available, **TYPE or PRINT** the following information in **Part A** of the form:
   - Patient's name (last, first)
   - Protocol number
   - Protocol case number (the patient's ECOG-ACRIN sequence number; for intergroup studies, include both the ECOG-ACRIN and other group's sequence numbers)
   - Patient's hospital number
   - Institution
   - Affiliate (if appropriate)

2. Complete blank areas of the pathologist's instructional memo and forward it, along with the List of Required Material and the Pathology Material Submission Form, to the appropriate pathologist.

3. The pathologist should return the required pathology samples and surgical pathology reports, along with the completed Pathology Material Submission Form (#638 v04.2) (Part B completed). If any other reports are required, they should be obtained from the appropriate department at this time.

4. Keep a copy of the Pathology Material Submission Form (#638 v04.2) for your records. (The original should be sent to the PCO.)

5. Double-check that ALL required forms, reports and pathology samples are included in the package to the Pathology Coordinating Office. (See appropriate List of Required Material.)

   **Pathology specimens submitted WILL NOT be processed by the Pathology Coordinating Office until all necessary items are received.**

6. Mail pathology materials to:

   ECOG-ACRIN Pathology Coordinating Office
   Robert H. Lurie Comprehensive Cancer Center
   of Northwestern University Medical School
   Olson Pavilion - Room 8421
   710 North Fairbanks Court
   Chicago, IL  60611

If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN Pathology Coordinating Office by telephone (312) 503-3384 or by fax (312) 503-3385.
List of Required Material

E7208: A Randomized Phase II Study of Irinotecan and Cetuximab with or without the Anti-Angiogenic Antibody, Ramucirumab, in Advanced, K-ras Wild-type Colorectal Cancer Following Progression on Bevacizumab-Containing Chemotherapy

Pre-Treatment
1. Pathology Material Submission Form (#638 v04.2) – Parts A & B completed. [or appropriate pathology submission form]
2. Institutional pathology report (must be included with EVERY pathology submission).
3. Biological materials
   • One H & E stained slide of the tumor
   • One paraffin block from representative sections of primary tumor
   • One paraffin block from normal colon tissue

NOTE: If tissue blocks are not available, please contact the ECOG-ACRIN Pathology Coordinating Office – Reference Laboratory (PCORL) at 312-503-3384 to discuss alternative submission requirements.
MEMORANDUM

TO: ______________________________________
    (Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
       ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: _____________________________________

SUBJECT: Submission of Pathology Materials for E7208: A Randomized Phase II Study of Irinotecan and Cetuximab with or without the Anti-Angiogenic Antibody, Ramucirumab, in Advanced, K-ras Wild-type Colorectal Cancer Following Progression on Bevacizumab-Containing Chemotherapy

The patient named on the attached Pathology Material Submission Form (#638 v04.2) has been entered onto an ECOG-ACRIN protocol by ______________________ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for banking for future research.

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

Blocks and slides submitted for this study will be retained at the ECOG-ACRIN Central Repository for future studies. Paraffin blocks will be returned upon written requested for purposes of patient management.

If you have any questions regarding this request, please contact the Pathology Coordinating Office at (312) 503-3384 or FAX (312) 503-3385.

The ECOG-ACRIN CRA at your institution is:

Name: ____________________________________
Address: _______________________________
Phone: ________________________________
**ECOG DIAGNOSTIC PATHOLOGY MATERIAL SUBMISSION FORM**

**Instructions:** This form is a required part of pathology submission. Please complete and submit along with all pathology material and corresponding pathology reports requested by the protocol. See list of required materials as specified in EACH protocol.

ECOG PCO-RL IS FULLY-COMPLIANT WITH DHHS, HIPAA, AND OHRP REGULATIONS

**PART A: To Be Completed By Data Manager/CRA**

|--------------------------|-----------|------------|---------|----------------|----------------------|---------------------|----------|---------------|-------|-------------|---|--------|-----------|----------------------|---------|

**DO NOT USE INITIALS – Submit Patient’s FULL Name**
(The Patient has authorized the use of PHI)

**PART B: TO BE COMPLETED BY DATA MANAGER/CRA AND SUBMITTING PATHOLOGIST**

<table>
<thead>
<tr>
<th>Status* (See Below)</th>
<th>Date Specimen Collected (M/D/Y)</th>
<th>Disease Site</th>
<th>Number of Slides/Vials</th>
<th>Specimen ID Numbers</th>
<th>Type of Stain</th>
<th>PCO ID Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete for Slides/Vials</td>
<td></td>
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<tr>
<td>Complete for Blocks/Punch</td>
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</tr>
</tbody>
</table>

*Status: Please identify the clinical status of the sample. List all that apply:

1. Original diagnostic material
2. AML/MDS diagnosis
3. Pre-protocol treatment biopsy/tissue
4. Post-protocol treatment biopsy/tissue
5. Post-surgery biopsy/tissue
6. Relapse/recurrence
7. Remission/response
8. Other, specify: ______________

**Did the patient consent to participate in the storage of samples for future research?** Yes No

**MATERIAL RETURN (All materials will be retained by the ECOG PCO unless return is requested here.)**

Does the submitting institution’s policy require the return of any submitted material (blocks, H&E slides, etc.)? Yes No

If so, please indicate which materials must be returned

If materials were not able to be submitted for this protocol and its correlative studies, please circle the reason for non-submission. Attach a formal letter referencing regulations, policy, and/or other explanation. If possible, include a copy of the policy.

Federal/State Regulations __________ Hospital/Institutional Policy ______ Insufficient Tissue ______ Other ______ (Specify) ______

Pathologist of Investigator’s Signature

**PART C: ECOG PATHOLOGY COORDINATING OFFICE USE ONLY**

<table>
<thead>
<tr>
<th>Date Sample Received at PCO</th>
<th>Date Sent to Reviewer</th>
<th>Date Sent to PI/Central Lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site Compliance %</td>
<td>Name of Reviewer</td>
<td>PI/Central Lab</td>
</tr>
<tr>
<td>PCO Comments:</td>
<td>Staff Init.</td>
<td></td>
</tr>
</tbody>
</table>

Investigator: Keep a copy for your files and submit original form to the destination specified in protocol.
Appendix III

Patient Thank You Letter

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

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

________________________________________________________________________

[ PATIENT NAME ]  [ DATE ]

[ PATIENT ADDRESS ]

Dear [ PATIENT SALUTATION ],

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

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

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

Sincerely,

[ PHYSICIAN NAME ]
Appendix IV

Clinical Study Product Request Form

To: Clinical Operations
Phone: 908-541-8129
Fax: 908-218-0963
Email: DrugRequests@ImClone.com

From: 
Institution / Site: 
Investigator: 
Date of Request: 

PROTOCOL NUMBER: E7208/MED-P12-10001

☐ Initial Drug Request
☐ Subsequent Drug Request, If Yes, check that the following has been reviewed and approved.
   ☐ IRB/EC Approval is current
   ☐ There are no compliance issues that would warrant suspension of drug

Clinical Study Product: Ramucirumab (IMC-1121B) 
Dosage Strength / Form: 50mL, 500mg/vial (10mg/mL)

Include MSDS: ☐ Yes ☐ No

Number of Vials Needed: 
Ship to: 
Address: 

Telephone: 

Drug Product needed no later than: (Please give 7 day notice for orders, drug requests will not be accepted after 2:00PM EST. Drug will not be shipped on Fridays.)

Please fax or email this form to Clinical Operations then file this document in your study binder.
To be completed by ImClone Systems:

COS/MED
(sign and print name): ____________________________

Requisition Number: ____________________________

(Medical Affairs or Clinical approval signature must be obtained for all drug shipments.)

SAP Material Code Number: ____________________________

Clinical Operations/Medical Affairs Management or designee

(sign and print name): ____________________________

(Medical Affairs or Clinical approval signature must be obtained for all drug shipments.)

To be completed by Logistics Warehouse:

Request Received By (sign and print name):

________________________________________________

Date (DDMMYYYY): ____________________________

Lot Number: ________________ Manufacture Date_______________

Quantity: ____________________________

Shipped by (sign and print name):

________________________________________________

Date (DDMMYYYY): ____________________________
Appendix V

Disposition Form

<table>
<thead>
<tr>
<th>To Be Completed By Site Personnel</th>
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</thead>
<tbody>
<tr>
<td>Investigator:</td>
</tr>
<tr>
<td>Site Name / No.:</td>
</tr>
<tr>
<td>Protocol Number: E7208/MED-P12-10001</td>
</tr>
<tr>
<td>Product: Ramucirumab (IMC-1121B)</td>
</tr>
<tr>
<td>Lot #:</td>
</tr>
<tr>
<td>Quantity:</td>
</tr>
<tr>
<td>☐ Returned</td>
</tr>
<tr>
<td>☐ Destroyed at Site: (Complete reason, method, and location of destruction)</td>
</tr>
<tr>
<td>☐ Transfer to:</td>
</tr>
<tr>
<td>Reason for Destruction:</td>
</tr>
<tr>
<td>Method of Destruction:</td>
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<tr>
<td>Location of Destruction:</td>
</tr>
<tr>
<td>Pharmacist:</td>
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<tr>
<td>Phone #:</td>
</tr>
<tr>
<td>Signature:</td>
</tr>
<tr>
<td>Date:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>To Be Completed By ImClone</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Reason for Return:</td>
</tr>
<tr>
<td>Is an Investigation Required?</td>
</tr>
<tr>
<td>II. Inspection:</td>
</tr>
<tr>
<td>Date Received:</td>
</tr>
<tr>
<td>Quantity Received:</td>
</tr>
<tr>
<td>Shipper Container Integrity</td>
</tr>
<tr>
<td>Product Container Integrity</td>
</tr>
<tr>
<td>Temperature Indicator</td>
</tr>
<tr>
<td>Comments:</td>
</tr>
<tr>
<td>III. Disposition:</td>
</tr>
<tr>
<td>☐ Preclinical Inventory</td>
</tr>
<tr>
<td>Quantity</td>
</tr>
<tr>
<td>Approval</td>
</tr>
<tr>
<td>Comments:</td>
</tr>
</tbody>
</table>
Appendix VI

Reimbursement Invoice

PLACE PATIENT ID LABEL HERE

Patient Initials (Last, First)__________________________
ECOG-ACRIN Protocol #______________
ECOG-ACRIN Patient ID ____________
Participating Group Protocol #______________
Participating Group Patient ID ____________
Institution/Affiliate ____________________________

Invoice Number
(ECC Use only) ____________________________

Payee Address
Payee/W-9 Name: ____________________________
Payee Tax ID #: ____________________________
Attention To: ____________________________
Street Address: ____________________________
City, State, Zip: ____________________________

Any Requested Reference on Payment (i.e. Invoice #): ____________

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Date of Service</th>
<th>Service Performed</th>
<th>Amount Requested (please itemize costs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

Please Note:
Amount requested may not exceed $150 per EKG, $50 per UPC and $75 per Pregnancy Test.

If a test falls outside of the scheduled cycle, please provide a brief explanation below:

☐ A copy of the test results for each service performed is attached.

If there are problems with this invoice, please contact:
Name ____________________________ Phone ____________________________
Fax ____________________________ Email ____________________________

If you have questions about the reimbursement process, please contact Meghan Cosby at cosby.meghan@jimmy.harvard.edu or 617-632-3610.
Please fax the completed form along with the related test results to 617-632-2063.
Appendix VII

Substitute W-9 Tax Form

Instructions

1. This form is a substitute to the Internal Revenue Service W-9 Tax Form. In addition to capturing all of the information required by the IRS, it also collects other information that is needed for our records. Questions regarding this form should be directed to the Pharmaceutical Liaison at the ECOG-ACRIN Operations Office – Boston 617-632-3610. Please note that only US-based institutions can use this form.

2. Complete all requested information and sign the substitute W-9 form. The original copy should be submitted to the ECOG-ACRIN Operations Office – Boston as soon as possible.

Please provide the legal name and address of the organization associated with the Federal Tax Identification Number listed in this section. (Generally, the corporate headquarters address of the university, hospital, or business should be provided. This information will be used for income reporting to the IRS and your organization).

Legal Name: ____________________________________________

Corporate Address: ______________________________________

City: __________________________ State: _______________ ZipCode: _______________

NCI CTEP ID: __________________________________________

Federal Tax Identification Number: _________________________ Phone Number: ____________________

Please identify the organization’s preferred payment address. ECOG-ACRIN will use this information for mailing checks to the organization. Please note that while ECOG-ACRIN can submit payment to an alternate address, it cannot make checks payable to a different organizational name or to a third party.

Payment Address: _______________________________________

City: __________________________ State: _______________ ZipCode: _______________

Phone Number: __________________ Fax Number: ______________ E-mail: ________________

Is this payment address affiliated with the Federal Tax ID listed above?: ____________________

Please identify whether the organization has a special status as defined by the following criteria: (Select all that apply)

Minority Business Enterprise (at least 51% minority-owned and managed business) __________________

Woman’s Business Enterprise (at least 51% woman-owned and managed business) __________________

Small Disadvantaged Business (as certified by the SBA) __________________

Veteran Business Enterprise (at least 51% veteran-owned business) __________________

Historically Underutilized Small Business (as certified by the SBA) __________________

None of the Above __________________

Under penalties of perjury, I certify that all of the information provided above is correct and that my organization is not subject to back-up withholding.

Printed Name: ______________________________ Title: ______________________________

Signature: ______________________________ Date: ______________________________
Appendix VIII

E7208 Temperature Excursion Form

Section 1

Protocol Number

Site Number

Investigator Name

Product Name

Label / Lot Batch No.

Order Number For Transit Excursion Only

Kit Numbers (If no Kit No. enter Qty)

Section 2

TempTale 4 Number

Mean Temperature °C

Highest Temperature °C

Total time above high temperature limit Minutes

Lowest Temperature °C

Total time below low temperature limit Minutes

Site Contact Name:

Site Contact Title:

Site Email:

Site Fax with Country Code:

Clinical Supply Logistics Authorization (To be completed by ImClone)

☐ Product is acceptable for use

☐ Product is not acceptable for use – Do Not Use This Drug

Print

Signature

Date

ImClone Systems Corporation. Branchburg, New Jersey 08876 Refer to LOG-SY-0003

Document printed on 2/24/2011

95
Enclosed are Addenda #5 and #6 for E7208, *A Randomized Phase II Study of Irinotecan and Cetuximab with or without the Anti-Angiogenic Antibody, Ramucirumab (IMC-1121B), in Advanced, K-ras Wild-type Colorectal Cancer Following Progression on Bevacizumab-Containing Chemotherapy.*

Addendum #5 and Addendum #6 are active effective June 6, 2014. E7208 is reopened to accrual effective the same date.

E7208 was closed to accrual on June 14, 2012 after 35 registrations were accrued as per pre-planned toxicity review. 18 patients (17 received treatment) were accrued to Arm A (IC) and 17 (16 received treatment) to Arm B (ICR). AdEERS reporting was reviewed and real time data were obtained on all treated patients. It was clear that more toxicity was seen in Arm B. (The toxicity per patient is summarized in Section 1.6 of the protocol.) The overall grade 3-5 toxicity rates were 17% for Arm A and 75% for Arm B. There were 2 toxic deaths in Arm B. Toxicities of higher incidence in Arm B included neutropenia, mucositis, diarrhea and GI perforation (including peri-anal abscess). In addition mean dose given in Arm B (mean % RDI) was considerably lower in Arm B: 65% for irinotecan, 85% for cetuximab and 92% for ramucirumab (even though no dose reductions were allowed in the protocol). This compares to 99% irinotecan and 98% cetuximab average %RDI in Arm A. Furthermore, only 3/17 patients in Arm A required dose reduction, compared to 15/16 in Arm B.

An analysis of the accrued patients at the time of the suspension found that those patients treated at reduced doses tolerated the ICR regimen, were treated longer, and had fewer disease progression events than those treated at fuller doses. Based on these finding we have modified the study by closing Arm B to further accrual, and replacing it with Arm C that employs reduced starting doses of the agents.

The amended protocol is modified in three ways: 1) A reduced dose regimen in Arm C (modified ICR) with irinotecan 150 mg/m², cetuximab 400 mg/m² and ramucirumab 6 mg/m² as starting doses, 2) Changes to the eligibility criteria (including no prior abscesses, obstruction or perforation within 6 months and more normal LFTs and albumin); and 3) Changes to the dose modifications for toxicity.

Due to new NCI requirements, the entire protocol has been reformatted. Please note that this reformattting includes the removal of the Informed Consent document from the protocol, as well as a complete pagination revision. The Informed Consent document will continue to be maintained as an independent document on the ECOG website. Please replace your current copy of the protocol with this updated version.

*A revised eligibility worksheet is attached.*

There are revised case report forms as a result of this amendment.

Full IRB review of Addendum #5 is required; however, ECOG-ACRIN will accept the method of review determined by the standard operating procedures for the IRB of record for this protocol.
Expedited IRB review of Addendum #6 is permitted, however, please consult your local IRB’s standard operating procedures, since their requirements may differ and require a full board review. It is the decision of the local IRB whether or not subjects are to be re-consented. The addenda must be submitted and reviewed by your IRB within 90 days of receipt of this notice, unless your local IRB has different written SOPs, which must be available at future ECOG-ACRIN audits.

Addenda 5 and 6 may be reviewed and approved by your IRB as either separate or combined submissions. If reviewed as a combined submission, each addendum must be referenced in the IRB approval letter.

Addendum #5 includes the following changes to the Protocol:

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Title Page</td>
<td>Updated version date and added study co-chair, Peter O’Dwyer, MD.</td>
</tr>
<tr>
<td>2. Table of Contents</td>
<td>Table of Contents has been reformatted and all subsequent pages of the protocol have updated pagination in order to comply with new NCI formatting requirements.</td>
</tr>
<tr>
<td>3. Study Contact Information</td>
<td>Inserted study co-chair contact information for Peter O’Dwyer, MD.</td>
</tr>
<tr>
<td>4. Schema</td>
<td>Updated Arm A box title from ‘Arm A” to “Arm A – (IC).”</td>
</tr>
<tr>
<td>5. Schema</td>
<td>Updated Arm B box title from “Arm B” to “Arm B – (ICR) CLOSED TO NEW ACCRUAL**.”  Shaded Arm B box gray. Removed arrow between “Randomize” and “Arm B” boxes.</td>
</tr>
<tr>
<td>7. Schema</td>
<td>Inserted footnote stating “**Arm B closed to accrual in Addendum #5. New patients are randomized to Arm A or Arm C.”</td>
</tr>
<tr>
<td>8. Schema</td>
<td>Updated accrual goal from 147 to 135 patients, including 35 patients accrued prior to Addendum #5. 100 patients will be accrued to the revised study.</td>
</tr>
<tr>
<td>9. Section 1.6</td>
<td>Inserted Summary of Toxicity Review section.</td>
</tr>
<tr>
<td>10. Section 2</td>
<td>Added subsection titles for study objectives to resolve formatting issues. The objectives have not changed, but are now labeled as “Progression Free Survival,” “Response Rate,” “Toxicity Rates,” and “Overall Survival.”</td>
</tr>
<tr>
<td>11. Section 3.1.8</td>
<td>Updated “Registration within 42 days of evidence of disease progression since last treatment” to “registration within 42 days of evidence of disease progression.”</td>
</tr>
<tr>
<td>12. Section 3.1.12.4</td>
<td>Updated “alanine transaminase (ALT) ≤ 3.0 x the upper limit of normal (ULN)” to “alanine transaminase (ALT) ≤ 3.0 x the institutional upper limit of normal (ULN).” Updated hepatic criteria to include “Albumin within institutional normal range” and “Albumin:______ Date:______”</td>
</tr>
<tr>
<td>13. Section 3.1.13</td>
<td>Updated to state “Chemotherapy drugs and bevacizumab may be stopped and started as long as no prior disease progression requiring change in chemotherapy agents occurred.”</td>
</tr>
<tr>
<td>14. Section 3.1.21</td>
<td>Inserted “No history of bowel obstruction, GI perforation, major abdominal surgery with bowel resection or peri-rectal/peri-anal abscess within 6 months prior to randomization.”</td>
</tr>
<tr>
<td>15. Section 4</td>
<td>Updated PMB phone number to 240-276-6575.</td>
</tr>
<tr>
<td>16. Section 5.1.1</td>
<td>Updated section title from “Treatment/ARM A” to “Treatment/ARM A – (IC).”</td>
</tr>
<tr>
<td>Section</td>
<td>Updated Section Title/Content</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>17.</td>
<td>Section 5.1.3 Updated section title from “Treatment/ARM B” to “Treatment/ARM B – (ICR).” Replaced section content with “(CLOSED to accrual in Addendum #5).”</td>
</tr>
<tr>
<td>18.</td>
<td>Section 5.1.3 Inserted “Treatment/ARM C – (mICR)” section.</td>
</tr>
<tr>
<td>19.</td>
<td>Section 5.2.1 Inserted “via AdEERS” in the second bullet point.</td>
</tr>
<tr>
<td>20.</td>
<td>Section 5.2.3 Updated the first bullet from “Arm A and Arm B” to “Arms A, B and C.”</td>
</tr>
<tr>
<td>21.</td>
<td>Section 5.2.7 Updated section title from “Steps to Determine if an Adverse Event is to be Reported in an Expedited Manner for Arm B” to “Steps to Determine if an Adverse Event is to be Reported in an Expedited Manner for Arms B and C.”</td>
</tr>
<tr>
<td>22.</td>
<td>Section 5.2.7.1 Updated section title from “Guidelines for adverse events OCCURRING WITHIN 30 DAYS of the last administration of the investigational agent(s)” to “Guidelines for adverse events OCCURRING WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS of the last administration of the investigational agent(s).”</td>
</tr>
<tr>
<td>23.</td>
<td>Section 5.2.8 Updated section title from “Expedited Reporting Requirements for Arm B on protocol E7208” to “Expedited Reporting Requirements for Arms B and C on protocol E7208.”</td>
</tr>
<tr>
<td>24.</td>
<td>Section 5.2.8 FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312) table: Removed the following note, as it is not relevant for this study: “NOTE: Protocol-specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.”</td>
</tr>
<tr>
<td>25.</td>
<td>Section 5.2.9 Updated section title from “Additional instructions, requirements and exceptions for Arm B on protocol E7208” to “Additional instructions, requirements and exceptions for Arms B and C on protocol E7208.” Updated note from “There are no additional protocol specific adverse event reporting requirements or exceptions for E7208” to “All grade 2 or higher GI perforations and peri-rectal abscess events, regardless of grade or whether or not the patient was hospitalized, must be reported via AdEERS within the timeframes specified in the table in Section 5.2.8.”</td>
</tr>
<tr>
<td>26.</td>
<td>Section 5.4.1 Updated the dose reductions table in item f to provide arm-specific dose reduction information for each agent.</td>
</tr>
<tr>
<td>27.</td>
<td>Section 5.4.3 Updated from “Dose modifications should be made only if patient is receiving intensive loperamide therapy” to “Dose modifications should be made for toxicity only when patient is receiving intensive loperamide therapy.”</td>
</tr>
<tr>
<td>28.</td>
<td>Section 5.4.3 In the diarrhea dose modification table, updated the second column in the Grade 3 row from “Be sure intensive loperamide is being taken. If so, do not dose modify and do not treat again until the toxicity resolves to &lt; grade 2” to “Be sure intensive loperamide is being taken. If so, and grade 3 diarrhea lasts longer than 48 hours, reduce irinotecan one dose level. Do not treat again until the diarrhea resolves to ≤ grade 2.”</td>
</tr>
<tr>
<td>Section</td>
<td>Action</td>
</tr>
<tr>
<td>---------</td>
<td>--------</td>
</tr>
</tbody>
</table>
| 29.     | Section 5.4.3 | In the diarrhea dose modification table, updated the second column in the Grade 4 row from "Be sure intensive loperamide is being taken. If so, hold irinotecan. If diarrhea resolves to < grade 2, irinotecan may be resumed at one lower dose level for subsequent cycles. If grade 4 diarrhea persists beyond 7 days, reduce cetuximab one dose level also. For subsequent cycles, continue both agents at the reduced dose levels from the previous cycle." to "Be sure intensive loperamide is being taken. Hold irinotecan. If diarrhea resolves to ≤ grade 2, irinotecan and cetuximab should be resumed at one lower dose level for subsequent cycles. For subsequent cycles, continue both agents at the reduced dose levels from the previous cycle."
| 30.     | Section 5.4.5 | In the mucositis dose modification table, updated the second column in the Grade 3 row from "Hold irinotecan. If mucositis resolves to ≤ Grade 2, resume irinotecan at one lower dose level for subsequent cycles. No modifications (or delays) will be made for Ramucirumab or cetuximab" to "Hold irinotecan. If mucositis resolves to ≤ Grade 2, resume both irinotecan and cetuximab at one lower dose level for subsequent cycles. No modifications (or delays) will be made for Ramucirumab."
| 31.     | Section 5.4.5 | In the mucositis dose modification table, updated the second column in the Grade 4 row from "Hold ALL protocol treatment. If mucositis resolves to ≤ Grade 2, continue all agents at the dose level from the previous cycle" to "Hold ALL protocol treatment. If mucositis resolves to ≤ Grade 2, reduce all agents one dose level for all subsequent cycles."
| 32.     | Section 5.5.6 | Corrected spelling of "acneiform" throughout Dermatology Management section, including Table 1-1. |
| 33.     | Section 7    | Inserted Albumin row in the Study Parameters table, with Xs indicating assessment to be performed pre-study and every 4 weeks. |
| 34.     | Section 8.1.7 | Updated section to reflect separate Irinotecan dose specifics for Arms A and B and Arm C. Inserted title “Arms A (IC) and B (ICR)” to subsection 8.1.7.1. Inserted entire subsection 8.1.7.2 with dose specifics for Arm C (mICR). |
| 35.     | Section 8.2.5 | Updated section to reflect separate Cetuximab dose specifics for Arm B and Arm C. Inserted title “Arms A (IC) and B (ICR)” to subsection 8.2.5.1. Inserted entire subsection 8.2.5.2 with dose specifics for Arm C (mICR). |
| 36.     | Section 8.3.5 | Updated section to reflect separate IMC-1121B dose specifics for Arm B and Arm C. Inserted title “Arm B (ICR)” to subsection 8.3.5.1. Inserted entire subsection 8.3.5.2 with dose specifics for Arm C (mICR). |
| 37.     | Section 9.1  | Inserted “Revised Statistical Design - Arms A (IC) and C (mICR)” section. |
| 39.     | Section 9.3  | Inserted “Study Monitoring” section. |
| 40.     | Section 9.4  | Updated Gender and Ethnicity table to reflect new revised statistical design and updated section number to 9.4. |
| 41.     | Appendix I   | Removed Informed Consent Document from protocol. The Informed Consent is now provided as a separate document in order to comply with new NCI requirements. |
Addendum #5 includes the following changes to the Informed Consent:

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Page 1</strong></td>
<td>Updated Version date. The Informed Consent Document has been reformatted and provided as a separate document to comply with new NCI formatting requirements. The pagination has been updated for the entire Informed Consent Document.</td>
</tr>
<tr>
<td>2. <strong>“Why is this study being done?”</strong></td>
<td>Inserted “in this setting” at the end of the first sentence.</td>
</tr>
<tr>
<td>3. <strong>“Why is this study being done?”</strong></td>
<td>Updated “Irinotecan and cetuximab are standard treatments for patients who have metastatic colon or rectal cancer, who have already received one previous chemotherapy that is no longer working, and do not have a specific type of mutated (altered) gene in their tumor” to “Irinotecan and cetuximab are standard treatments for patients who have metastatic colon or rectal cancer, who have already received one previous chemotherapy that is no longer working, and do not have a specific type of mutation (alteration) of the K-ras gene in their tumor.”</td>
</tr>
<tr>
<td>4. <strong>“Why is this study being done?”</strong></td>
<td>Inserted “Because there were more side effects at higher doses of the ramucirumab regimen, a new arm (Arm C) was added to replace Arm B. Arm C was revised to include lower starting doses of all three drugs (irinotecan, cetuximab and ramucirumab) reflecting the tolerated doses previously, and also greater dose reductions for toxicity.”</td>
</tr>
<tr>
<td>5. <strong>“How many people will take part in the study?”</strong></td>
<td>Updated from “About 147 patients in the United States and Canada will take part in this study” to “About 135 patients in the United States and Canada will take part in this study (including those previously enrolled in the study with Arm B).”</td>
</tr>
<tr>
<td>6. <strong>“Before you begin the study?”</strong></td>
<td>Updated “evaluate your health status” to “evaluate your tumor status.”</td>
</tr>
<tr>
<td>7. <strong>“What will happen if I take part in this research study?”</strong></td>
<td>Inserted “(Arm A or Arm C)” in the first sentence.</td>
</tr>
<tr>
<td>8. <strong>“What will happen if I take part in this research study?”</strong></td>
<td>In the Arm A subsection, updated “The first time you receive cetuximab it will be over 120 minutes to minimize and possible allergic reactions to the drug” to “The first time you receive cetuximab it will be over 120 minutes to minimize any possible allergic reactions to the drug.”</td>
</tr>
<tr>
<td>9. <strong>“What will happen if I take part in this research study?”</strong></td>
<td>Inserted entire Arm C subsection.</td>
</tr>
<tr>
<td>10. <strong>“What will happen if I take part in this research study?”</strong></td>
<td>Removed Arm B treatment information and inserted “(Removed in Addendum # 5.)”</td>
</tr>
<tr>
<td>11. <strong>Study Chart</strong></td>
<td>“Arm A” box: Updated “Irinotecan &amp; Cetuximab by vein every 14 days” to “Cetuximab &amp; Irinotecan by vein every 14 days” to reflect the order in which drugs are administered.</td>
</tr>
<tr>
<td>12. <strong>Study Chart</strong></td>
<td>“Arm C” box: Replaced “Arm B” with “Arm C.” Updated “Irinotecan, Cetuximab &amp; Ramucirumab by vein every 14 days” to “Ramucirumab, Cetuximab &amp; Irinotecan by vein every 14 days.”</td>
</tr>
<tr>
<td>13. <strong>“What side effects or risks can I expect from being in the study?”</strong></td>
<td>In the list of Uncommon Side Effects for Ramucirumab, inserted in “(causing intestinal perforation – a hole in the wall)” the fourth bullet point.</td>
</tr>
<tr>
<td>14.</td>
<td>&quot;What side effects or risks can I expect from being in the study?&quot;</td>
</tr>
<tr>
<td>15.</td>
<td>&quot;What side effects or risks can I expect from being in the study?&quot;</td>
</tr>
<tr>
<td>16.</td>
<td>&quot;What other choices do I have if I do not take part in this study?&quot;</td>
</tr>
<tr>
<td>17.</td>
<td>&quot;What other choices do I have if I do not take part in this study?&quot;</td>
</tr>
<tr>
<td>18.</td>
<td>&quot;What other choices do I have if I do not take part in this study?&quot;</td>
</tr>
<tr>
<td>19.</td>
<td>&quot;Will my medical information be kept private?&quot;</td>
</tr>
<tr>
<td>20.</td>
<td>&quot;What are the costs of taking part in this study?&quot;</td>
</tr>
<tr>
<td>22.</td>
<td>&quot;About using specimens for research&quot;</td>
</tr>
</tbody>
</table>
Addendum #6 includes the following changes to the Protocol:

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>42. Title Page</td>
<td>Replaced ECOG logo with ECOG-ACRIN logo.</td>
</tr>
<tr>
<td>43. Title Page</td>
<td>Updated version date.</td>
</tr>
<tr>
<td>44. Title Page</td>
<td>Updated “Study Participants” section to indicate ALLIANCE, NRG, and SWOG as participating groups. E7208 is open to US sites only.</td>
</tr>
<tr>
<td>45. Global change throughout protocol</td>
<td>Changed references to “ECOG” to “ECOG-ACRIN,” references to “ECOG Coordinating Center” to “ECOG-ACRIN Operations Office - Boston,” and references to “ECOG PCO-RL” to “ECOG-ACRIN PCORL.” Page headers updated from “Eastern Cooperative Oncology Group” to “ECOG-ACRIN Cancer Research Group.” Removed “ECOG” from all form references for administrative simplicity.</td>
</tr>
<tr>
<td>46. Section 1.6</td>
<td>Updated entire section to reflect 17 patients treated on Arm A and 16 patients treated on Arm B out of 35 total registrations.</td>
</tr>
<tr>
<td>47. Section 4</td>
<td>Removed CTSU Help Desk hours due to varying schedule. Please refer to the CTSU website for the latest hours.</td>
</tr>
<tr>
<td>48. Section 5.2</td>
<td>Updated entire section to reflect the new CTEP-AERS system.</td>
</tr>
<tr>
<td>49. Section 5.2.9</td>
<td>Replaced “NOTE” with “E7208 specific expedited reporting requirements: GI Events:” for greater clarity. The content of the reporting requirement note has not changed.</td>
</tr>
<tr>
<td>50. Section 9</td>
<td>Updated AdEERS references to CTEP-AERS throughout Section 9.</td>
</tr>
<tr>
<td>51. Section 9.1</td>
<td>In the second paragraph, updated “No toxic deaths were observed in Arm A prior to suspension among 18 treated patients” to “No toxic deaths were observed in Arm A prior to suspension among 17 treated patients.”</td>
</tr>
<tr>
<td>52. Section 9.1</td>
<td>In the third paragraph, inserted the following information: In addition to the above safety monitoring plan, the study will suspend upon the report of any colonic perforation event, regardless of treatment attribution or grade. A detailed review of the circumstances surrounding the event will be conducted and, in the case of the event occurring on Arm C, the feasibility of the revised regimen will be evaluated by the study team and toxicity monitor. The colonic perforation rate on Arm B (ICR) prior to study suspension was 2/16 patients or 12.5%. With 16 patients on Arm C (mICR) evaluated under the new regimen the probability of observing 1 or more colonic perforations is 81.5% if the true rate is 10% and 88.2% under a rate of 12.5%. No toxic deaths were observed in Arm A prior to suspension among 17 treated patients.</td>
</tr>
<tr>
<td>53. Section 9.1</td>
<td>Replaced “AdEERS” with “CTEP-AERS” in the Additional Safety Monitoring section.</td>
</tr>
</tbody>
</table>
Addendum #6 includes the following changes to the Informed Consent:

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>23.</td>
<td>Page 1</td>
</tr>
</tbody>
</table>
| 25.     | Page 1 | In the second paragraph under “Why is this study being done,” inserted the following two sentences:  
“In the first 17 patients enrolled on Arm B, there were two deaths due to gastrointestinal perforation (a hole in the intestinal wall).”  
“In addition, some patients at greater risk for developing perforations will no longer be allowed to participate in the study.” |

Enclosure
Eastern Cooperative Oncology Group

A Randomized Phase II Study of Irinotecan and Cetuximab with or without the Anti-Angiogenic Antibody, Ramucirumab (IMC-1121B), in Advanced, K-ras Wild-type Colorectal Cancer Following Progression on Bevacizumab-Containing Chemotherapy

STUDY CHAIR: Howard S. Hochster, MD
STUDY CO-CHAIR: Deirdre Cohen, MD
Peter O’Dwyer, MD
STUDY STATISTICIAN: Paul Catalano, Sc D
GI COMMITTEE CHAIR: Al B. Benson III, MD
SWOG CO-CHAIR: Howard S. Hochster, MD

Version Date: December 17, 2013

Irinotecan (NSC #616348) Commercially available for this study
Cetuximab (NSC #714692) Commercially available for this study
Ramucirumab (NSC #749128) (IND 109448) Supplied by ImClone Systems for this study

STUDY PARTICIPANTS
ECOG-US Sites Only
SWOG-US Sites Only
Cancer Trials Support Unit (CTSU)*

*NOTE: This study is supported by the NCI Cancer Trials Support Unit (CTSU). Institutions not aligned with ECOG will participate through the CTSU mechanism as outlined in the protocol.

ACTIVATION DATE
October 8, 2010
Addendum #1 – Prior to Activation
Addendum #2 – Prior to Activation
Addendum #3 – 12/11
Addendum #4 – 7/12
Addendum #5 – 6/14
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STUDY CHAIR
Howard S. Hochster, MD
Yale Cancer Center
333 Cedar Street, Box 208028
New Haven, CT 06520
Telephone: 203-785-2360 (work hours)
203-200-4422 (evenings and weekends)
Email: howard.hochster@yale.edu

STUDY CO-CHAIR
Peter O’Dwyer, MD
University of Pennsylvania Cancer Center
1223 Penn Tower
3400 Spruce Street
Philadelphia, PA 19104
Phone: (215) 662-7268
Fax: (215) 243-3268
Email: peter.odwyer@uphs.upenn.edu
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

<table>
<thead>
<tr>
<th>To submit site registration documents:</th>
<th>For patient enrolments:</th>
<th>Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTSU Regulatory Office</td>
<td>Please refer to the patient enrollment section for instructions on using the OPEN system.</td>
<td>ECOG Coordinating Center, FSTRF, 900 Commonwealth Avenue Boston, MA 02215 (ATTN: DATA). Phone # 617-632-3610 Fax # 617-632-2990 Data should be sent via postal mail (preferred), however fax is accepted. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.</td>
</tr>
<tr>
<td>1818 Market Street, Suite 1100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Philadelphia, PA 19103</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phone – 1-866-651-CTSU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fax – 215-569-0206</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The study protocol and all related forms and documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol.

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

For patient eligibility or treatment-related questions Contact the Study PI of the Coordinating Group.

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

For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members’ website https://www.ctsu.org

The CTSU Web site is located at https://www.ctsu.org
Eligibility: metastatic or advanced CRC, K-ras wild-type, first line therapy with oxaliplatin-containing Chemotherapy and bevacizumab, now progressing.

Stratify:
1) PS (0 vs. 1)
2) Discontinuation of Oxaliplatin first-line therapy prior to progression (yes vs. No)
3) Progression \( \leq \) 6 months of last treatment vs. > 6 months

Primary endpoint: PFS; 90% power to detect difference between 4.5 months for control vs. 7.65 months for experimental arm \((\alpha = 0.10, \beta = 0.10)\)

* Treatment should not be started until at least 28 days after last bevacizumab dose.

** Arm B closed to accrual in Addendum #5. New patients are randomized to Arm A or Arm C.

Accrual Goal = 135
1. Introduction

1.1 Colon Cancer

1.1.1 Background

Colorectal cancer (CRC) is a significant cause of cancer mortality. The worldwide incidence of CRC in 2000 was estimated as 944,700 cases (males: 498,000; females: 446,000 cases) (1). In the United States (US) colorectal cancer accounts for approximately 11% of all cancer deaths (2). At diagnosis, 40% of the world’s CRC population have metastatic or “synchronous metastases.” In the US, approximately 20% of newly diagnosed patients with CRC will have synchronous metastatic cancer (3). Approximately 25% of patients with localized disease at diagnosis will ultimately develop metastatic disease. Unfortunately only a small number of patients with stage IV cancer can be cured with multimodality therapy. The majority of patients with metastatic, stage IV CRC will ultimately die of their disease (4).

Newly developed, and now standard, therapies for patients with stage IV CRC have dramatically improved survival and enhanced quality of life. Thus, in the U.S., initial therapy with combinations of 5-fluorouracil (5FU) and oxaliplatin (FOLFOX) or 5FU and irinotecan (FOLFIRI) have increased response rates to approximately 45 percent (5). The addition of bevacizumab to either FOLFOX or FOLFIRI has produced response rates of 60%. Indeed, for approximately eight percent of patients with stage IV CRC, the addition of surgery to successful chemotherapy will produce a cure (6). Upon progression after so-called “first-line therapy,” approximately 20% of patients will respond to a second systemic treatment combination. Most important, median survival for patients with stage IV CRC is now approaching 2.5 years (7). It is likely that with a better understanding of how to incorporate intratumoral molecular parameters such as mutations in the k-ras gene and/or quantitation of a tumor’s repair genes such ERCC-1 or XRCC-1 and/or targets such as thymidylate synthase into treatment strategies, complete responses and cure rates will continue to improve.

1.1.2 First Line therapy

A series of clinical trials in the first line therapy of metastatic CRC have improved survival from a median of 12 months to nearly 24 months. A series of trial showed that combination therapy using oxaliplatin (FOLFOX4) or irinotecan (IFL or FOLFIRI) gave improved RR, OS and PFS compared with FU and LV bolus or infusion therapy. This was confirmed in the N971 US Intergroup trial showing improved RR, OS and PFS for FOLFOX compared with the control arm of IFL (5). Shortly thereafter a randomized trial of IFL with or without bevacizumab showed and improved HR for PFS and OS for the addition of the anti-VEGF antibody. This has been adopted into standard practice with all 5FU based first line therapies, including FOLFIRI or FOLFOX. A more recent study (NO16966) demonstrated
improved PFS with the addition of bevacizumab to either FOLFOX or CapeOX therapy, though of a smaller benefit due to early stopping of chemotherapy (7). As FOLFOX has become the standard first-line chemotherapy platform, particularly in the US, second line therapy has relied on irinotecan based programs.

1.1.3 Second Line Therapy

A study performed by the GERCOR demonstrated that the sequence FOLFOX followed by FOLFIRI was equivalent to the reverse sequence (8). As a result, US practice has evolved to use irinotecan based regimens as second-line therapy. Either FOLFIRI or irinotecan seem equally useful in this situation and either may be used as there is no study showing a synergistic effect of fluoropyrimidines with irinotecan. In the GERCOR multi-center study, patients with advanced CRC were treated with FOLFOX followed by FOLFIRI at the time of progression or the reverse sequence. In the FOLFOX first arm, the response rate for second line FOLFIRI was 4% and PFS was 2.5 months. A larger second line study was performed to examine the role of the anti-EGF antibody, cetuximab as second line therapy on patients progressing on FOLFOX. In this 1300 patient study, the subjects were randomized to irinotecan alone or irinotecan plus cetuximab (9). The patient populations were not selected for Kras status. Again the response rate for second line irinotecan was 4.2% and PFS was 2.6 months (n = 650).

Recent reports of the predictive value of K-ras gene mutation (36,37) have demonstrated convincingly that patients with mutations in codon 12 and 13 (as determined by RT-PCR from FFPET) do not benefit from the use of anti-EGFR antibodies, either as single agent or in combination with chemotherapy programs (10). As such, two treatment tracks exist for second-line therapy, based on cetuximab use in the K-ras wild-type group and irinotecan based therapy alone in those with Kras mutations. In this study, the patient population will be limited to those with Kras wild-type status, as both arms will receive cetuximab and irinotecan.

1.1.4 Biweekly Dosing of Cetuximab

Cetuximab is approved for previously treated colon cancer with non-mutated K-ras ("wild type"). The standard dose and schedule is 400 mg/m^2 loading dose x 1, then weekly 250 mg/m^2. Because of the long half-life of therapeutic monoclonal antibodies, such as cetuximab, many such agents have alternate dosing schedules of q2 weeks or even q3 weeks. In this study we have chosen the dose of 500 mg/m^2 every two weeks, for the reasons detailed below, and also to facilitate co-administration with the irinotecan (180 mg/m^2) biweekly schedule.

Data supporting the biweekly dose of cetuximab 500 mg/m^2 have been presented and published. Taberner, et al (Taberner, Cervantes, Martinelli, et. Al, J Clin Oncol, 24 (18 Suppl), 142s) performed a phase I/PK study demonstrating equivalent pharmacokinetic parameters for the drug on the q2w schedule. 10 patients treated on the standard dose/schedule were used in
comparison. No significant differences were seen with respect to AUC, half-life, or steady-state clearance between the two schedules (Table 1). In addition, the Phase I portion of the study escalated cetuximab dose to achieve a gr 2-3 skin rash, reaching doses of 700 mg/m² q2w safely. The study was continuing at the time of presentation.

Table 1

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Cmin (µg/mL)</th>
<th>AUC (µg/mL*h)</th>
<th>t½ (h)</th>
<th>CLss (L/h/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400/250 mg/m² q1w</td>
<td>47.0 (37.3)</td>
<td>17278 (5205)</td>
<td>110 (24)</td>
<td>0.016 (0.004)</td>
</tr>
<tr>
<td>400 mg/m² q2w</td>
<td>25.6 (11.8)</td>
<td>27655 (6965)</td>
<td>124 (25)</td>
<td>0.015 (0.004)</td>
</tr>
<tr>
<td>500 mg/m² q2w</td>
<td>35.2 (13.8)</td>
<td>34953 (6275)</td>
<td>134 (33)</td>
<td>0.015 (0.003)</td>
</tr>
</tbody>
</table>

Mean (SD)

This combination of irinotecan 180 mg/m² and cetuximab 500 mg/m² q2w has also been reported in a Spanish phase II study (Martin-Martorell, et.al. Br J Ca 99: 455-458, 2008). Forty patients were treated and a response rate of 23% was reported (compared with 20% in the EPIC trial, N =1147), with a Disease Control Rate of 60%. Median time to progression was 3.4 months and overall survival was 8 months. This also is approximately equivalent to the cetuximab arm of the EPIC trial. Toxicity of grade 3-4 severity was reported as diarrhea = 10%, neutropenia = 7.5% and skin toxicity = 7.5%, which are all somewhat lower than similarly reported toxicity rates in the EPIC trial. In short, this phase II study suggests the activity and toxicity is not substantially different using irinotecan and cetuximab q2w compared with irinotecan every 3 weeks with weekly cetuximab. This biweekly schedule has been widely adopted in practice by US oncologists.

1.2 Vascular Endothelial Growth Factor and Angiogenesis

Angiogenesis, the formation of new capillaries and blood vessels, is a tightly-controlled, multistep process that is a component of normal physiology (including development of the embryonic vasculature, wound healing, ovulation, and menstruation). Pathologic angiogenesis contributes to tumor growth and metastasis, as well as other human diseases such as diabetic retinopathy, rheumatoid arthritis, and psoriasis (11-13). A number of growth factors have been identified as positive regulators of angiogenesis, including members of the vascular endothelial growth factor (VEGF) family, basic fibroblast growth factor, transforming growth factor alpha, transforming growth factor beta, tumor necrosis factor, platelet-derived endothelial growth factor, hepatocyte growth factor, angiogenin, interleukin-8, and placental growth factor (14,15). VEGF-A is one of several related cytokines; it is distinct in that it acts as an endothelial cell-specific mitogen and is the growth factor most consistently found in conditions associated with angiogenesis (16-19). The biological activity of VEGF-A (hereafter VEGF) is principally mediated by two structurally-related, high affinity tyrosine kinase receptors: the 180 kDa fms-like tyrosine kinase (VEGFR-1 or Flt-1) (20,21); and the 200 kDa receptor (VEGFR-2 or kinase insert domain-containing receptor [KDR]), or its murine homologue, fetal liver kinase-1 (Flk-1)(20,21). Targeted deletion of genes encoding VEGF, VEGFR-1, or VEGFR-2 in mice is lethal to the
embryo, demonstrating the physiological importance of the VEGF pathway in blood vessel formation. Mice lacking even a single VEGF allele die prior to birth due to vascular abnormalities (24,25). VEGFR-2-deficient mice have impaired blood island formation and lack mature endothelial cells (26), whereas VEGFR-1 null embryos have abundant endothelial cell-like cells, but fail to develop normal vasculature (27).

1.3 The Role of VEGF and VEGFR-2 in Angiogenesis and Tumor Growth

The importance of VEGF and VEGFR-2 in angiogenesis and tumor growth has been demonstrated in several animal models. VEGFR-2 expression is associated with activated endothelium and is strongly upregulated in tumor endothelium (16,28). Inhibiting the function of the VEGF/VEGFR-2 pathway via a number of approaches, including anti-VEGF antibodies, anti-VEGFR-2 antibodies, anti-VEGF antisense ribonucleic acid expression, VEGF-based immunotoxins, soluble VEGF receptors, ribozymes to VEGF receptors, and small molecule VEGFR-2 tyrosine kinase inhibitors, has been shown to inhibit new blood vessel formation and tumor growth in a variety of animal models (29-32).

VEGF and VEGFR-2 are overexpressed in the great majority of human cancers, including carcinomas of the gastrointestinal tract, pancreas, breast, cervix, bladder, ovary, uterus, endometrium, and kidney; Kaposi's sarcoma; glioblastoma multiforme; and hemangioblastomas. In addition, messenger ribonucleic acid for both VEGFR-1 and VEGFR-2 is greatly upregulated in tumor-associated endothelial cells, but not in the vasculature of the surrounding normal tissue. A correlation between VEGFR-2 expression and tumor microvessel density has been associated with poor prognosis, advanced disease, increased risk of metastasis and recurrence, and lower relapse-free survival in patients with a variety of cancers (13,32).

Accumulating evidence suggests that the dual autocrine/paracrine mechanism also may play an important role in the growth and metastasis of certain solid tumors. For example, a VEGF/VEGFR autocrine loop was proposed as a mediator of growth and metastasis of several types of tumors, including carcinomas of prostate, ovary, pancreas, and breast; malignant pleural mesothelioma; and melanoma (32). These observations suggest that anti-VEGFR-2 antibodies may have potential as antiangiogenic and antitumor agents.

1.4 IMC-1121B (Ramucirumab)

Ramucirumab is a recombinant human monoclonal antibody (MAb) of the immunoglobulin G, subclass 1 (IgG1) that specifically binds to the extracellular domain of VEGFR-2 with high affinity. This antibody potently blocks the binding of the VEGF ligand to VEGFR-2, inhibits VEGF-stimulated activation of both VEGFR-2 and p44/p42 MAP kinases, and neutralizes VEGF-induced mitogenesis of human endothelial cells.

Ramucirumab has been shown to block the interaction of VEGF and VEGFR-2 (with a concentration that inhibits binding by 50% of approximately 1 nM), and to inhibit VEGF-stimulated proliferation of endothelial cells and VEGF induced migration of human leukemia cells (33,34).

Preclinical pharmacodynamic data demonstrate that Ramucirumab binds specifically and with high affinity to the VEGFR-2, and is capable of inhibiting certain in vitro biological processes. These include VEGF/VEGFR-2 interaction,
VEGF-stimulated VEGFR-2 activation, proliferation of human endothelial cells, VEGF-induced migration of human leukemia cells, and VEGF-induced phosphorylation of VEGF-2 in both human umbilical vein endothelial cells and porcine aortic endothelial cells engineered to overexpress VEGFR-2 (34). These processes are likely involved in tumor angiogenesis. Potent angiogenic and antitumor effects are observed when DC101, an antibody to murine VEGFR-2, is administered to mice bearing syngeneic tumors or human tumor xenografts. The results of these preclinical pharmacodynamic studies support the investigation of Ramucirumab in the treatment of solid tumors.

Two repeat-dose toxicology studies (5 weeks and 39 weeks) were conducted in cynomolgus monkeys. In the 5-week repeat-dose study, Ramucirumab was administered intravenously at doses of 0, 4, 12, or 40 mg/kg. There were no Ramucirumab-related effects seen in clinical signs, body weights, food consumption, urinalysis, blood pressure, hematology, coagulation, and serum chemistry. There were also no Ramucirumab-related effects found at gross pathology evaluation. Histopathology evaluation revealed focal muscle fiber degeneration and mononuclear cell infiltration in skeletal muscle (quadriceps femoris) in test article-treated animals only. These effects were concluded to be not treatment-related due to the focal nature of the lesions and the low incidence in females. The Ramucirumab injection sites had mild reactions consisting of mononuclear cells or mononuclear and polymorphonuclear cells in perivascular areas. Based on the results of this study, intravenous administration of Ramucirumab was well tolerated at dose levels from 4 to 40 mg/kg for four doses and the no-observable-effect level (NOEL) in this study was ≥ 40 mg/kg, the highest dose administered.

In the 39-week repeat-dose study, Ramucirumab was administered via intravenous infusion at dose levels of 5, 16, and 50 mg/kg to cynomolgus monkeys for 11 weekly doses over 12 weeks (females only) or weekly for 39 weeks (males and females) of study. There were no Ramucirumab-related effects noted in animals treated at up to 50 mg/kg for 12 weeks of study. Thickening and osteochondropathy of the epiphyseal growth plate was noted at 5 mg/kg and above in animals treated for 39 weeks. This was an anticipated mechanism-related effect. Treatment with Ramucirumab resulted in renal toxicity at the 16- and 50-mg/kg dose levels after 39 weeks. In addition, clinical chemistry and urinalysis parameters indicated that the renal toxicity had manifested at 16 mg/kg and 50 mg/kg after 26 weeks. A NOEL of Ramucirumab could not be established when administered intravenously once a week for 39 weeks in male or female cynomolgus monkeys.

1.4.1 Clinical Studies

Two Phase 1 studies are being conducted to evaluate the safety and antitumor effects of Ramucirumab administered either weekly (CP12-0401) or every other week or every third week (CP12-0402) at doses ranging from 2 mg/kg through 20 mg/kg in patients with advanced cancer. Two mechanism-based, dose-limiting toxicities were observed at the weekly schedule of 16 mg/kg, symptomatic hypertension and deep vein thrombosis, both of which occurred after several cycles of Ramucirumab infusion. Thus, the maximum tolerated dose for the weekly study was determined as 13 mg/kg.
administered on a weekly schedule. The MTD has not been reached for the every other week or the every third week schedules.

A total of 37 patients have been enrolled in study CP12-0401 (Ramucirumab administered weekly) at doses of 2 to 16 mg/kg; this patient population includes 23 males and 14 females, ranging in age from 36 to 76 years. Adverse events ≥ grade 3 considered to be at least possibly-related to Ramucirumab were reported in 10 patients and include hypertension, deep vein thrombosis, headache, vomiting, anemia, increased amylase, hyperphosphatemia, and proteinuria. To date, four confirmed partial responses (in melanoma, gastric and neuroendocrine tumors, and uterine leiomyosarcoma) have been reported, and at least nine patients have experienced prolonged stable disease (> 6 months). At least one of these patients had been treated previously with the anti-VEGF agent bevacizumab. Importantly, other evidence of clinical benefit has also been noted. In particular, several patients (melanoma [1 patient], gastric cancer [1 patient], and thyroid cancer [2 patients]) experienced significant pain relief along with reductions in analgesic requirements, and a patient with refractory pleural effusions experienced significant reductions in fluid retention and a lower frequency of thoracenteses.

A total of 25 patients have been enrolled in study CP12-0402 (Ramucirumab administered every other week or every 3 weeks), of whom 24 have received treatment at doses ranging from 6 mg/kg to 20 mg/kg. The MTD has not been reached for the every-other-week or the every-third-week schedules; the study is ongoing but currently closed to enrollment.

A total of 13 of 24 (54.2%) patients to date have experienced events that were considered possibly, probably, or definitely related (related) to treatment with Ramucirumab. The most common (> 10%) treatment-related events were proteinuria (16.7%), diarrhea (12.5%), and hypertension (12.5%). Adverse events ≥ Grade 3 considered to be at least possibly related to Ramucirumab were reported in three patients and include duodenal ulcer hemorrhage (Grade 4), hypertension, and fatigue.

As of 1 September 2008, 19 patients were evaluable for response; of these patients, 12 have experienced a best overall response of stable disease, including five with SD ≥ 6 months. These five patients had cancers of the colon (2 patients), liver (2 patients), and kidney (1 patient). Three of these patients have had ongoing SD for > 10 months duration. Six patients remain on study (two patients in the 10-mg/kg every other week cohort, two patients in the 15-mg/kg every three week cohort, and two patients in the 20-mg/kg every three week cohort).

As of January 18, 2010, at least 454 patients had received at least one dose of IMC-1121B on ImClone sponsored phase 1-2 studies and at least 83 patients had received at least one dose of blinded IMC-1121B/placebo on ImClone sponsored randomized phase III studies. Data safety monitoring committee reviews have been performed regularly on phase 2 studies in melanoma (involving combination with
dacarbazine), prostate cancer (involving combination with mitoxantrone/prednisone), ovarian cancer (monotherapy), colorectal cancer (involving combination with mFOLFOX-6) and breast cancer (involving combination with docetaxel).

Some of the published data include:

a) The Phase 1 Monotherapy Study (Spratlin et al. J Clin Oncol 2010; 28: e-published 4 Jan 2010). 37 patients treated with advanced, refractory solid tumors. Ramucirumab was given weekly as monotherapy. Reported results included PR in 4/27 (15%) patients with measurable disease and PR or SD ≥ 6 months in 11/37 (30%) of patients.

b) Initial Phase 2 Presentation for metastatic, TKI-refractory Renal Cancer (Garcia et al. ESMO/ECCO Berlin 2009. 40 patients were given ramucirumab 8mg/kg q 2 wk. Of these, 50% had prior sunitinib, 35% prior sunitinib and sorafenib and15% prior sorafenib. The preliminary median PFS is 6 months and 3/40 (7%) had confirmed PR. The drug was well-tolerated.

Additional phase II studies are underway in RCC, HCC, melanoma, prostate cancer, NSCLC, ovarian cancer, GBM, colorectal, breast and bladder cancer. Phase 3 studies are underway in breast cancer, with others planned in HCC, colorectal cancer. Further phase 2 results will be presented at GU ASCO (RCC update), ASCO (melanoma, HCC, NSCLC) in 2010.

Additional toxicities (observed in preliminary phase 2 studies) and potential toxicities (based on the known toxicity profiles of agents which inhibit the VEGF or VEGF-receptor pathway) are presented in the most recent Investigator Brochure. No additional safety patterns have been demonstrated conclusively beyond those observed, discussed and reported in the most recent Investigator Brochure.

1.4.2 Dose Rationale

Nonclinical data obtained from a murine BxPC-3 xenograft model have demonstrated that the efficacy of DC101, a murine analogue to Ramucirumab, was evident in vivo at trough concentrations of 20 µg/mL. The target serum concentration for Ramucirumab is hypothesized to be one that maintains Ramucirumab at trough plasma concentrations ≥ 20 µg/mL. Preliminary pharmacokinetic (PK) data from studies CP12-0401 and CP12-0402 indicate that the minimum 20 µg/mL target trough concentrations are attainable. In the every-other-week protocol, following the initial dose of 6 mg/kg, mean serum trough concentrations (immediately prior to the next dose) of Ramucirumab were 31 µg/mL (range: 18–64 µg/mL [n=7]). Analysis of the initial 8-mg/kg dose at the same time point yielded a mean serum trough concentration of 115 µg/mL (range: 18 - 205 µg/mL [n=3]). To provide a suitable margin above the 20 µg/mL Ramucirumab target concentration, the proposed dose and regimen for this Phase 3 study will be 8 mg/kg Ramucirumab given every other week. At this dose and regimen, the half-life following the initial infusion of IMC-Ramucirumab is approximately 155 hours; following
later infusions during the first cycle, the half-life is approximately 300 hours, suggesting that steady state is being approached. Supporting this observation is the finding that as the dose of IMC-Ramucirumab was increased from 6 to 13 mg/kg, clearance decreased from 0.237 mL/hr/kg to a plateau of 0.06 mL/hr/kg (clearance at 8 mg/kg was approximately 0.113 mL/hr/kg).

1.5 Summary and Study Rationale

First line therapy of CRC at this time generally includes bevacizumab plus combination chemotherapy, which most commonly in the US includes oxaliplatin, leucovorin and 5FU (a modified FOLFOX regimen). Whether continuing anti-angiogenic therapy after first line therapy is beneficial remains an open question. Studies to date have shown benefit for addition of bevacizumab in first line therapy and in second line therapy in bevacizumab-naïve patients. In the case of patients with Kras wild-type cancers, standard second line therapy would generally include irinotecan with cetuximab, based on the EPIC trial which demonstrated a doubling in PFS (9). We have chosen this regimen as the control arm for this study, which will compare addition of the anti-VEGFR antibody, Ramucirumab. The goal of this study is to show improved PFS with the addition of a novel second line anti-angiogenic antibody.
1.6 Summary of Toxicity Review

The study was closed to accrual on June 14, 2012 after 35 patients were accrued as per pre-planned toxicity review. 18 patients were accrued to Arm A (IC) and 17 to Arm B (ICR). AdEERS Reporting was reviewed and real time data were obtained on all treated patients. It was clear that more toxicity was seen in Arm B. Worst toxicity per patient is seen in the figure below. The overall grade 3-5 toxicity rates were 17% for Arm A and 75% for Arm B. There were 2 toxic deaths in Arm B. Toxicities of higher incidence in Arm B included neutropenia, mucositis, diarrhea and GI perforation (including peri-anal abscess). In addition mean dose given in Arm B (mean % RDI) was considerably lower in Arm B: 65% for irinotecan, 85% for cetuximab and 92% for ramucirumab (even though no dose reductions were allowed in the protocol). This compares to 99% irinotecan and 98% cetuximab average %RDI in Arm A. Furthermore, only 3/18 patients in Arm A required dose reduction, compared to 15/17 in Arm B. On the other hand with a median of 8 cycles preliminary analysis showed that fewer patients in Arm B went off treatment for progression compared with Arm A, and more remained on treatment at the time of the analysis. Of the 18 in Arm A, 8 out of 9 patients off study had progression (PD), while in Arm B, of the 16 treated, only 1 out of 5 who went off study, went off for PD. These findings suggest potential benefit for the addition of ramucirumab among patients who can tolerate therapy. Therefore, we propose a reduced dose regimen in Arm C (modified ICR) with irinotecan 150 mg/m², cetuximab 400 mg/m² and ramucirumab 6 mg/m² as starting doses, more strict eligibility criteria, and more aggressive dose modifications for toxicity. Because those patients on protocol who did tolerate the ICR regimen at the reduced doses seemed to stay on study longer, we believe the study should be continued as modified at those lower doses. The Arm C starting doses are equal to the actual “percent recommended dose intensity” received by patients in Arm B.

![Worst Toxicity Per Patient](image-url)
2. Objectives

2.1 Progression Free Survival
To evaluate the Progression Free Survival (PFS) for the addition of the anti-angiogenic antibody, Ramucirumab, in combination with irinotecan and cetuximab as second line therapy for patients with K-ras wild-type colorectal cancer, as compared to the patients without the antibody.

2.2 Response Rate
To evaluate the Response Rate for irinotecan, cetuximab and Ramucirumab in this patient population.

2.3 Toxicity Rates
To evaluate the Grade 3-4 toxicity rates for the combination in this patient population.

2.4 Overall Survival
To evaluate Overall Survival for irinotecan, cetuximab, and ramucirumab in this patient population.
3. **Selection of Patients**

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient’s eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient’s chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG Patient No. _____________________________

Patient’s Initials (L, F, M) _____________________________

Physician Signature and Date _____________________________

**NOTE:** All questions regarding eligibility should be directed to the study chair or study chair liaison.

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

3.1 **Eligibility Criteria**

_____ **3.1.1** Age ≥ 18 years.

_____ **3.1.2** Women must not be pregnant or breast-feeding due to potential danger to the fetus, by therapy including Ramucirumab. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy.

Female of child bearing potential? (Yes or No) ______

If yes: Date of blood test or urine study: _______________

If no, reason: Post menopausal, date of LMP ______

Status post TAH: Date of surgery ______

Status post tubal ligation: Date of surgery ______

_____ **3.1.3** Women of childbearing potential and sexually active males must use an accepted and effective method of contraception or agree to abstain from sexual intercourse during their participation in the study and for 3 months following completion of their participation.

_____ **3.1.4** Patients must have measurable disease as defined in Section 6.1.2.

_____ **3.1.5** Histologically documented adenocarcinoma (including the histologic variants of adenocarcinoma) of the colon or rectum.

_____ **3.1.6** Patients K-ras status must be wild type (not mutated). K-ras status determination may be based on either primary or metastatic tumor.

**NOTE:** The assay must be performed by a Clinical Laboratory Improvement Amendments (CLIA) approved laboratory.

_____ **3.1.7** Patients must have had prior first-line therapy with oxaliplatin-based fluoropyrimidine-containing chemotherapy and bevacizumab for metastatic colorectal cancer.
3.1.8 Registration within 42 days of evidence of disease progression.

3.1.8.1 Current date ______________

3.1.8.2 Date of progression ________________

3.1.8.3 Date of last chemotherapy ______________

3.1.8.4 Date of last bevacizumab ______________

3.1.9 [Deleted in Addendum #3]

3.1.10 Was oxaliplatin discontinued before date of progression?

3.1.10.1 Yes _____________ No ______________

3.1.11 Performance Status 0-1.

3.1.11.1 PS 0 _________ 1 __________

3.1.12 Adequate Organ Function ≤ 4 weeks prior to registration.

3.1.12.1 Hematologic: Absolute neutrophil count (ANC) ≥ 1500/µL, hemoglobin ≥ 9 g/dL, and platelets ≥ 75,000/µL.

ANC: ______ Date: _______

Hemoglobin: ______ Date: _______

Platelets: ______ Date: _______

3.1.12.2 Renal: Serum creatinine ≤ 1.5 x the ULN, or creatinine clearance (measured via 24-hour urine collection) ≥ 40 mL/minute.

Serum creatinine: ______ Date: _______

Creatinine clearance: ______ Date: _______

3.1.12.3 Proteinuria: Urinary protein ≤ 1+ on dipstick or routine urinalysis (UA); if urine dipstick or routine analysis is ≥ 2+, a 24-hour urine collection for protein must demonstrate < 1000 mg of protein in 24 hours to allow participation in the study.

Urinary protein ≤ 1+ (Yes / No) ______ Date: _______

If no, is the 24-hour collection < 1000 mg protein? ______

3.1.12.4 Hepatic: Total bilirubin ≤ 2.0 mg/dL, and aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 x the institutional upper limit of normal (ULN) [or 5.0 x the ULN in the setting of liver metastases]. Albumin within institutional normal range.

Total bilirubin: ______

AST: ______ Date: _______

ALT: ______ Date: _______

Albumin: ____________ Date: __________

Liver metastases? (Yes / No): ______ Date: _______

3.1.12.5 Coagulation: International Normalized Ratio (INR) ≤ 1.6 (unless receiving anticoagulation therapy). Patients on full-
dose anticoagulation must be on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin. If receiving warfarin, the patient must have an INR ≤ 3.0 and no active bleeding (i.e., no bleeding within 14 days prior to first dose of study therapy).

INR: _____ Date: ______

Is patient receiving warfarin? (Yes / No): ____

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3.1.13 No prior therapy with drugs other than oxaliplatin and a fluoropyrimidine plus bevacizumab for this disease. Chemotherapy drugs and bevacizumab may be stopped and started as long as no prior disease progression requiring change in chemotherapy agents occurred.

3.1.14 No clinically significant (equivalent to NCI CTCAE grade 3-4) bleeding episodes within the prior 3 months.

3.1.15 No active infection, symptomatic congestive heart failure, unstable angina pectoris, symptomatic or poorly controlled cardiac arrhythmia, uncontrolled thrombotic or hemorrhagic disorder.

3.1.16 No uncontrolled or poorly-controlled hypertension despite standard medical management (e.g. consistently SBP > 160 and DBP > 90 mmHg).

3.1.17 No major surgery within 28 days prior to randomization, or subcutaneous venous access device placement within 7 days prior to randomization.

3.1.18 No history of acute arterial thrombotic events within 6 months (including CVA, TIA, MI or unstable angina).

3.1.19 No brain or CNS metastases.

3.1.20 No other cancer requiring therapy within last three years (except in situ carcinoma or non-melanoma skin cancer).

3.1.21 Patients must not have an acute or subacute intestinal obstruction. No history of bowel obstruction, GI perforation, major abdominal surgery with bowel resection, or peri-rectal/peri-anal abscess within 6 months prior to randomization.

3.1.22 Patient must not have a history of inflammatory bowel disease requiring pharmacological and/or surgical intervention within the 12 months prior to randomization.

3.1.23 Patient must not have a known allergy to any of the treatment components.
4. Registration and Randomization Procedures

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

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) or by calling the PMB at 240-276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for E7208 site registration:

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

Submitting Regulatory Documents

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

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

Required Protocol Specific Regulatory Documents

1. CTSU Regulatory Transmittal Form.
   
   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.
3. A. CTSU IRB Certification Form.
   Or
   B. Signed OMB No. 0990-0263
   Or
   C. IRB Approval Letter
**NOTE:** The above submissions must include the following details:

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

4. The CTSU encourages you to link to the following CTSU RSS webpage so that more information on RSS2.0 as well as the submission forms can be accessed. Log into [http://www.ctsu.org](http://www.ctsu.org) and click on the Regulatory tab to access the RSS webpage. If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail CTSUContact@westat.com. **Monday through Friday, 9:00am - 8:30pm.**

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

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

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member.
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

**NOTE:** The OPEN system will provide the site with a printable confirmation of randomization. Please print this confirmation for your records.
Further instructional information is provided on the OPEN tab of the CTSU members’ side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Patients must not start protocol treatment prior to registration.

Treatment should start within 7 working days after registration but not less than 28 days after last dose of bevacizumab.

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

4.1 Protocol Number

4.2 Investigator Identification
- Institution and affiliate name
- Investigator's name

4.3 Patient Identification
- Patient's initials and chart number
- Patient's Social Security number
- Patient demographics
  - Sex
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment

4.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.0. An eligibility checklist has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG Coordinating Center.

STRATIFICATION FACTORS:
- Performance Status 0 vs. 1
- Discontinuation of oxaliplatin before disease progression: Yes vs. No
- Time since treatment with chemotherapy or bevacizumab ≤ 6 months vs. > 6 months.

4.5 Additional Requirements
- Patients must provide a signed and dated, written informed consent form.
4.5.2 Specimens are to be submitted as outlined in Section 10.

4.6 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted according to the instructions in the E7208 Forms Packet. Document the reason for not starting protocol treatment on the off-treatment form. Also report the date and type of the first non-protocol treatment that the patient receives on the Non-Protocol Therapy Form.

4.7 EKG, UPC and Pregnancy Test Reimbursement Guidelines

ImClone has agreed to provide reimbursement towards the non-standard of care pregnancy, UPC and EKG time points while patients are on protocol treatment. These tests should not be submitted to the patient's insurance for reimbursement. Institutions should submit these costs to the ECOG Coordinating Center using the E7208 EKG/UPC/Pregnancy Test Reimbursement Invoice (Appendix VI).

Baseline pregnancy test is considered standard of care and should be submitted to the patient's insurance for reimbursement. All additional pregnancy tests, all UPC and all EKG time points as outlined in Section 7 of the protocol are considered non-standard of care.

Please refer to the table below for reimbursable time points:

<table>
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<th></th>
<th>Baseline</th>
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<th>End of Treatment</th>
<th>30 Days After End of Treatment</th>
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<tr>
<td>UPC</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

*Baseline pregnancy test is standard of care and should be submitted to patient’s insurance for reimbursement.

In order to authorize reimbursement, the results of the EKG, UPC and Pregnancy test must accompany the E7208 Reimbursement Invoice (Appendix VI) as well as the Substitute W-9 Tax Form (Appendix VII). These items should be sent to the ECOG Coordinating Center, Attn: Drug Orders (fax: 617-632-2063). The ECOG Coordinating Center will review/approve the invoices and submit for payment on a quarterly basis.

If you have any questions about this process, please contact a member of the ECOG Industry Team at the ECOG Coordinating Center (617-632-3610).
5. Treatment Plan

NOTE: Patients must not start treatment until at least 28 days from last dose of bevacizumab.

5.1 Administration Schedule

5.1.1 Treatment/ARM A – (IC)

5.1.1.1 Cetuximab 500 mg/m² IV q 14 days
- The first infusion is to be administered over 120 minutes with subsequent infusions over 60 minutes

5.1.1.2 Irinotecan 180 mg/m² IV over 60-90 minutes q 14 days
Cetuximab should be given prior to irinotecan.
Repeat cycles every 14 days until progression.

NOTE: It is recommended that 50mg of diphenhydramine be administered prior to the initial 3 doses of ramucirumab, and may or may not be continued for subsequent doses per the investigator’s discretion.

NOTE: Irinotecan pre-medication should be given per standard institutional practice.

5.1.2 Treatment/ARM B – (ICR)
CLOSED to accrual in Addendum #5

5.1.3 Treatment/ARM C – (mICR)

5.1.3.1 Ramucirumab 6 mg/kg IV over 60 minutes q 14 days
- The dose of ramucirumab is to be recalculated should the patients weight change by 10% or more.

5.1.3.2 Cetuximab 400 mg/m² IV q 14 days
- The first infusion is to be administered over 120 minutes with subsequent infusions over 60 minutes.

5.1.3.3 Irinotecan 150 mg/m² IV over 60-90 minutes q 14 days
Ramucirumab should be given first, followed by cetuximab and then irinotecan.
Repeat cycles every 14 days until progression.

NOTE: It is recommended that 50mg of diphenhydramine be administered prior to the initial 3 doses of ramucirumab, and may or may not be continued for subsequent doses per the investigator’s discretion.

NOTE: Irinotecan pre-medication should be given per standard institutional practice.
5.2 Adverse Event Reporting Requirements

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

- **Routine reporting**: Adverse events are reported in a routine manner at scheduled times during a trial (please refer to the E7208 Forms Packet for the list of forms with directions and timeframes for routine adverse event reporting).

- **Expedited reporting**: In addition to routine reporting, certain adverse events must be reported in an expedited manner via AdEERS for timelier monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

5.2.2 Terminology

- **Adverse Event (AE)**: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be **ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.**

- **Attribution**: An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

<table>
<thead>
<tr>
<th>ATTRIBUTION</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated</td>
<td>The AE is <em>clearly NOT related</em> to treatment</td>
</tr>
<tr>
<td>Unlikely</td>
<td>The AE is <em>doubtfully related</em> to treatment</td>
</tr>
<tr>
<td>Possible</td>
<td>The AE <em>may be related</em> to treatment</td>
</tr>
<tr>
<td>Probably</td>
<td>The AE is <em>likely related</em> to treatment</td>
</tr>
<tr>
<td>Definite</td>
<td>The AE is <em>clearly related</em> to treatment</td>
</tr>
</tbody>
</table>

- **CAEPR (Comprehensive Adverse Events and Potential Risks List)**: An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator’s Brochure, the Package Insert, as well as company safety reports.

- **CTCAE**: The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.

- **Hospitalization (or prolongation of hospitalization)**: For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
• **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.

• **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in ANY of the following outcomes:
  - Death
  - A life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours).
  - 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 a serious adverse event when it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

### 5.2.3 Reporting Procedure

This study requires that expedited adverse event reporting use the NCI’s Adverse Event Expedited Reporting System (AdEERS). The NCI’s guidelines for AdEERS can be found at [http://ctep.cancer.gov](http://ctep.cancer.gov).

An AdEERS report must be submitted electronically to ECOG and the appropriate regulatory agencies via the AdEERS Web-based application located at [http://ctep.cancer.gov](http://ctep.cancer.gov).

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

• the AE Team at ECOG (617-632-3610) for Arms A, B and C and

• the FDA (1-800-332-1088) for Arm A

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

**Supporting and follow up data:** Any supporting or follow up documentation must be faxed to ECOG (617-632-2990), Attention: AE within 48-72 hours. In addition, supporting or follow up documentation must be faxed to

• the FDA (800-332-0178), for Arm A, in the same timeframe.

**NCI Technical Help Desk:** For any technical questions or system problems regarding the use of the AdEERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457 or 301-840-8202.

### 5.2.4 Determination of Reporting Requirements

Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

• the phase (0, 1, 2, or 3) of the trial
• whether the patient has received an investigational or commercial agent or both
• the seriousness of the event
• the Common Terminology Criteria for Adverse Events (CTCAE) grade
• whether or not hospitalization or prolongation of hospitalization was associated with the event
• when the adverse event occurred (within 30 days of the last administration of investigational agent vs. > 30 days after the last administration of investigational agent)
• the relationship to the study treatment (attribution)

Using these factors, the instructions and tables in the following sections have been customized for protocol E7208 and outline the specific expedited adverse event reporting requirements for study E7208.
5.2.5 **Steps to Determine if an Adverse Event is to be Reported in an Expedited Manner for Arm A**

1. Identify the **type and grade** of the event using CTCAE v4.0

2. Determine if the event is related to the protocol treatment (**attribution**)

3. Determine the **expectedness** of the event. An unexpected event is defined as one where the type of severity of the event is not listed in the investigator’s brochure, package insert or protocol.

4. With this information, review the chart in Section 5.2.6 to determine if event is reportable via AdEERS

5. Is the event reportable?

   - No
   - Yes

   - **Yes**: Report the event via AdEERS

6. Refer to footnote b in Section 5.2.6 to determine if the event meets the protocol specific reporting requirements for this study. If so, report the event via AdEERS
### 5.2.6 Expedited Reporting Requirements for Arm A on Protocol E7208

**Commercial Agents: Irinotecan and Cetuximab**

<table>
<thead>
<tr>
<th>Attribution</th>
<th>Grade 4</th>
<th>Grade 5&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ECOG and Protocol-Specific Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unexpected</td>
<td>Expected</td>
<td>Unexpected</td>
</tr>
<tr>
<td><strong>Unrelated or Unlikely</strong></td>
<td></td>
<td></td>
<td>7 calendar days</td>
</tr>
<tr>
<td><strong>Possible, Probable, Definite</strong></td>
<td>7 calendar days</td>
<td>7 calendar days</td>
<td>7 calendar days</td>
</tr>
</tbody>
</table>

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

- **a** This includes all deaths within 30 days of the last dose of treatment regardless of attribution. **NOTE:** Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event.
- **b** Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:
  - **Serious Events:** Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported via AdEERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events via AdEERS, please contact the NCI AdEERS Help Desk at 301-897-7497.
5.2.7 Steps to Determine if an Adverse Event is to be Reported in an Expedited Manner for Arms B and C

5.2.7.1 Guidelines for adverse events OCCURRING WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS of the last administration of the investigational agent(s).

Determine if the event meets the definition of a **Serious Adverse Event** (SAE) as outlined by the six criteria in the top portion of the table below in Section 5.2.8.

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Identify the type and grade</strong> of the event using CTCAE v4.0</td>
<td><strong>Refer to Section 5.2.9 to determine if the event meets the protocol specific reporting requirements for this study. If so, report the event via AdEERS</strong></td>
</tr>
<tr>
<td><strong>Determine if the patient was hospitalized for ≥ 24 hours for the event</strong></td>
<td><strong>Refer to Section 5.2.9 to determine if the event meets the protocol specific reporting requirements for this study. If so, report the event via AdEERS</strong></td>
</tr>
<tr>
<td>With this information, review the chart in Section 5.2.8 to determine if event is reportable via AdEERS</td>
<td><strong>Is the event reportable?</strong></td>
</tr>
<tr>
<td><strong>Yes</strong></td>
<td><strong>No</strong></td>
</tr>
<tr>
<td>Report the event via AdEERS</td>
<td><strong>Refer to Section 5.2.9 to determine if the event meets the protocol specific reporting requirements for this study. If so, report the event via AdEERS</strong></td>
</tr>
</tbody>
</table>
5.2.7.2 Guidelines for adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational agent(s).

If the adverse event meets the definition of a **Serious Adverse Event (SAE)** as outlined by the six criteria in the top portion of the table below in Section 5.2.8, AND has an attribution of possible, probably or definite, the following events require reporting as follows:

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

**NOTE:** Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported via AdEERS even if the patient is off study

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

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**5.2.8 Expedited Reporting Requirements for Arms B and C on protocol E7208**

Investigational Agents: Ramucirumab (IMC-1121B)

Commercial Agents: Irinotecan and Cetuximab

*When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events follow the guidelines for investigational agents.*

**Late Phase 2 and Phase 3 Studies**

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND **within 30 Days of the Last Administration of the Investigational Agent/Intervention**

**NOTE:** Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.
FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

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

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

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

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

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

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

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

**Expedited 24-hour notification followed by complete report within 5 calendar days for:**

- All Grade 4, and Grade 5 AEs

**Expedited 10 calendar day reports for:**

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

**5.2.9 Additional instructions, requirements and exceptions for Arms B and C on protocol E7208**

**Additional Instructions:**

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via AdEERS, please contact the NCI Medical Help
NOTE: All grade 2 or higher GI perforations and peri-rectal abscess events, regardless of grade or whether or not the patient was hospitalized, must be reported via AdEERS within the timeframes specified in the table in Section 5.2.8.

5.2.10 Other recipients of adverse event reports and supplemental data

ECOG will forward AdEERS reports to the appropriate regulatory agencies and pharmaceutical company, if applicable.

The drug supporter is obliged to forward reported AEs to the FDA. A drug supporter representative may call a site for additional or supplemental information regarding a serious adverse event. Any additional written AE information requested by the drug supporter MUST be submitted to BOTH ECOG and the drug supporter.

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

5.2.11 Second Primary Cancer Reporting Requirements

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

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

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

     ECOG Coordinating Center
     FSTRF
     900 Commonwealth Avenue
     Boston, MA 02215

  2. Submit a copy of the pathology report to ECOG confirming the diagnosis.

  3. If the patient has been diagnosed with AML/MDS, submit a copy of the cytogenetics report (if available) to ECOG

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

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

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

3. Submit a copy of the pathology report to ECOG and NCI/CTEP confirming the diagnosis.

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

**NOTE:** The ECOG Second Primary Form and the AdEERS report should not be used to report recurrence or development of metastatic disease.

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

**NOTE:** Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via AdEERS or by the ECOG Second Primary Form.
5.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Cetuximab (NSC 714692)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. They are developed and continuously monitored by the CTEP Investigational Drug Branch (IDB). The information listed in the CAEPR(s) below, as well as the other resources described in the 'Determination of reporting requirements' part of the Adverse Event Reporting section in this protocol, can be used to determine expectedness of an event when evaluating if the event is reportable via AdEERS Arm A. Frequency is provided based on 2282 patients. Below is the CAEPR for Cetuximab.

### Adverse Events with Possible Relationship to Cetuximab (CTCAE 4.0 Term) [n= 2282]

<table>
<thead>
<tr>
<th>Likely (&gt;20%)</th>
<th>Less Likely (&lt;=20%)</th>
<th>Rare but Serious (&lt;3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLOOD AND LYMPHATIC SYSTEM DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EAR AND LABYRINTH DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>External ear inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinnitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EYE DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry eye</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uveitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watering eyes</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheilitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucositis oral</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema limbs</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flu like symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Infusion related reaction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-cardiac chest pain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IMMUNE SYSTEM DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### INFECTIONS AND INFESTATIONS

<table>
<thead>
<tr>
<th>Infection</th>
<th>Infections and infestations – Other (aseptic meningitis)</th>
</tr>
</thead>
</table>

### INVESTIGATIONS

<table>
<thead>
<tr>
<th>Neutrophil count decreased</th>
<th>Weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell decreased</td>
<td></td>
</tr>
</tbody>
</table>

### METABOLISM AND NUTRITION DISORDERS

<table>
<thead>
<tr>
<th>Anorexia</th>
<th>Dehydration</th>
<th>Hypocalcemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Hypomagnesemia</td>
</tr>
</tbody>
</table>

### MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS

<table>
<thead>
<tr>
<th>Arthralgia</th>
<th>Back pain</th>
<th>Myalgia</th>
</tr>
</thead>
</table>

### NERVOUS SYSTEM DISORDERS

<table>
<thead>
<tr>
<th>Headache</th>
<th>Syncope</th>
</tr>
</thead>
</table>

### RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS

<table>
<thead>
<tr>
<th>Allergic rhinitis</th>
<th>Bronchospasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>Dyspnea</td>
</tr>
<tr>
<td>Hoarseness</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pneumonitis</th>
</tr>
</thead>
</table>

### RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS - Other (non-cardiogenic pulmonary edema)

### SKIN AND SUBCUTANEOUS TISSUE DISORDERS

<table>
<thead>
<tr>
<th>Dry skin</th>
<th>Alopecia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nail loss</td>
<td>Palmar-plantar erythrodynesthesia syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Photosensitivity</th>
<th>Pruritus</th>
<th>Purpura</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Rash acneiform</th>
<th>Rash maculo-papular</th>
<th>Skin ulceration</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Urticaria</th>
</tr>
</thead>
</table>

### VASCULAR DISORDERS

<table>
<thead>
<tr>
<th>Hypotension</th>
<th>Thromboembolic event</th>
</tr>
</thead>
</table>

---

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

2. Infection could include all 75 sites of infections under the INFECTIONS AND INFESTATIONS SOC.
Also reported on cetuximab trials but with the relationship to cetuximab still undetermined:

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Disseminated intravascular coagulation; Hemolysis

**CARDIAC DISORDERS** - Atrial fibrillation; Atrial flutter; Chest pain - cardiac; Left ventricular systolic dysfunction; Myocardial infarction; Paroxysmal atrial tachycardia; Pericardial effusion; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia

**EAR AND LABYRINTH DISORDERS** - Hearing impaired

**EYE DISORDERS** - Blurred vision; Extraocular muscle paresis; Eyelid function disorder; Keratitis; Photophobia; Vitreous hemorrhage

**GASTROINTESTINAL DISORDERS** - Colitis; Dysphagia; Esophagitis; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal hemorrhage (including Colonic or Gastric hemorrhage or hemorrhage in other sites under the GASTROINTESTINAL DISORDERS SOC); Gastrointestinal perforation (Colonic perforation, Duodenal perforation, or perforation in other sites under the GASTROINTESTINAL DISORDERS SOC); Gastrointestinal ulcer (ulcer includes Duodenal ulcer, Rectal ulcer, or ulcer in other sites under the GASTROINTESTINAL DISORDERS SOC); Ileus; Pancreatitis; Rectal fistula

**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Edema face; Sudden death NOS

**HEPATOBILIARY DISORDERS** - Cholecystitis; Hepatic failure

**INJURY, POISONING AND PROCEDURAL COMPLICATIONS** - Bruising; Wound dehiscence

**INVESTIGATIONS** - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Creatinine increased; Platelet count decreased; Serum amylase increased

**METABOLISM AND NUTRITION DISORDERS** - Hyperkalemia; Hyperuricemia; Hypokalemia; Hyponatremia; Hypophosphatemia

**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (myasthenia); Musculoskeletal and connective tissue disorder - Other (Sudeck's Atrophy)

**NERVOUS SYSTEM DISORDERS** - Ataxia; Dizziness; Dysgeusia; Extrapyramidal disorder; Intracranial hemorrhage; Nervous system disorders - Other (cholinergic syndrome); Neuralgia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Tremor

**PSYCHIATRIC DISORDERS** - Agitation; Depression

**RENAL AND URINARY DISORDERS** - Hematuria; Renal and urinary disorders - Other (acute renal failure)

**REPRODUCTIVE SYSTEM AND BREAST DISORDERS** - Reproductive system and breast disorders - Other (balanitis); Vaginal inflammation

**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Adult respiratory distress syndrome; Atelectasis; Bronchopulmonary hemorrhage; Epistaxis; Pleural effusion; Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterator-organized pneumonia [BOOP])

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Hirsutism; Skin hypopigmentation; Skin and subcutaneous tissue disorders - Other (skin fissures)

**VASCULAR DISORDERS** - Flushing; Hypertension; Lymphedema; Vasculitis

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

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

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

5.4.1 General Considerations

a. A new cycle of treatment may begin when the ANC is ≥ 1,500/mcl, the platelet count is ≥ 75,000/mcl, and any treatment-related GI toxicity is resolved to ≤ Grade 1.

b. If the initiation of a new cycle, or treatment during a cycle is delayed for ≥ 4 weeks, the patient should be removed from protocol treatment.

c. Held doses are not to be made up.

d. If one therapeutic agent is permanently discontinued secondary to toxicity, then therapy with the other study agents should continue and the patient should remain on-study with full adherence to all protocol-related requirements.

e. In the event of serious or life-threatening conditions, hold the offending agent. If the patient is to continue on therapy, all agents should be held until the toxicity resolves to grade < 2.

f. Dose reductions for all agents are as follows:

<table>
<thead>
<tr>
<th>ARM</th>
<th>AGENT</th>
<th>INITIAL DOSE</th>
<th>LEVEL -1</th>
<th>LEVEL -2</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (IC)</td>
<td>Cetuximab</td>
<td>500 mg/m²</td>
<td>400 mg/m²</td>
<td>250 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Irinotecan</td>
<td>180 mg/m²</td>
<td>150 mg/m²</td>
<td>120 mg/m²</td>
</tr>
<tr>
<td>B (ICR)</td>
<td>Ramucirumab</td>
<td>8 mg/kg</td>
<td>6 mg/kg</td>
<td>5 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Cetuximab</td>
<td>500 mg/m²</td>
<td>400 mg/m²</td>
<td>250 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Irinotecan</td>
<td>180 mg/m²</td>
<td>150 mg/m²</td>
<td>120 mg/m²</td>
</tr>
<tr>
<td>C (mICR)</td>
<td>Ramucirumab</td>
<td>6 mg/kg</td>
<td>5 mg/kg</td>
<td>4 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Cetuximab</td>
<td>400 mg/m²</td>
<td>250 mg/m²</td>
<td>200 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Irinotecan</td>
<td>150 mg/m²</td>
<td>120 mg/m²</td>
<td>90 mg/m²</td>
</tr>
</tbody>
</table>

NOTE: In the event that an agent is given at dose level (-2) and dose modification rules call for further reduction, the agent should be discontinued.
5.4.2 Hematologic toxicities

No Ramucirumab or cetuximab dose modifications (or delays) will be made for hematologic toxicity. Continue Ramucirumab or cetuximab when irinotecan is held for hematologic toxicities.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Reduce irinotecan one dose level at the next cycle. For subsequent cycles, resume at the previous dose levels, provided ANC ≥ 1,500/mcl and platelets ≥ 75,000/mcl.</td>
</tr>
<tr>
<td>3-4</td>
<td>Hold irinotecan. If counts recover to ANC ≥ 1,500/mcl and platelets ≥ 75,000/mcl, irinotecan may be resumed at one lower dose level at next cycle. For subsequent cycles, continue at the reduced dose levels from the previous cycle.</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>Hold irinotecan. If fever resolves and counts recover to ANC ≥ 1,500/mcl and platelets ≥ 75,000/mcl, irinotecan may be resumed at one lower dose level at next cycle. For subsequent cycles, continue at the reduced dose levels from the previous cycle.</td>
</tr>
</tbody>
</table>

5.4.3 Diarrhea

No Ramucirumab dose delay will be made for diarrhea. Continue Ramucirumab when other agents are held. Dose modifications should be made for toxicity only when patient is receiving intensive loperamide therapy.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Be sure intensive loperamide is being taken. For subsequent cycles, resume all agents at the previous dose levels, provided diarrhea has fully resolved before restarting treatment.</td>
</tr>
<tr>
<td>3</td>
<td>Be sure intensive loperamide is being taken. If so, and grade 3 diarrhea lasts longer than 48 hours, reduce irinotecan one dose level. Do not treat again until the diarrhea resolves to ≤ grade 2.</td>
</tr>
<tr>
<td>4</td>
<td>Be sure intensive loperamide is being taken. Hold irinotecan. If diarrhea resolves to ≤ grade 2, irinotecan and cetuximab should be resumed at one lower dose level for subsequent cycles. For subsequent cycles, continue both agents at the reduced dose levels from the previous cycle.</td>
</tr>
</tbody>
</table>

5.4.4 Nausea and/or vomiting

These dose modifications for nausea and/or vomiting should be made only if they persist/occur despite two treatments with adequate (combination) antiemetics therapy.

No Ramucirumab or cetuximab dose modifications (or delays) will be made for nausea/vomiting. Continue Ramucirumab or cetuximab when irinotecan is held.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4</td>
<td>Reduce <em>irinotecan</em> one dose level. For subsequent cycles, continue irinotecan at the reduced dose level from the previous cycle.</td>
</tr>
</tbody>
</table>
5.4.5 Mucositis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Reduce irinotecan one dose level for subsequent cycles. No modifications (or delays) will be made for Ramucirumab or cetuximab.</td>
</tr>
<tr>
<td>3</td>
<td>Hold irinotecan. If mucositis resolves to ≤ Grade 2, resume both irinotecan and cetuximab at one lower dose level for subsequent cycles. No modifications (or delays) will be made for Ramucirumab.</td>
</tr>
<tr>
<td>4</td>
<td>Hold ALL protocol treatment. If mucositis resolves to ≤ Grade 2, reduce all agents one dose level for all subsequent cycles.</td>
</tr>
</tbody>
</table>

5.4.6 Pulmonary Toxicity

5.4.6.1 For Grade 2 or worsening pulmonary symptoms unrelated to underlying cancer, cetuximab treatment should be stopped and symptoms investigated. Cetuximab treatment may resume at one lower dose level when symptoms resolve to ≤ Grade 1 and cetuximab-related pneumonitis is ruled out.

5.4.6.2 For ≥ Grade 3 cough, dyspnea, hypoxia, pneumonitis, or pulmonary infiltrates, hold cetuximab until interstitial lung disease is ruled out. Continue Ramucirumab and irinotecan. Discontinue all protocol treatment if interstitial lung disease is confirmed.

5.4.7 Hypomagnesemia has been seen with cetuximab. For Grade 3-4 hypomagnesemia, hold cetuximab until hypomagnesemia resolves to ≤ Grade 2. Then restart cetuximab at the -1 dose. For any grade of hypomagnesemia, magnesium supplementation should be provided.

5.4.8 Hypertension (Dose delays for Ramucirumab only)

<table>
<thead>
<tr>
<th>Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (SBP 120-139 mmHg or DBP 80-89 mm Hg)</td>
</tr>
<tr>
<td>Grade 2 asymptomatic (SBP 140-159 mmHg or DBP 90-99 mm Hg)</td>
</tr>
<tr>
<td>• Grade 2 symptomatic (SBP 140-160 mmHg or DBP 90-100 mm Hg)</td>
</tr>
<tr>
<td>• Grade 3 (≥ SBP 160 mmHg or ≥ DBP 100 mmHg)</td>
</tr>
<tr>
<td>• Grade 4 (Hypertensive crisis or malignant hypertension)</td>
</tr>
</tbody>
</table>

Patients who hold or discontinue Ramucirumab due to hypertension may continue other protocol treatment.

5.4.9 Venous Thrombotic Events

Patients should be carefully monitored for evidence of thromboembolic disease during treatment.
5.4.9.1 Grade 3 venous thrombosis or asymptomatic pulmonary embolism: Hold Ramucirumab. Ramucirumab 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 be on stable dose of low molecular weight heparin prior to restarting Ramucirumab treatment;
- The patient must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels);
- The patient must not have had hemorrhagic events while on study.

5.4.9.2 Grade 4 or for recurrent/worsening venous thromboembolic events after resumption of Ramucirumab: Discontinue Ramucirumab.

5.4.9.3 For symptomatic pulmonary embolism, patients will discontinue all protocol treatment.

5.4.10 Arterial Thrombotic Events

5.4.10.1 For Grade 2 arterial thrombotic events not present at baseline or worsened since the initiation of protocol therapy, discontinue Ramucirumab. Patients may continue other protocol treatment.

5.4.10.2 For Grade 3 cerebrovascular ischemia, and/or peripheral or visceral arterial ischemia, discontinue Ramucirumab. Patients may continue other protocol treatment.

5.4.10.3 For Grade 3 cardiac ischemia/infarction, discontinue Ramucirumab. Patients may continue other protocol treatment.

5.4.10.4 For any Grade 4 arterial thrombotic event, including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia, discontinue all protocol treatment.

5.4.11 Left Ventricular Dysfunction

5.4.11.1 Grade 3 LV dysfunction: Symptomatic CHF responsive to intervention.
- Discontinue cetuximab (for patients on the control arm) or cetuximab and ramucirumab (for patients on the experimental arm). Patients may continue other protocol treatment.

5.4.11.2 Grade 4 LV dysfunction: Poorly controlled refractory CHF; intervention such as ventricular assist device or heart transplant is indicated.
- Discontinue all protocol treatment.
5.4.12 Hemorrhage/bleeding

5.4.12.1 For Grade 3 hemorrhage/bleeding, permanently discontinue Ramucirumab and hold other protocol treatment; once hemorrhage or bleeding resolves, other protocol treatment may be continued at the treating physician’s discretion.

5.4.12.2 For Grade 4 hemorrhage/bleeding, discontinue all protocol treatment.

5.4.13 Proteinuria (Dose delays for Ramucirumab only)

5.4.13.1 For proteinuria ≥ 2+ or UPC (urinary protein: creatinine ratio) > 1.0: Confirm total urine protein with a 24-hour urine collection. For 2+ proteinuria, the scheduled dose of Ramucirumab may be given while awaiting the results of the 24-hour collection. For > 2+ proteinuria, hold Ramucirumab while awaiting results of the 24-hour urine collection. Other protocol treatment may be continued. If proteinuria is 2-3 g/24 hours, hold Ramucirumab until urine protein recovers to < 2 g/24 hours, then resume at the -1 dose level. Continue other protocol treatment. A second dose reduction (to 5 mg/kg every other week) is permitted if the protein level > 2g/24 hours recurs. Ramucirumab will be discontinued permanently if the protein level is > 3g/24 hours, if there is a third occurrence of proteinuria > 2 g/24 hours, or if the protein level does not return to < 2g/24 hours within 2 weeks.

5.4.13.2 If nephrotic syndrome (Grade 4 proteinuria) occurs, discontinue Ramucirumab.

5.4.14 Cutaneous toxicity (Dose modifications for cetuximab only)

<table>
<thead>
<tr>
<th>Grade 3 Rash</th>
<th>Cetuximab</th>
<th>Outcome</th>
<th>Cetuximab Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st occurrence</td>
<td>Hold infusion 1 to 2 wks</td>
<td>If improvement: Continue at current dose</td>
<td></td>
</tr>
<tr>
<td>2nd occurrence</td>
<td>Hold infusion 1 to 2 wks</td>
<td>If improvement: Reduce one dose level</td>
<td></td>
</tr>
<tr>
<td>3rd occurrence</td>
<td>Hold infusion 1 to 2 wks</td>
<td>If improvement: Reduce two dose levels</td>
<td></td>
</tr>
<tr>
<td>4th occurrence</td>
<td>Discontinue cetuximab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4 Rash</td>
<td>Discontinue cetuximab</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5.4.15 Infusion Reactions

<table>
<thead>
<tr>
<th>Grade</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Slow the infusion rate by 50%. Monitor the patient for worsening of the condition. For subsequent infusions, premedicate with diphenhydramine 50mg IV (or equivalent); additional premedication may be administered at the investigator’s discretion.</td>
</tr>
<tr>
<td>2</td>
<td>Stop the infusion. Administer diphenhydramine 50mg IV (or equivalent), acetaminophen 650 mg orally for fever, and oxygen. Resume the infusion at 50% of the prior rate once the infusion reaction has resolved or decreased to grade 1; the infusion duration should not exceed 2 hours. For subsequent infusions, premedicate with diphenhydramine 50mg IV (or equivalent); additional premedication may be administered at the investigator’s discretion.</td>
</tr>
<tr>
<td>3 and 4</td>
<td>Immediately and permanently discontinue the offending agent. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms.</td>
</tr>
</tbody>
</table>

For grade 1 or 2 reactions manifesting only as delayed drug fever, see Section 5.4.16.

For grade 4 or allergy related edema and angioedema and hypotension, permanently discontinue all medications.

For a second Grade 1 or 2 infusion reaction, administer dexamethasone 10mg IV (or equivalent); then, for subsequent infusions, premedicate with diphenhydramine 50mg IV (or equivalent), acetaminophen 650 mg orally, and dexamethasone 10mg IV (or equivalent).

5.4.16 Drug Fever

In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the study drug or to an infectious etiology. If a patient experiences isolated drug fever, for the next dose, pre-treat with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion); repeat antipyretic dose 6 and 12 hours after cetuximab infusion. The infusion rate will remain unchanged for future doses.

If a patient experiences recurrent isolated drug fever following premedication and post-dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be 50% of previous rate. If fever recurs following infusion rate change, the investigator should assess the patient’s level of discomfort with the event and use clinical judgment to determine if the patient should receive further cetuximab.
5.4.17 Other Grade 3 and 4 Toxicities

For grade 3 events hold the offending agents until the toxicity resolves to grade ≤ 1. If grade 4, please discuss with the study chair.

5.5 Supportive Care

5.5.1 All supportive measures consistent with optimal patient care will be given throughout the study.

5.5.2 Diarrhea Management

For symptoms of diarrhea and/or abdominal cramping that occur at any time during a treatment cycle with irinotecan, patients will be instructed to begin taking loperamide. Loperamide should be started at the earliest sign of (1) a poorly formed or loose stool or (2) the occurrence of 1 to 2 more bowel movements than usual in 1 day or (3) an increase in stool volume or liquidity. Loperamide should be taken in the following manner: 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around the clock until diarrhea-free for at least 12 hours. Patients may take loperamide 4 mg every 4 hours during the night. Loperamide should not be used for more than 48 hours. Patients should be provided with loperamide at the initial treatment visit so that they have sufficient supply on hand in case antidiarrheal support is required. Additional antidiarrheal measures may be used at the discretion of the treating physician. Patients should be instructed to increase fluid intake to help maintain fluid and electrolyte balance during episodes of diarrhea.

5.5.3 Antibiotics

Oral fluoroquinolone treatment should be initiated for any of the following:
- Diarrhea persisting for more than 24 hours despite loperamide
- ANC < 500/mcl (even in the absence of diarrhea or fever)
- Fever with diarrhea (even in the absence of neutropenia)
- Antibiotic therapy should also be initiated in patients who are hospitalized with prolonged diarrhea (even in the absence of neutropenia).

5.5.4 Lacrimation, rhinorrhea, miosis, diaphoresis, hot flashes, flushing, abdominal cramping, diarrhea, or other symptoms of early cholinergic syndrome may occur during or shortly after receiving irinotecan. Atropine, 0.25-1.0 mg IV or SC may be used to treat these symptoms. In patients with troublesome or recurrent symptoms, prophylactic administration of atropine shortly before irinotecan therapy may be considered. Additional antidiarrheal measures may be used at the discretion of the treating physician. Combination anticholinergic medications containing barbiturates or other agents (e.g., Donnatal®) should not be used because these may affect irinotecan metabolism. Anticholinergics should be used with caution in patients with potential contraindications (e.g., obstructive uropathy, glaucoma, tachycardia, etc.).
Late diarrhea (e.g., developing more than 24 hours after irinotecan) should be managed with loperamide as described above.

5.5.5 Pegfilgrastim, epoetin and darbepoetin alfa may be administered at the treating investigator's discretion.

5.5.6 Dermatology Management

Suggested algorithm for management of cutaneous toxicity and paronychia:

In this protocol, acneiform rash and paronychia will be graded according to version 4.0 of the NCI-CTCAE definitions of rash/desquamation and nail changes. The patient should be followed until resolution of these toxicities.

Acneiform rash and paronychia should be managed according to the algorithms in Table 1-1 and Table 1-2. Cetuximab therapy treatment adjustments should be made according to Tables 1-3. Cetuximab dose reductions will be permanent (i.e., no dose re-escalations).
Table 1-1: Algorithm for Management of Acneiform Rash

Dermatological Evaluation

Mild (Grade 1)
- STCN 50 mg BID and Topicals BID
  - Reassess in 2 weeks
  - 2 Weeks STCN and Continue Topicals
    - Reassess in 2 weeks

Moderate or Severe (Grades 2+3)
- STCN 100 mg BID and Topicals BID
  - Reassess in 2 weeks
  - 2 Weeks STCN and Continue Topicals
    - Oral Steroids and STCN and Continue Topicals
      - Reassess in 2 weeks
      - Consider: Dose Modification or Oral Isotretinoin

Key:
- Improvement
- Worse/No Change

STCN: Semisynthetic tetracyclines (doxycycline or minocycline)
Topicals: Hydrocortisone 2.5% cream or alclomethasone 0.05% cream
Oral Steroids: Methylprednisolone dose pack
Isotretinoin: Low doses (10-20 mg a day) or isotretinoin as a single agent
Table 1-2: Algorithm for Management of Paronychia

Dermatological Evaluation

Mild (Grade 1)
- Emollients and/or Topical Corticosteroids
  - Reassess in 2 weeks

Moderate or Severe (Grades 2+3)
- Culture and Sensitivity, then (appropriate) Topical or Oral Antibiotics or Intralesional Steroids
  - Reassess in 2 weeks

Mild (Grade 1)
- Emollients and/or Topical Corticosteroids
  - Culture and Sensitivity, then (appropriate) Topical or Oral Antibiotics
    - Reassess in 2 weeks

Moderate or Severe (Grades 2+3)
- Emollients and/or Topical Antibiotics
  - Partial or Total Nail Avulsion
    - Consider: Dose Modification or Partial or Total Nail Avulsion

Key:
- Improvement
- Worse/No Change

STCN: Semisynthetic tetracyclines (doxycycline or minocycline)
Topicals: Hydrocortisone 2.5% cream or alclomethasone 0.05% cream
Oral Steroids: Methylprednisolone dose pack
Isotretinoin: Low doses (10-20 mg a day) or isotretinoin as a single agent
5.6 **Duration of Therapy**

Patients will receive protocol therapy unless:

5.6.1 Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the E7208 Forms Packet.

5.6.2 Patient withdraws consent.

5.6.3 Patients should be treated on study with medications as assigned until discontinuation for toxicity or disease progression by RECIST criteria.

5.7 **Duration of Follow-up**

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 5 years from the date of registration. All patients must also be followed through completion of all protocol therapy.
6. Measurement of Effect

6.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every eight weeks.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in RECIST.

- The following general principles must be followed:
  1. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before registration.
  2. Measurable disease is defined by the presence of at least one measurable lesion.
  3. All measurements should be recorded in metric notation by use of a ruler or calipers.
  4. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

6.1.1 Definitions

Evaluable for Objective Response

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

(NOTE: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response

Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target lesion assessment. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.1.2 Disease Parameters

Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm
with calipers by clinical exam. All tumor measurements must be recorded in millimeters.

Malignant Lymph Nodes
To be considered pathologically enlarged and measurable, a lymph node must be \( \geq 15 \text{ mm} \) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease
All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with \( \geq 10 \) to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. Non-measurable also includes lesions that are < 20 mm by chest x-ray.

**NOTE:** Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target Lesions
All measurable lesions up to a maximum of 2 lesions per organ and 5 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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum of the diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.
Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of unequivocal progression of each should be noted throughout follow-up.

6.1.3 Methods 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 registration.

The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (e.g., skin nodules). 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

This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up must be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image
acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

**PET-CT**

At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

**Ultrasound**

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

**Endoscopy, Laparoscopy**

The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

**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 guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

**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.

**FDG-PET**

FDG-PET may not be used as a response assessment in this study.

### 6.1.4 Response Criteria

#### 6.1.4.1 Evaluation of Target Lesions

**Complete Response (CR)**

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

**Partial Response (PR)**

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

**Progressive Disease (PD)**

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression, See Section 6.1.4.3).

**Stable Disease (SD)**

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. (Note: a change of 20% or less that does not increase the sum of the diameters by 5 mm or more is coded as stable disease)

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of eight weeks.

#### 6.1.4.2 Evaluation of Non-Target Lesions

**Complete Response (CR)**

Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis)

**NOTE:** If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Non-CR/Non-PD
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 (see Section 6.1.4.3). Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest “increase” in the size of one or more on-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from “trace” to “large”, an increase in nodal disease from “localized” to “widespread”, or an increase sufficient to require a change in therapy.

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

6.1.4.3 Evaluation of New Lesions
The appearance of new lesions constitutes Progressive Disease (PD).

6.1.4.4 Evaluation of Best Overall Response
The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence or non-protocol therapy (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.
For Patients with Measurable Disease (i.e., Target Disease)

<table>
<thead>
<tr>
<th>Target Lesions</th>
<th>Non-Target Lesions</th>
<th>New Lesions*</th>
<th>Best Overall Response</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>Non-CR/Non-PD</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>Not evaluated</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>Non-PD/not evaluated</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>Non-PD/not evaluated</td>
<td>No</td>
<td>SD</td>
<td>Documented at least once ≥ 8 wks. from study entry</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
<td>No prior SD, PR or CR</td>
</tr>
<tr>
<td>Any</td>
<td>PD**</td>
<td>Yes or No</td>
<td>PD</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
<td></td>
</tr>
</tbody>
</table>

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

**In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

NOTE: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

Duration of Response

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 progressive disease is objectively documented.

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, including the baseline measurements.

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of eight weeks.
7. Study Parameters

7.1 Therapeutic Parameters

1. Prestudy scans and x-rays used to assess all measurable or non-measurable sites of disease must be done within 4 weeks prior to randomization/registration.

2. Prestudy CBC (with differential and platelet count) should be done ≤ 4 weeks before randomization/registration.

3. All required prestudy chemistries, as outlined in Section 3, should be done ≤ 4 weeks before randomization/registration – unless specifically required on Day 1 as per protocol.

<table>
<thead>
<tr>
<th>Test / Assessment</th>
<th>Pre-Study</th>
<th>Every 2 weeks</th>
<th>Every 4 weeks</th>
<th>Every 6 weeks</th>
<th>Every 8 weeks until progression</th>
<th>Follow-up¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>History and Physical</td>
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<td>X</td>
<td></td>
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<td>Weight and Performance Status</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Blood Pressure²</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Toxicity Assessment</td>
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<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease Assessment</td>
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<td></td>
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<td></td>
<td></td>
</tr>
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<td>EKG</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>X³</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC/diff/plts</td>
<td>X²</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry Panel (chem. 6 including creatinine)</td>
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<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>X</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>X</td>
<td></td>
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<td></td>
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<tr>
<td>Magnesium</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver Panel (AST/ALT/Bilirubin)</td>
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</tr>
<tr>
<td>Urine Protein:Creatinine Ratio⁸</td>
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<tr>
<td>Blood or Urine Pregnancy Test³</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>X⁹</td>
</tr>
<tr>
<td>K-ras mutation Status</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RADIOLOGIC EVALUATION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT scans (chest/abd/pelvis)</td>
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<td></td>
<td></td>
<td></td>
<td>X⁴</td>
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<tr>
<td>Pathology Submissions</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Every 3 months if patient is < 2 years from study entry, every 6 months if patient is 2-5 years from study entry. No specific requirements if patient is more than 5 years from study entry.

2. CBCs (with differential and platelet count) which includes WBC, ANC, Platelets, Hbg, and Hct required for protocol therapy must be done < 24 hours prior to the treatment cycle.

3. Within 2 weeks prior to registration for women of childbearing potential; and every 6 weeks during treatment or per institutional guidelines, whichever is shorter.

4. CT scans every 4 cycles until progression.

5. At the end of treatment. Repeat as clinically indicated.

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6. Toxicity Assessment every 2 cycles for the first 4 cycles on study and then every 2 cycles thereafter. An assessment is also required at the end of treatment and 30 days after the end of treatment.

7. Blood pressure should be monitored twice per week for the first 4 weeks and then every 2 weeks thereafter.

8. Urine dipstick may be used. However, in the occurrence of 2+ urine, UPC must be used.

9. At the end of treatment with a 30 day safety followup. Repeat as clinically indicated.

10. Submit from patients who consent "Yes" to "May your coded samples and related coded information be kept for use in research to learn about, prevent, find or treat cancer?" See Section 10.
8. **Drug Formulation and Procurement**

8.1 **Irinotecan (CPT-11) (NSC-616348)**

**Other Names** Irinotecan hydrochloride trihydrate [CPT- 1 1, (4S)-4, 1 1- diethyl-4-hydroxy-9- [(4-piperidinopiperidino) carbonyloxy] -IHpyranolo [3',4' :6, 7l indolzino [1 ,2-bl quino line-3, 14(4H, I2H)dione hydrochloride trihydrate] is a topoisomerase I inhibitor.

8.1.1 **Classification**

Topoisomerase I inhibitor

8.1.2 **Toxicology**

**Human Toxicity:** Virtually all Phase I and II studies of irinotecan 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 include nausea and vomiting, anorexia, abdominal cramping, cumulative asthenia, thrombocytopenia, renal insufficiency, increase in transaminase level and hair loss. Sporadic cases of pulmonary toxicity, manifested as shortness of breath and nonproductive cough, have also been reported.

8.1.3 **Mode of Action**

Causes single stranded DNA breakage by inhibition of the intranuclear enzyme topoisomerase-1. Leads to apoptotic cell death via defects in DNA repair.

8.1.4 **Pharmacology**

**Pharmacokinetics:** Several studies describing the pharmacokinetic characteristics of irinotecan (CPT-11) and its active metabolite, SN-38, when administered alone or in combination with other agents (including cisplatin) in patients with small cell or non-small cell lung cancer have been reported in published literature. CPT- 11 is converted by carboxylesterases to its more active metabolite, SN-38. In vitro, SN-38 is 250 to 1,000 fold more potent than CPT-11 in the inhibition of topoisomerase I activity. A reversible, pH-dependent hydrolysis converts the closed lactone E ring form of both CPT-11 and SN-38 to the open, carboxylate form of each compound. Only the closed ring (lactone) forms of CPT-11 and SN-38 are effective topoisomerase I inhibitors. The mean terminal half-life of SN-38 in plasma is slightly longer than that for CPT-11; 11.5 ± 3.8 hours versus 6.3 ± 2.2 hours for the lactone forms. Peak plasma concentrations for CPT-11 occur at the end of the infusion. The time to peak for SN-38 is highly inter-patient dependent occurring at variable times points 30 to 90 minutes after the end of infusion. Murine studies suggest that the liver may concentrate, convert CPT-11 to SN-38, and eliminate both compounds as well as the glucuronide conjugate of SN-38 (SN-38G) via biliary secretion. In rats, 55% of radiolabeled CPT-11 was excreted unchanged in the bile within 24 hours, while 21.7% was transformed to SN-38. It recently was demonstrated that plasma
concentrations of SN-38G in patients occur 0.5 to 3 hr after the SN38 peak and plasma levels generally exceeded that of SN-38. Overall, 73% of the radioactivity could be recovered from the feces of rats and 25% from the urine. Bile concentrations of CPT-11 were 10 to 60 fold higher than plasma concentrations in one patient during the first 6 hours following administration, while bile concentrations of SN-38 were 2 to 9 fold higher. Renal clearance has not been reported to be a major route of elimination for these compounds in humans.

8.1.5 Formulation

The drug is supplied in two forms: 2 ml vials containing 40 mg of drug and 5 ml vials containing 100 mg of drug. The drug is supplied in brown vials and appears as a pale-yellow-to-yellow crystalline powder and pale yellow transparent solution when reconstituted.

8.1.6 Storage and Stability

Irinotecan vials must be stored in a cool, dry place, protected from light in a locked cabinet accessible only to authorized individuals. It is stable for at least three years at room temperature. Irinotecan is stable for 24 hours in glass bottles or plastic bags after reconstitution with D5W.

8.1.7 Dose Specifics

8.1.7.1 Arm A (IC) and B (ICR)

Irinotecan will be given at a dose of 180 mg/m² intravenously over 60-90 minutes every 2 weeks.

8.1.7.2 Arm C (mICR)

Irinotecan will be given at a dose of 150 mg/m² intravenously over 60-90 minutes every 2 weeks.

8.1.8 Preparation

Irinotecan will be diluted with D5W to a total volume of 500 ml and infused intravenously over 60-90 minutes. Nothing else should be added to the bag.

8.1.9 Route of Administration

Intravenous administration only.

8.1.10 Incompatibilities

Do not mix with any other compound.

8.1.11 Availability

This drug is commercially available for purchase by a third party. This drug will not be supplied by the NCI.

8.1.12 Side Effects

Hematologic: Leukopenia, neutropenia, anemia, thrombocytopenia, neutropenic fever, hemorrhage
Gastrointestinal: Diarrhea (early and late – see administration above), nausea and vomiting, anorexia, abdominal pain, flatulence, stomatitis, dyspepsia, dehydration

Hepatic: Elevated transaminases.

Cardiovascular: Vasodilation, hypotension, myocardial infarction, stroke, edema

CNS: Dizziness, confusion, somnolence, insomnia, back pain

Respiratory: Pulmonary embolism,

Dermatologic: Alopecia, rash

Other: Asthenia, thrombophlebitis, sweating, weight loss, chills

8.1.13 Nursing/Patient Implications

Premedicate with antiemetics in anticipation of mild to moderate nausea and vomiting. When used in combination with 5-fluroruracil and leucovorin the nausea and vomiting will likely be worse.

Fatalities have been reported with thromboembolic events and neutropenic sepsis in patients receiving 5-fluorouracil, leucovorin and irinotecan.

Monitor for diarrhea. Diarrhea occurring within one hour of irinotecan has been treated with atropine 0.25 to 1mg IV or SC. Loperamide has been effective in treating later diarrhea and the patient should be instructed on its immediate use at the first loose stool following the irinotecan (see Section 5.5.2).

Monitor CBC, platelets, and liver function tests.

Dose modifications per the protocol or the package insert should be followed for hematologic and gastrointestinal toxicity.

Advise patient of likely post-treatment neutropenia and instruct in appropriate neutropenic precautions.

Administration of an oral quinolone antibiotic may decrease the risk of neutropenic sepsis in patients receiving 5-fluorouracil/leucovorin and irinotecan.

8.2 Cetuximab

8.2.1 IMC-C225, Erbitux®, NSC-714692

8.2.2 Classification

Anti-EGF Receptor antibody

8.2.3 Mode of Action

Cetuximab, a chimerized antibody of the IgG1 subclass, was originally derived from a mouse myeloma cell line. Cetuximab was genetically engineered by cloning the heavy and light chains of cetuximab and adapting them for expression together with the constant regions of the human kappa light chain and human gamma 1 heavy chain. The chimerization resulted in an antibody with binding affinity to epidermal...
growth factor receptors (EGFR) greater than the natural ligand epidermal growth factor (EGF). Cetuximab blocks binding of EGF and transforming growth factor alpha (TGFα) to EGFR and inhibits ligand-induced activation of this tyrosine kinase receptor. Cetuximab also stimulates EGFR internalization, effectively removing the receptor from the cell surface for interaction with ligand.

### 8.2.4 Storage and Stability

Cetuximab is an anti-EGFR human-to-murine chimeric antibody. Cetuximab is expressed in SP2/0 myeloma cell line, grown in large scale cell culture bioreactors and purified to a high level purity using several purification steps including protein A chromatography, ion exchange chromatography, low pH treatment and nanofiltration. Cetuximab is not known to be a vesicant.

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F). DO NOT FREEZE. Increased particulate formation may occur at temperatures at or below 0°C. This product contains no preservatives. Preparations of cetuximab in infusion containers are chemically and physically stable for up to 12 hours at 2°C to 8°C (36°F to 46°F) and up to 8 hours at controlled room temperature (20°C to 25°C; 68°F to 77°F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2°C to 8°C. Discard any unused portion of the vial.

### 8.2.5 Dose Specifics

#### 8.2.5.1 Arms A (IC) and B (ICR)

Cetuximab will be given as a 500 mg/m² dose every 2 weeks.

#### 8.2.5.2 Arm C (mICR)

Cetuximab will be given as a 400 mg/m² dose every 2 weeks.

### 8.2.6 Preparation

The product is formulated to 2 mg protein/mL with phosphate buffered saline, pH 7.2 ± 0.2 and aseptically filled into sterile glass vials, 100 mg per 50 cc vial, and stored as a liquid at 2 to 8°C. Each vial contains the following active and inactive ingredients per 1.0 mL: 2 mg of cetuximab, 145 nmol/L sodium chloride, and 10 mmol/L sodium phosphate.

**Preparation and Administration:** Cetuximab is supplied as a 50-mL, single-use vial containing 100 mg of cetuximab at a concentration of 2 mg/mL in phosphate buffered saline. The solution should be clear and colorless and may contain a small amount of easily visible white amorphous cetuximab particulates. DO NOT SHAKE OR DILUTE.

- Cetuximab must not be administered as an IV push or bolus.
- Cetuximab must be administered with the use of a low protein binding 0.22-micrometer in-line filter.
Cetuximab can be administered via infusion pump.

8.2.7 Route of Administration

Administration of Cetuximab: In an effort to prevent a hypersensitivity reaction, all patients should be premedicated with diphenhydramine hydrochloride 50 mg (or an equivalent antihistamine) by IV given 30-60 minutes prior to the first dose of cetuximab. Premedication may be administered prior to subsequent doses, but at the Investigator’s discretion, the dose of diphenhydramine (or a similar agent) may be reduced.

The initial dose of cetuximab is 500 mg/m² intravenously administered over AT LEAST 120 minutes, followed by ONE HOUR infusions every 2 weeks. **Cetuximab should not be given at a rate faster than 5 ml/min for the first dose.** Patients must be continuously observed during the infusion for signs of anaphylaxis.

Patients will be closely monitored for treatment-related adverse events, especially hypersensitivity reactions, during the infusion and the post-infusion observation hour. For the duration that patients are on study therapy, adverse event monitoring will be done continuously. Patients will be evaluated for adverse events at each visit and are to be instructed to call their physician to report any clinically significant adverse events between visits.

Severe infusion reactions occurred with the administration of cetuximab in approximately 3% (17/633) of patients, rarely with fatal outcome (< 1 in 1,000). Approximately 90% of severe infusion reactions were associated with the first infusion of cetuximab despite the use of prophylactic antihistamines. These reactions were characterized by the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria and/or hypotension. Caution must be exercised with every cetuximab infusion, as there were patients who experienced their first severe infusion reaction during later infusions.

Cetuximab can be administered via infusion pump or syringe pump.

Infusion Pump:

1. Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike or other appropriate transfer device may be used).
2. Fill cetuximab into a sterile evacuated container or bag such as glass containers, polyolefin bags (e.g., Baxter Intravia), ethylene vinyl acetate bags (e.g., Baxter Clintec), DEHP plasticized PVC bags (e.g., Abbott Lifecare), or PVC bags.
3. Repeat procedure until the calculated volume has been put in to the container. Use a new needle for each vial.
4. Administer through a low protein binding 0.22-micrometer in-line filter (placed as proximal to the patient as practical).
5. Affix the infusion line and prime it with cetuximab before starting the infusion.
6. Maximum infusion rate should not exceed 5 mL/min.
7. Use 0.9% saline solution to flush line at the end of infusion.

Cetuximab should be piggybacked to the patient’s infusion line. Following the cetuximab infusion, a 1-hour observation period is recommended.

8.2.8 Incompatibilities

Cetuximab should not be mixed with any other drug.

8.2.9 Availability

Cetuximab is approved for this indication and is commercially available. Please refer to the commercial package insert for complete prescribing and toxicity information.

8.2.10 Anticipated Adverse Events

Except where indicated, the data described below reflect exposure to cetuximab in 633 patients with advanced metastatic colorectal cancer. Cetuximab was studied in combination with irinotecan (n=354) or as monotherapy (n=279). Patients receiving cetuximab plus irinotecan received a median of 12 doses (with 88/354 [25%] treated for over 6 months), and patients receiving cetuximab monotherapy received a median of 7 doses (with 26/279 [9%] treated for over 6 months). The population had a median age of 59 and was 60% male and 91% Caucasian. The range of dosing for patients receiving cetuximab plus irinotecan was 1-84 infusions, and the range of dosing for patients receiving cetuximab monotherapy was 1-63 infusions.

The most serious adverse reactions associated with cetuximab were:

- Infusion reaction (3%);
- Dermatologic toxicity (1%);
- Interstitial lung disease (0.5%);
- Fever (5%);
- Sepsis (3%);
- Kidney failure (2%);
- Pulmonary embolus (1%);
- Dehydration (5%) in patients receiving cetuximab plus irinotecan, 2% in patients receiving cetuximab monotherapy;
- Diarrhea (6%) in patients receiving cetuximab plus irinotecan, 0% in patients receiving cetuximab monotherapy.

Thirty-seven (10%) patients receiving cetuximab plus irinotecan and 14 (5%) patients receiving cetuximab monotherapy discontinued treatment primarily because of adverse events.

The most common adverse events seen in 354 patients receiving cetuximab plus irinotecan were acneiform rash (88%),
asthenia/malaise (73%), diarrhea (72%), nausea (55%), abdominal pain (45%), and vomiting (41%).

The most common adverse events seen in 279 patients receiving ERBITUX monotherapy were acneiform rash (90%), asthenia/malaise (49%), fever (33%), nausea (29%), constipation (28%), and diarrhea (28%).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Data in patients with advanced colorectal carcinoma in the following table are based on the experience of 354 patients treated with cetuximab plus irinotecan and 279 patients treated with cetuximab monotherapy. [ERBITUX™ (Cetuximab) package insert. ImClone Systems Incorporated and Bristol-Myers Squibb Company. 2004 ER-B00001-02-04].

**NOTE:** There have been reports of hypomagnesemia during cetuximab therapy. The majority of the cases have been documented as decreased serum magnesium levels observed in routine electrolyte monitoring, and not as a result of clinical symptoms.
## Incidence of Adverse Events (≥ 10%) in Patients with Advanced Colorectal Carcinoma

<table>
<thead>
<tr>
<th>Body System</th>
<th>ERBITUX plus Irinotecan (n=354)</th>
<th>ERBITUX Monotherapy (n=279)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1 - 4</td>
<td>Grades 3 and 4</td>
</tr>
<tr>
<td><strong>% of Patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Body as a Whole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia/Malaise</td>
<td>73</td>
<td>16</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>45</td>
<td>8</td>
</tr>
<tr>
<td>Fever</td>
<td>34</td>
<td>4</td>
</tr>
<tr>
<td>Pain</td>
<td>23</td>
<td>6</td>
</tr>
<tr>
<td>Infusion Reaction</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>Infection</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Back Pain</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td><strong>Digestive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>72</td>
<td>22</td>
</tr>
<tr>
<td>Nausea</td>
<td>55</td>
<td>6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>41</td>
<td>7</td>
</tr>
<tr>
<td>Anorexia</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td>Constipation</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td><strong>Hematic/Lymphatic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>Anemia</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td><strong>Metabolic/Nutritional</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Loss</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Dehydration</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td><strong>Nervous</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>Cough Increased</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td><strong>Skin/Appendages</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acneiform Rash</td>
<td>88</td>
<td>14</td>
</tr>
<tr>
<td>Alopecia</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Skin Disorder</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Nail Disorder</td>
<td>12</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>14</td>
<td>1</td>
</tr>
</tbody>
</table>

1. Adverse events that occurred (toxicity Grades 1 through 4) in ≥10% of patients with refractory colorectal carcinoma treated with ERBITUX plus irinotecan or in ≥10% of patients with refractory colorectal carcinoma treated with ERBITUX monotherapy.
2. Asthenia/malaise is defined as any event described as “asthenia”, “malaise”, or “somnolence”.
3. Includes cases reported as infusion reaction.
4. Infusion reaction is defined as any event described at any time during the clinical study as “allergic reaction” or “anaphylactoid reaction”, or any event occurring on the first day of dosing described as “allergic reaction”, “anaphylactoid reaction”, “fever”, “chills”, “chills and fever” or “dyspnea”.
5. Acneiform rash is defined as any event described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis”.

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1 Adverse events that occurred (toxicity Grades 1 through 4) in ≥10% of patients with refractory colorectal carcinoma treated with ERBITUX plus irinotecan or in ≥10% of patients with refractory colorectal carcinoma treated with ERBITUX monotherapy.
2 Asthenia/malaise is defined as any event described as “asthenia”, “malaise”, or “somnolence”.
3 Includes cases reported as infusion reaction.
4 Infusion reaction is defined as any event described at any time during the clinical study as “allergic reaction” or “anaphylactoid reaction”, or any event occurring on the first day of dosing described as “allergic reaction”, “anaphylactoid reaction”, “fever”, “chills”, “chills and fever” or “dyspnea”.
5 Acneiform rash is defined as any event described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis”.
8.2.11 Nursing/Patient Implications

Resuscitation equipment and medications to treat hypersensitivity reactions should be available during and for one hour following each cetuximab infusion.

Blood pressure, pulse and temperature should be taken pre-infusion, at midpoint, end of infusion and one hour post-infusion.

Patients should be observed for 1 hour following the initial dose and 30 minutes following the weekly doses.

Patients should be observed for signs of hypersensitivity/anaphylaxis.

Safety Precautions

Appropriate mask, protective clothing, eye protection, gloves, and Class II vertical-laminar-airflow safety cabinets are recommended during preparation and handling. Opened vials must be disposed of at the investigational center as chemotherapy or biohazardous waste provided documented procedures for destruction are in place. Otherwise, opened vials must be returned to BMS for disposal. For questions regarding cetuximab destruction please contact BMS at 866 339-4267 or 203 677-7017.

Cetuximab therapy should be used with caution in patients with known hypersensitivity to cetuximab, murine proteins, or any component of this product.

It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving cetuximab as sunlight can exacerbate any skin reactions that may occur.

8.3 IMC 1121B

8.3.1 Other Names
Ramucirumab, 1121B

8.3.2 Classification:
Recombinant anti-VEGF human monoclonal antibody

8.3.3 Mode of Action:
IMC-1121B is a recombinant human monoclonal antibody of the IgG1 subclass that specifically binds to the extracellular domain of the VEGFR-2. This antibody effectively blocks VEGF/VEGFR-2 interaction, inhibits VEGF-stimulated activation of VEGFR-2 and p44/p42 mitogen-activated protein kinases, and neutralizes VEGF-induced mitogenesis of human endothelial cells.

8.3.4 Storage and Stability
Chemical and physical in-use stability has been demonstrated for up to 24 hours below 25°C (77°F). DO NOT FREEZE OR SHAKE IMC-1121B. From a microbiological point of view, the prepared product should be used immediately. If not used immediately, in-use storage time and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C (36°F - 46°F). IMC-
1121B should be protected from light when being stored. In the event of a temperature excursion, please complete the E7208 Temperature Excursion Form (Appendix VIII) and email to TempExcursions@Imclone.com.

8.3.5 Dose Specifics

8.3.5.1 Arm B (ICR):
Patients will receive 8 mg/kg of IMC-1121B every 2 weeks, administered as an I.V. infusion over 1 hour. The dose of IMC-1121B will be dependent upon the patient’s baseline body weight in kilograms. This dose will be recalculated if there is a 10% change in body weight from baseline. IMC-1121B is formulated at 10 mg/mL (with a dose of 8 mg/kg).

Premedication
Premedication is recommended but not required prior to infusion of ramucirumab. Recommended premedication agents include histamine H1 antagonists such as diphenhydramine hydrochloride 50 mg I.V. (or equivalent). Additional premedication may be provided at investigator discretion.

8.3.5.2 Arm C (mICR):
Patients will receive 6 mg/kg of IMC-1121B every 2 weeks, administered as an I.V. infusion over 1 hour. The dose of IMC-1121B will be dependent upon the patient’s baseline body weight in kilograms. This dose will be recalculated if there is a 10% change in body weight from baseline. IMC-1121B is formulated at 10 mg/mL (with a dose of 8 mg/kg).

Premedication
Premedication is recommended but not required prior to infusion of ramucirumab. Recommended premedication agents include histamine H1 antagonists such as diphenhydramine hydrochloride 50 mg I.V. (or equivalent). Additional premedication may be provided at investigator discretion.

8.3.6 Preparation
IMC-1121B drug product are sterile, preservative-free, injectable liquids in single-use 50-mL vials containing 500 mg/50 mL IMC-1121B in a histidine-buffered formulation at a final concentration of 10 mg/mL. Each vial is packaged and labeled in accordance with local regulations.

The dose of IMC-1121B should be aseptically withdrawn from the vial and transferred to a sterile AVIVA, ethylene vinyl acetate, polyolefin, or polyvinyl chloride I.V. bag, or an evacuated United States Pharmacopeia Type II (or local equivalent) glass I.V. container. For dose volumes < 250 mL, a sufficient quantity of sterile normal saline (0.9% weight/volume) solution must be added to the container (or...
removed in the case of a prefilled bag such as AVIVA) to make the total volume 250 mL. For dose volumes > 250 mL, the addition of sterile normal saline is not required.

The container should be gently inverted to ensure adequate mixing. Different drug product lots or formulations must not be mixed in a single infusion.

Chemical and physical in-use stability has been demonstrated for up to 24 hours below 25°C (77°F). **DO NOT FREEZE OR SHAKE IMC-1121B.** From a microbiological point of view, the prepared product should be used immediately. If not used immediately, in-use storage time and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C (36°F - 46°F). IMC-1121B should be protected from light when being stored.

8.3.7 Route of Administration

The infusion should be delivered over 60 minutes. The infusion rate should not exceed 25 mg/minute. An infusion set (non-vented for plastic or vented for glass container) equipped with a downstream in-line, 0.2-µm or 0.22-µm protein-sparing filter is required for administration of IMC-1121B or placebo. The infusion tubing must be flushed with normal saline to ensure delivery of the calculated dose.

8.3.8 Incompatibilities

No formal drug interaction studies have been performed with IMC-1121B in humans.

8.3.9 Availability

Ramucirumab is an investigational agent (IND 109448), available free of charge and distributed by ImClone Systems. Ramucirumab is available as an injectable solution, in single-use, 50-ml vials containing 500 mg at a concentration of 10mg/ml. The histidine buffer contains 10mM histidine, 75mM sodium chloride, 133mM glycine and 0.01% Tween® -80.

**Starter Supply**

Following submission and approval of the required regulatory documents as outlined in Section 4 a five cycle starter supply (ten 50-ml vials containing 500 mg at a concentration of 10mg/ml) of Ramucirumab may be ordered from ImClone Systems.

Investigators must fax a completed E7208 Drug Request Form (See Appendix IV) to ImClone Systems at 908-218-0963. **When completing the E7208 Drug Request Form indicate “Starter Supply” under number of vials.**

Ramucirumab will be shipped to a responsible person (e.g., a pharmacist) at the investigator’s institution. Vials are shipped in refrigerated shippers to maintain temperature between 2°C - 8°C. Vials must be kept refrigerated between 2°C - 8°C at all times. IMC-1121B should be protected from light when being stored. **DO NOT FREEZE OR SHAKE IMC-1121B.**
Institutions should allow 7 business days (excluding Fridays) for shipment of drug from ImClone Systems from receipt of the E7208 Drug Request Form. Shipments will be made from ImClone Systems on Monday through Thursday for delivery on site Tuesday through Friday. There will be no weekend or holiday delivery of drugs. The E7208 Drug Request Form can be downloaded from the ECOG website in WORD format.

**Initial Drug Orders for Each Patient**

Following submission and approval of the required regulatory documents and patient registration, a supply of Ramucirumab may be ordered from ImClone Systems. Investigators must fax a completed E7208 Drug Request Form (See Appendix IV) to ImClone Systems at 908-218-0963.

Ramucirumab will be shipped to a responsible person (e.g., a pharmacist) at the investigator's institution. Vials are shipped in refrigerated shippers to maintain temperature between 2ºC - 8ºC. Vials must be kept refrigerated between 2ºC - 8ºC at all times. IMC-1121B should be protected from light when being stored. DO NOT FREEZE OR SHAKE IMC-1121B.

The initial request will be for a sufficient number of vials to complete three cycles (i.e. six week supply at 8mg/kg IV every two weeks) based on the patient's weight in "kg" at the time of patient registration.

Institutions should allow 7 business days (excluding Fridays) for shipment of drug from ImClone Systems from receipt of the E7208 Drug Request Form. Shipments will be made from ImClone Systems on Monday through Thursday for delivery on site Tuesday through Friday. There will be no weekend or holiday delivery of drugs. The E7208 Drug Request Form can be downloaded from the ECOG website in WORD format.

**Important Reorder Instructions**

Once it is determined that the patient will continue treatment, please reorder study drug immediately. Reorders should be a sufficient number of vials to complete three cycles (i.e. six week supply at 8mg/kg IV every two weeks) based on the patient’s weight in “kg” at the time of patient registration. Dose and volume of the drug are dependent upon the patient’s baseline body weight in kilograms. The dose should be recalculated if there is a 10% change in body weight from baseline.

Institutions should allow 7 business days (excluding Fridays) for shipment of drug from ImClone Systems from receipt of the E7208 Drug Request Form. Shipments will be made from ImClone Systems on Monday through Thursday for delivery on site Tuesday through Friday. There will be no weekend or holiday delivery of drugs. The E7208 Drug Request Form can be downloaded from the ECOG website in WORD format.
Drug Destruction and Return

When all patients have completed treatment at your institution, all unused, partially used, expired or empty containers must be destroyed at the site according to the institution’s policy for drug destruction. Please maintain appropriate records of the disposal, including dates and quantities. Sites are required to complete the Investigational Agent Disposition Form located in Appendix V. A copy of this form should be sent to Lisa Kennedy at lisa.kennedy@imclone.com.

Drug Inventory Records

Investigational Product Records at Investigational Site(s): It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried.

Please note that expiration dates are not listed on the vials. Lot numbers and related expiration dates are listed on the Drug Product Request Shipment Form which is shipped with the vials. Sites should keep a copy of this form as part of their drug inventory records.

8.3.10 Side Effects

Adverse events of concern, which may or may not be associated with IMC-1121B therapy, include infusion reactions, hypertension, arterial or venous thrombotic events, proteinuria, bleeding, headache and fatigue.

8.3.11 Nursing/Patient Implications

1. Monitor patient closely during infusion, for infusion related events.
2. Monitor blood pressure prior to each dose to assess for development of hypertension.
3. Instruct patient to monitor and report signs/symptoms of: bleeding (nose bleeds, blood in sputum), wound healing problems, abdominal pain, thromboembolic problems (chest or leg pain, dyspnea, vision changes, severe headache, cough, swelling)
4. Baseline urine protein must be performed and repeated every six weeks. If elevated, 24 hour urine collection must be performed.
5. Treat pain, arthralgias, etc. with acetaminophen, or other pain relief strategies that do not interfere with the clotting cascade.

Safety Precautions

Appropriate mask, protective clothing, eye protection, gloves, and Class II vertical-laminar-airflow safety cabinets are recommended during preparation and handling. Opened vials must be disposed of at the investigational center as chemotherapy or biohazardous waste provided documented procedures for destruction are in place. Otherwise, opened vials must be returned to Imclone for disposal. For questions regarding IMC-1121B destruction please contact Imclone at 866 339-4267 or 203 677-7017.
IMC-1121B therapy should be used with caution in patients with known hypersensitivity to cetuximab, murine proteins, or any component of this product.

It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving IMC-1121B as sunlight can exacerbate any skin reactions that may occur.
9. **Statistical Considerations**

9.1 Revised Statistical Design - Arms A (IC) and C (mICR)

**Safety Monitoring**

The revised investigational regimen (that is, Arm C (mICR), a revision of the previous investigational Arm B) will be examined among the first 16 patients enrolled to Arm C post the re-activation of the randomized trial. Randomization will commence to Arms A and C and for purposes of adverse event evaluation, close monitoring of the study will occur until 16 patients have been enrolled to Arm C and followed through 2 cycles of therapy. During this safety evaluation period all patients will be followed closely with monthly conference calls of the study team and independent toxicity monitor to review all real-time AdEERS reports and any case report form reported treatment-related adverse events. At the time of suspension of this study prior to reactivation, the accrual rate was about 3-4 patients per month. Given this expected recruitment pattern upon initially re-opening the study, it appears reasonable to have calls on a monthly basis. Once fully reactivated, the accrual rate should be 10 patients per month. If the accrual pattern is substantially higher during the first few months after reactivation, the study team will convene calls every two weeks.

The toxic death rate on Arm B (ICR) prior to study suspension was 2/16 patients or 12.5%. With 16 patients on Arm C (mICR) evaluated under the new regimen the probability of observing 1 or more toxic deaths is 81.5% if the true toxic death rate is 10% and 88.2% under a true toxic death rate of 12.5%. No toxic deaths were observed in Arm A prior to suspension among 18 treated patients. Under the revised design with 16 patients evaluated on Arm C (mICR) the probability of observing one or more toxic deaths under a true toxic death rate of 0.77% is 11.6%. If one or more toxic deaths occur at any point during the 16 patient evaluation of Arm C, the study will close to accrual and the regimen will be abandoned.

The safety evaluation will also closely assess all treatment-related toxicities other than those of grade 5 with a particular emphasis on evaluating grade 3 and 4 events. Prior to suspension the grade 3 or higher treatment-related adverse event rate on Arm A was 16.7%. With 16 patients on Arm C there is 81% power to detect a true grade 3 or higher toxicity rate of 39% (versus a null of 16.7%) and 90% power to detect a true rate of 44% using a one-sided exact binomial test at the 11% significance level (evaluating Arm C separately as the power for the two-group comparison is limited). The observed grade 3 or higher toxicity rate on Arm B was 87.5%. If the grade 3 or higher toxicity test is significant after 16 patients on Arm C, the study will suspend accrual and the feasibility of the revised regimen will be evaluated by the study team and independent toxicity monitor, including a detailed review of all grade 3 or higher treatment related events.

In addition, the evaluation of 16 patients randomized to Arm C will allow estimation of any given toxicity with a 90% confidence interval that is no wider than 44.3 percentage points and there is 56.0% probability of observing any given event (1 or more out of 16 patients) with a true frequency of 5% and 81.5% probability observing 1 or more events with true frequency of 10%.
Primary Efficacy Design

Patients will be randomized equally between the two treatment arms A (IC) and C (mICR) with stratification based on performance status (0 vs. 1), discontinuation of oxaliplatin before disease progression (Yes vs. No), and time frame of progression (within 6 months of last treatment vs. > 6 months since last treatment). Patients previously randomized to arms A and B before the redesign of the experimental regimen will not be part of the formal efficacy evaluation and will be reported separately.

With 48 eligible patients per arm followed for progression-free survival (disease progression or death without evidence of progression), this study has over 85% power to detect a difference of 4.5 months median PFS in the control arm A (40% PFS at 6 months assuming exponential failure) versus 7.65 months median PFS (58% PFS at 6 months) in the experimental arm (Arm C) using a one-sided stratified log rank test conducted with 15% type 1 error. The study will require approximately 10 months of accrual at 10 patients per month and 6 additional months of follow-up to achieve the events required (67 PFS events) to provide at least 85% power for the stated alternative of a 48% increase in median PFS. Response, overall survival, and toxicity are secondary endpoints and will be reported at the time of primary PFS analysis. With 48 eligible patients per arm, the width of any 90% confidence interval on a binomial proportion will be no wider than 26 percentage points. In addition, the probability of observing a rare (2% probability) toxicity in either arm is greater than 62% at full accrual. Allowing for roughly 5% ineligibility and including the 35 patients who were previously randomized to Arms A and B of the study prior to its redesign, this study will require a total of 135 patients and 100 patients will be accrued to the revised study (Arm A versus Arm C).

This study will be monitored by the ECOG Data Safety Monitoring Committee (DSMC) for early stopping due to efficacy and futility. One interim stratified log rank test for efficacy will be performed at 60% PFS information (40 PFS events), expected to occur roughly at the time accrual completes and six months before full information is achieved. Type I error control will be accomplished using an O'Brien-Fleming type boundary, with Lan-Demets use function methodology to adjust the boundary for the exact information time achieved at the interim analysis. If the study is positive, the DSMC may recommend early reporting; there is at least 55% probability of rejecting the null at the interim analysis if the alternative hypothesis is true. At the interim analysis time, the PFS hazard ratio will also be computed from a stratified proportional hazards regression model. If the HR exceeds 1 (that is, evidence that PFS is worse in the experimental Arm C), the DSMC may recommend abandoning the regimen and early reporting of negative results. The effect of the interim analysis on the operating characteristics of the trial is fairly small (less than 1% absolute effect on significance level and power).

Additional Safety Monitoring

In addition to the safety monitoring that will occur in the first 16 patients randomized to Arm C (described above), interim analyses of toxicity are performed twice yearly for all ECOG studies. Reports of these analyses are sent to the ECOG Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 5.2 and ECOG Coordinating Center’s real-time monitoring.
of events through AdEERS report notifications will be in place for this trial. This system provides monthly notifications to the study chair, study statistician and independent toxicity monitor of certain reportable grade 4 or higher events and all grade 5 events.

Rev. 6/14

9.2 Original Statistical Design (Arms A and B)

Patients will be randomized equally between the two treatment arms with stratification based on performance status (0 vs. 1), discontinuation of oxaliplatin before disease progression (Yes vs. No), and time frame of progression (within 6 months of last treatment vs. > 6 months since last treatment). With 70 eligible patients per arm followed for progression-free survival (disease progression or death without evidence of progression), this study has 90% power to detect a difference of 4.5 months median PFS in the control arm (40% PFS at 6 months assuming exponential failure) versus 7.65 months median PFS (58% PFS at 6 months) in the experimental arm using a one-sided log rank test conducted with 10% type 1 error. The study will require approximately 7 months of accrual at 20 patients per month and 7 additional months of follow-up to achieve the events required (100 PFS events) to provide 90% power for the stated alternative of a 70% increase in median PFS. Response, overall survival, and toxicity are secondary endpoints and will be reported at the time of primary PFS analysis. With 70 eligible patients per arm, the width of any 90% confidence interval on a binomial proportion will be no wider than 21 percentage points. In addition, the probability of observing a rare (1% probability) toxicity in either arm is greater than 50% at full accrual. Allowing for 5% ineligibility, this study will require a total of 147 patients.

Safety Monitoring

Interim analyses of toxicity are performed twice yearly for all ECOG studies. Reports of these analyses are sent to the ECOG Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 5.2 and ECOG Coordinating Center’s real-time monitoring of events through AdEERS report notifications will be in place for this trial. This system provides monthly notifications to the study chair, study statistician and independent toxicity monitor of certain reportable grade 4 or higher events and all grade 5 events.

In addition to ECOG’s routine semi-annual reporting of case report form toxicities through interim study reports and real-time monitoring of adverse events through AdEERS, this study will include a detailed toxicity review of both treatment arms after 20 patients on each arm have been treated with at least two cycles of therapy. After 20 patients have been randomized per arm, the study will suspend accrual. After the first 20 patients have been treated with at least 2 cycles of therapy, there will be a formal toxicity review once all cycle 2 treatment forms and associated adverse event forms through this treatment period have been submitted to the ECOG Coordinating Center. The study statistician will prepare a report of all case report form and AdEERS reportable events for review by the study team and independent toxicity monitor. The study will remain suspended until the review is complete.

With 20 patients per arm, there is greater than 55% probability of observing one or more rare (true probability of 4%) toxicities on either arm and greater than 87% chance of observing one or more toxicities with true rate in excess of 10%.
If 4 or more patients experience grade 4 or worse treatment-related events in an arm, consideration will be given to closing the trial or modifying the treatment regimens. Under this monitoring rule, there is less than 2% probability of meeting the monitoring boundary if the true grade 4 or higher toxicity probability is 5% but 89% chance of meeting the boundary if the true probability is 30%. For other true grade 4 probabilities of 10%, 20% and 25%, the corresponding probabilities of reaching the boundary are 13%, 59% and 77%, respectively. Toxicity analyses will be conducted separately in each arm. In addition to grade 4 toxicities, differences between the treatment arms with respect to all grade toxicities, grade 3-4 toxicities, and non-hematologic toxicities will be assessed. If it is deemed necessary by the study team/independent toxicity monitors, an additional interim safety assessment will be conducted.

Grade 5 events will also be separately monitored and reported. The recently reported EPIC trial (Sobrero et al., 2008) observed a toxic death rate of 0.77% in the cetuximab plus irinotecan arm (5 deaths among 650 patients). Taking 0.77% as the null toxic death rate for either arm in this trial and 5% or higher as an unacceptable alternative toxic death rate, we will consider modifying or closing the trial if in either arm 1 or more treatment-related toxic deaths are observed among the first 20 treated patients. Under the null hypothesis there is a 14% probability of observing one or more grade 5 events in the first 20 patients and 64% probability under the alternative. If the true grade 5 event rate is as high as 10%, there is 88% probability of observing 1 or more toxic deaths in the first 20 patients treated on an arm. In addition to the toxicity analysis at suspension, grade 5 events will be continuously monitored, reported and reviewed as indicated above. At full accrual, the probability of observing 2 or more grade 5 events out of 70 patients in an arm is 10% under the null hypothesis and 87% under the alternative hypothesis.

9.3 Study Monitoring

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

Based on previous data from E3200 the anticipated accrual in subgroups defined by gender and race is:

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>0</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>50</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of all subjects</strong></td>
<td>50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Category</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Black or African American</td>
<td>5</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>45</td>
<td>78</td>
<td>123</td>
</tr>
<tr>
<td><strong>Racial Category: Total of all subjects</strong></td>
<td>50</td>
<td>85</td>
<td>135</td>
</tr>
</tbody>
</table>

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.
10. Pathology Review

Paraffin-embedded tumor and normal mucosa tissue specimens are to be submitted for research from patients who consent “Yes” to “May your coded samples and related coded information be kept for use in research to learn about, prevent, find or treat cancer?” Paraffin blocks are being collected from this study for the purpose of tissue banking for use in future research and will be retained indefinitely at the ECOG Central Repository for use in future studies.

Appendix II, Pathology Submission Guidelines, is available for distribution to the pathologist, outlining the submission requirements.

NOTE: ECOG requires that all samples submitted must be entered and tracked via the online ECOG Sample Tracking System for purposes of monitoring compliance and determination of reimbursement levels. See Section 10.3.

10.1 Materials Required For This Protocol

10.1.1 Forms – Must be sent with each submission

- ECOG Pathology Material Submission Form (#638 v04.2), Parts A & B completed. Please identify the clinical status of the submitted material (i.e., pretreatment as opposed to remission and relapse).
- A copy of the surgical pathology report
- Immunologic studies, if available
- Sample Tracking System Shipping Manifest

10.1.2 Biological Material

- One H & E stained slide of the tumor
- One paraffin block from representative sections of primary tumor
- One paraffin block from normal colon tissue

NOTE: If tissue blocks are not available, please contact the ECOG Pathology Coordinating Office – Reference Laboratory (PCORL) at 312-503-3384 to discuss alternative submission requirements. If pathology materials cannot be submitted, please indicate the reason on the ECOG Pathology Material Submission Form (#638 v04.2) and include a letter of explanation.

10.2 Shipping Procedures

Tissue specimens and the required forms and reports are to be submitted within 1 month of patient registration to:

ECOG Pathology Coordinating Office
Robert H. Lurie Comprehensive Cancer Center
of Northwestern University Medical School
Olson Pavilion - Room 8421
710 North Fairbanks Court
Chicago, IL 60611
Tel: (312) 503-3384
FAX: (312) 503-3385
10.3 ECOG Sample Tracking System

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

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

**Important:** Any case reimbursements associated with specimen submissions may not be captured if specimens are not logged into STS. Additionally, please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: [http://www.ecog.org/general/stsinfo.html](http://www.ecog.org/general/stsinfo.html). Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest should be shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to [ecog.tst@jimmy.harvard.edu](mailto:ecog.tst@jimmy.harvard.edu)

**Study Specific Notes**

If STS is unavailable at time of sample submission, submit the specimens with the required documentation and retroactively enter the information when STS is available. Notify the PCORL the day of shipment either by phone or e-mail ([ecogpcorl@jimmy.harvard.edu](mailto:ecogpcorl@jimmy.harvard.edu)).

10.4 Banking

Specimens submitted will be retained at the ECOG Central Repository for possible use in future ECOG approved studies. Residual blocks will be available for purposes of individual patient management on specific written request. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

10.5 Sample Inventory Submission Guidelines

Inventories of all samples collected, aliquoted, and used on the above mentioned laboratory correlative study(ies) will be submitted to the ECOG Coordinating Center on a monthly basis. Inventories will be submitted electronically or by diskette by any laboratory holding and/or using any specimens associated with this study. Electronic submissions should be submitted to [ecog/labdata@jimmy.harvard.edu](mailto:ecog/labdata@jimmy.harvard.edu). All other correspondence should be addressed to the attention of the Correlative Science Team.
11. Records to Be Kept

Please refer to the E7208 Forms Packet for the forms submission schedule and copies of all forms. The E7208 Forms Packet may be downloaded by accessing the ECOG World Wide Web Home Page (http://www.ecog.org). Forms must be submitted to the ECOG Coordinating Center, FSTRF, 900 Commonwealth Avenue, Boston, MA 02215 (ATTN: DATA).

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG Coordinating Center to CTEP by electronic means.

11.1 Records Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study is being conducted under an IND. All records pertaining to the trial (including source documents) must be maintained for:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

Please contact the ECOG Coordinating Center prior to destroying any source documents.

12. Patient Consent and Peer Judgment

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

13. References


36. Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, Simes RJ, Chalchal H, Shapiro JD, Robitaille S, Price TJ, Shepherd L, Au HJ,

A Randomized Phase II Study of Irinotecan and Cetuximab with or without the Anti-Angiogenic Antibody, Ramucirumab, in Advanced, K-ras Wild-type Colorectal Cancer Following Progression on Bevacizumab-Containing Chemotherapy

Appendix I

Informed Consent Template for Cancer Treatment Trials (English Language)
[Deleted in Addendum #5]

INFORMED CONSENT INTENTIONALLY REMOVED FROM PROTOCOL DOCUMENT

Appendix I was removed from the protocol document in Addendum #5 and is posted as a separate document on the ECOG website. This was removed from the protocol to comply with NCI formatting guidelines.
Appendix II

Pathology Submission Guidelines

The following items are included in Appendix II:

1. Guidelines for Submission of Pathology Materials
   (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. List of Required Materials for E7208
4. ECOG Pathology Submission Form (#638 v04.2)
Guidelines for Submission of Pathology Materials

The following items should always be included when submitting pathology materials to the ECOG Pathology Coordinating Office:

- Institutional Surgical Pathology Report
- Pathology materials (see attached List of Required Material)
- ECOG Pathology Material Submission Form (#638 v04.2)

Instructions:

1. Place the Patient ID label provided by the ECOG Coordinating Center in Part A of the ECOG Pathology Material Submission Form.

   If a label is not available, TYPE or PRINT the following information in Part A of the form:
   - Patient's name (last, first)
   - Protocol number
   - Protocol case number (the patient's ECOG sequence number; for intergroup studies, include both the ECOG and other group's sequence numbers)
   - Patient's hospital number
   - Institution
   - Affiliate (if appropriate)

2. Complete blank areas of the pathologist's instructional memo and forward it, along with the List of Required Material and the ECOG Pathology Material Submission Form, to the appropriate pathologist.

3. The pathologist should return the required pathology samples and surgical pathology reports, along with the completed ECOG Pathology Material Submission Form (#638 v04.2) (Part B completed). If any other reports are required, they should be obtained from the appropriate department at this time.

4. Keep a copy of the ECOG Pathology Material Submission Form (#638 v04.2) for your records. (The original should be sent to the PCO.)

5. Double-check that ALL required forms, reports and pathology samples are included in the package to the Pathology Coordinating Office. (See appropriate List of Required Material.)

   Pathology specimens submitted WILL NOT be processed by the Pathology Coordinating Office until all necessary items are received.

6. Mail pathology materials to:

   ECOG Pathology Coordinating Office
   Robert H. Lurie Comprehensive Cancer Center
   of Northwestern University Medical School
   Olson Pavilion - Room 8421
   710 North Fairbanks Court
   Chicago, IL  60611

If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG Pathology Coordinating Office by telephone (312) 503-3384 or by fax (312) 503-3385.
List of Required Material

**E7208:** A Randomized Phase II Study of Irinotecan and Cetuximab with or without the Anti-Angiogenic Antibody, Ramucirumab, in Advanced, K-ras Wild-type Colorectal Cancer Following Progression on Bevacizumab-Containing Chemotherapy

**Pre-Treatment**

1. ECOG Pathology Material Submission Form (#638 v04.2) – Parts A & B completed. *[or appropriate pathology submission form]*

2. Institutional pathology report *(must be included with EVERY pathology submission).*

3. Biological materials
   - One H & E stained slide of the tumor
   - One paraffin block from representative sections of primary tumor
   - One paraffin block from normal colon tissue

**NOTE:** If tissue blocks are not available, please contact the ECOG Pathology Coordinating Office – Reference Laboratory (PCORL) at 312-503-3384 to discuss alternative submission requirements.
MEMORANDUM

TO: ___________________________________________________________
   (Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
       ECOG Laboratory Science and Pathology Committee

DATE: __________________________________________________________

SUBJECT: Submission of Pathology Materials for E7208: A Randomized Phase II
          Study of Irinotecan and Cetuximab with or without the Anti-Angiogenic
          Antibody, Ramucirumab, in Advanced, K-ras Wild-type Colorectal
          Cancer Following Progression on Bevacizumab-Containing
          Chemotherapy

The patient named on the attached ECOG Pathology Material Submission Form (#638
v04.2) has been entered onto an ECOG protocol by ________________________
(ECOG Investigator). This protocol requires the submission of pathology materials for
banking for future research.

Please complete PART B of the Submission Form. Keep a copy for your records and
return the completed Submission Form, the surgical pathology report(s), the slides
and/or blocks and any other required material (see List of Required Material) to the
Clinical Research Associate (CRA). The CRA will forward all required pathology
material to the ECOG Pathology Coordinating Office.

Blocks and slides submitted for this study will be retained at the ECOG Central
Repository for future studies. Paraffin blocks will be returned upon written requested for
purposes of patient management..

If you have any questions regarding this request, please contact the Pathology
Coordinating Office at (312) 503-3384 or FAX (312) 503-3385.

The ECOG CRA at your institution is:

Name: _________________________________________________________
Address: _____________________________________________________
Phone: ________________________________________________________

ECOG Laboratory Science and Pathology Committee
Eastern Cooperative Oncology Group
Coordinating Center
Frontier Science
900 Commonwealth Avenue • Boston, MA 02215
(617) 632-3610 • Fax: (617) 632-2990
Randomization: (617) 632-2022
ECOG DIAGNOSTIC PATHOLOGY MATERIAL SUBMISSION FORM

Instructions: This form is a required part of pathology submission. Please complete and submit along with all pathology material and corresponding pathology reports requested by the protocol. See list of required materials as specified in EACH protocol.

ECOG PCO-RL IS FULLY-COMPLIANT WITH DHHS, HIPAA, AND OHRP REGULATIONS
Tel. 312-503-3384
Fax 312-503-3385

PART A: To Be Completed By Data Manager/CRA

<table>
<thead>
<tr>
<th>Date sample sent to ECOG</th>
<th>Status* (See Below)</th>
<th>Date Specimen Collected (M/D/Y)</th>
<th>Disease Site</th>
<th>Number of Slides/Vials</th>
<th>Specimen ID Numbers</th>
<th>Type of Stain</th>
<th>PCO ID Numbers</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Complete for Blocks/Punch</th>
<th>Status* (See Below)</th>
<th>Date Specimen Collected (M/D/Y)</th>
<th>Disease Site</th>
<th>Number of Blocks/Punch</th>
<th>Specimen ID Numbers</th>
<th>Fixative</th>
<th>PCO ID Numbers</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td></td>
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</tr>
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<td></td>
<td></td>
<td>/ /</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Status: Please identify the clinical status of the sample. List all that apply:
1. Original diagnostic material
2. AML/MDS diagnosis
3. Pre-protocol treatment biopsy/tissue
4. Post-protocol treatment biopsy/tissue
5. Post-surgery biopsy/tissue
6. Relapse/recurrence
7. Remission/response
8. Other, specify: ______________

PART B: TO BE COMPLETED BY DATA MANAGER/CRA AND SUBMITTING PATHOLOGIST

PCO-RL Use Only

Did the patient consent to participate in the storage of samples for future research? Yes No

MATERIAL RETURN (All materials will be retained by the ECOG PCO unless return is requested here.)

Does the submitting institution’s policy require the return of any submitted material (blocks, H&E slides, etc.)? Yes No

If so, please indicate which materials must be returned

If materials were not able to be submitted for this protocol and its correlative studies, please circle the reason for non-submission. Attach a formal letter referencing regulations, policy, and/or other explanation. If possible, include a copy of the policy.

Federal/State Regulations _____ Hospital/Institutional Policy _____ Insufficient Tissue _____ Other _____ (Specify) ______

Pathologist of Investigator’s Signature ______________

PART C: ECOG PATHOLOGY COORDINATING OFFICE USE ONLY

Date Sample Received at PCO / / Date Sent to Reviewer / / Date Sent to PI/Central Lab / / Site Compliance %

Name of Reviewer ___________ PI/Central Lab ___________

PCO Comments: ______________

Investigator: Keep a copy for your files and submit original form to the destination specified in protocol. 2/05
Appendix III

Patient Thank You Letter

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

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

________________________________________________________________________

PATIENT NAME          DATE
PATIENT ADDRESS

Dear PATIENT SALUTATION,

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

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of INSTITUTION and the Eastern Cooperative Oncology Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]
A Randomized Phase II Study of Irinotecan and Cetuximab with or without the Anti-Angiogenic Antibody, Ramucirumab, in Advanced, K-ras Wild-type Colorectal Cancer Following Progression on Bevacizumab-Containing Chemotherapy

Appendix IV

Clinical Study Product Request Form

To: Clinical Operations
Phone: 908-541-8129
Fax: 908-218-0963
Email: DrugRequests@ImClone.com

From:

Institution / Site:
Investigator:
Date of Request:

PROTOCOL NUMBER: E7208/MED-P12-10001

☐ Initial Drug Request
☐ Subsequent Drug Request, If Yes, check that the following has been reviewed and approved.
  ☐ IRB/EC Approval is current
  ☐ There are no compliance issues that would warrant suspension of drug

Clinical Study Product: Ramucirumab (IMC-1121B) Include MSDS: ☐ Yes  ☐ No
Dosage Strength / Form: 50mL, 500mg/vial (10mg/mL)

Number of Vials Needed:

Ship to:
Address:

Telephone:

Drug Product needed no later than:
(Please give 7 day notice for orders, drug requests will not be accepted after 2:00PM EST. Drug will not be shipped on Fridays.)

Please fax or email this form to Clinical Operations then file this document in your study binder.
**To be completed by ImClone Systems:**

COS/MED
(sign and print name):

(Medical Affairs or Clinical approval signature must be obtained for all drug shipments.)

Requisition Number:

SAP Material Code Number:

Clinical Operations/Medical Affairs Management or designee
(sign and print name):

(Medical Affairs or Clinical approval signature must be obtained for all drug shipments.)

**To be completed by Logistics Warehouse:**

Request Received By (sign and print name):

Date (DDMMYYYY):_______________

Lot Number: ____________ Manufacture Date_______________

Quantity:_______________________

Shipped by (sign and print name):

______________________________

Date (DDMMYYYY):_______________
**Appendix V**

**Disposition Form**

**To Be Completed By Site Personnel**

<table>
<thead>
<tr>
<th>Investigator:</th>
<th>Site Name / No.:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Protocol Number:** E7208/MED-P12-10001  
**Product:** Ramucirumab (IMC-1121B)

**Lot #:**  
**Quantity:**

☐ Returned  ☐ Destroyed at Site: (Complete reason, method, and location of destruction)  ☐ Transfer to:

**Reason for Destruction:**

**Method of Destruction:**

**Location of Destruction:**

**Pharmacist:**

**Phone #:**

**Signature:**

**Date:**

**To Be Completed By ImClone**

**I. Reason for Return:**

☐ Is an Investigation Required?  ☐ Yes  ☐ No

**II. Inspection:**

<table>
<thead>
<tr>
<th>Date Received:</th>
<th>Quantity Received:</th>
</tr>
</thead>
</table>

☐ Satisfactory  ☐ Unsatisfactory

<table>
<thead>
<tr>
<th>Shipper Container Integrity</th>
<th>Product Container Integrity</th>
<th>Temperature Indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Satisfactory</td>
<td>☐ Satisfactory</td>
<td>☐ Satisfactory</td>
</tr>
<tr>
<td>☐ Unsatisfactory</td>
<td>☐ Unsatisfactory</td>
<td>☐ Unsatisfactory</td>
</tr>
</tbody>
</table>

**Comments:**

**III. Disposition:**

☐ Preclinical Inventory  ☐ Destroyed

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Quantity</th>
</tr>
</thead>
</table>

**Approval**

**Signature**

**Comments:**
A Randomized Phase II Study of Irinotecan and Cetuximab with or without the Anti-Angiogenic Antibody, Ramucirumab, in Advanced, K-ras Wild-type Colorectal Cancer Following Progression on Bevacizumab-Containing Chemotherapy

Appendix VI

Reimbursement Invoice

PLACE PATIENT ID LABEL HERE

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Date of Service</th>
<th>Service Performed</th>
<th>Amount Requested (please itemize costs)</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

Please Note:
Amount requested may not exceed $150 per EKG, $50 per UPC and $75 per Pregnancy Test.

If a test falls outside of the scheduled cycle, please provide a brief explanation below:

__________________________________________________________________________

A copy of the test results for each service performed is attached.

If there are problems with this invoice, please contact:

Name ___________________________ Phone ___________________________ Fax ___________________________ Email ___________________________

If you have questions about the reimbursement process, please contact Meghan Cosby at cosby.meghan@jimmy.harvard.edu or 617-632-3610.

Please fax the completed form along with the related test results to 617-632-2063.
Appendix VII

Substitute W-9 Tax Form

Instructions

1. This form is a substitute to the Internal Revenue Service W-9 Tax Form. In addition to capturing all of the information required by the IRS, it also collects other information that is needed for our records. Questions regarding this form should be directed to the Pharmaceutical Liaison at the ECOG Coordinating Center 617-632-3610. Please note that only US-based institutions can use this form.

2. Complete all requested information and sign the substitute W-9 form. The original copy should be submitted to the ECOG Coordinating Center as soon as possible.

<table>
<thead>
<tr>
<th>Please provide the legal name and address of the organization associated with the Federal Tax Identification Number listed in this section. (Generally, the corporate headquarters address of the university, hospital, or business should be provided. This information will be used for income reporting to the IRS and your organization).</th>
</tr>
</thead>
</table>
| Legal Name:  
Corporate Address:  
City:  
State:  
ZipCode:  
NCI CTEP ID:  
Federal Tax Identification Number:  
Phone Number: |

<table>
<thead>
<tr>
<th>Please identify the organization’s preferred payment address. ECOG will use this information for mailing checks to the organization. Please note that while ECOG can submit payment to an alternate address, it cannot make checks payable to a different organizational name or to a third party.</th>
</tr>
</thead>
</table>
| Payment Address:  
City:  
State:  
ZipCode:  
Phone Number:  
Fax Number:  
E-mail:  
Is this payment address affiliated with the Federal Tax ID listed above?: |

<table>
<thead>
<tr>
<th>Please identify whether the organization has a special status as defined by the following criteria: (Select all that apply)</th>
</tr>
</thead>
</table>
| Minority Business Enterprise (at least 51% minority-owned and managed business)  
Woman’s Business Enterprise (at least 51% woman-owned and managed business)  
Small Disadvantaged Business (as certified by the SBA)  
Veteran Business Enterprise (at least 51% veteran-owned business)  
Historically Underutilized Small Business (as certified by the SBA)  
None of the Above |

Under penalties of perjury, I certify that all of the information provided above is correct and that my organization is not subject to back-up withholding.

| Printed Name:  
Title:  
Signature:  
Date: |
## Appendix VIII

### E7208 Temperature Excursion Form

<table>
<thead>
<tr>
<th>DOCUMENT NUMBER: LOG-FR-0346</th>
<th>REVISION NUMBER: 03</th>
<th>PAGE: 1 of 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE: Clinical Supplies Temperature Out Of Range Form</td>
<td>LOCATION: ALL</td>
<td></td>
</tr>
<tr>
<td>APPROVAL DATE: 11/22/10</td>
<td>EFFECTIVE DATE: 11/23/10</td>
<td>SUPERSEDES DATE: 08/23/10</td>
</tr>
</tbody>
</table>

**Clinical Site Excursion**
Complete Section 1 of this form and send with temperature data to tempexcursions@imclone.com or fax this form to 1-908-203-6840 or 1-877-784-3508

**TempTale 4 Transit Excursion**
Complete Sections 1 and 2 of this form and send to tempexcursions@imclone.com or fax this form to 1-908-203-6840 or 1-877-784-3508, then return TempTale 4 to distributor

**TempTale USB Transit Excursion**
Complete Section 1 of this form, download temperature data and send both to tempexcursions@imclone.com, or fax this form and data to 1-908-203-6840 or 1-877-784-3508

### Section 1

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**Site Contact Name:**
**Site Contact Title:**
**Site Email:**
**Site Fax with Country Code:**

**Clinical Supply Logistics Authorization (To be completed by ImClone)**

- [ ] Product is acceptable for use
- [ ] Product is not acceptable for use – Do Not Use This Drug

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ImClone Systems Corporation. Branchburg, New Jersey 08876 Refer to LOG-SY-0003
Document printed on 2/24/2011
A Randomized Phase II Study of Irinotecan and Cetuximab with or without the Anti-Angiogenic Antibody, Ramucirumab, in Advanced, K-ras Wild-type Colorectal Cancer Following Progression on Bevacizumab-Containing Chemotherapy

Version Date: December 17, 2013

Informed Consent Template for Cancer Treatment Trials
(English Language)

You are being asked voluntarily to take part in this study because you have colon or rectal cancer that has spread to other organs or has come back locally with the first choice of treatment and your tumor is now progressing while being treated with standard first-line therapy. This research is being done because current treatment does not help everyone with your disease.

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

**WHY IS THIS STUDY BEING DONE?**

The purpose of this study is to determine what good or bad effects the drug, ramucirumab, may have and to determine whether it is safe and effective for patients to receive in this setting. Irinotecan and cetuximab are standard treatments for patients who have metastatic colon or rectal cancer, who have already received one previous chemotherapy that is no longer working, and do not have a specific type of mutation (alteration) of the K-ras gene in their tumor. Ramucirumab is an experimental (not yet FDA-approved) drug that has been found to block a pathway that allows tumors to grow in animals and humans. It is unknown if adding a drug of this type to a standard second line therapy for colorectal cancer is beneficial. You will receive either the chemotherapy with the experimental drug or the chemotherapy alone, but you will not get both. Because there were more side effects at higher doses of the ramucirumab regimen, a new arm (Arm C) was added to replace Arm B. Arm C was revised to include lower starting doses of all three drugs (irinotecan, cetuximab and ramucirumab) reflecting the tolerated doses previously, and also greater dose reductions for toxicity. You and your doctors will know what treatment you are receiving. The chemotherapy with ramucirumab is considered experimental in this study.

**HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?**

About 135 patients in the United States and Canada will take part in this study (including those previously enrolled in the study with Arm B).
BEFORE YOU BEGIN THE STUDY

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

- A physical examination including your vital signs (body temperature, pulse rate, breathing and blood pressure), height and weight, questions about your medical history, and a list of medicines you are taking.
- Samples of your blood and urine will be collected.
- Female subjects of childbearing potential will have a pregnancy test.
- Imaging studies to assess your disease, which may include CT scans (a type of computerized x-ray) of your chest, abdomen, and pelvis to evaluate your tumor status.
- EKG

You will be evaluated based on the results of these tests in order to determine if you are eligible to participate in this study. If your physician finds that you are not eligible, then you will not receive this treatment as part of the study.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will be "randomized" into one of the study groups (Arm A or Arm C) described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in either of the two treatment arms. You and your study doctor will not be able to choose which study treatment you receive.

Arm A:

You will receive irinotecan and cetuximab every 14 days and it will take approximately 3 hours in the clinic for each treatment. Medications are given before chemotherapy to prevent nausea, vomiting and allergic reaction to the drugs given. Both of the chemotherapy drugs will be given intravenously (through a vein). The first time you receive cetuximab it will be over 120 minutes to minimize any possible allergic reactions to the drug. If there is no reaction to the drug all future doses may be given over 60 minutes. Irinotecan is given over 60-90 minutes.
Arm C:

You will receive Irinotecan, Cetuximab and the study drug Ramucirumab every 14 days and it will take approximately 4 hours in the clinic for each treatment. Medications are given before chemotherapy to prevent nausea, vomiting and allergic reaction to the drugs given. All of the chemotherapy drugs will be given intravenously (through a vein). Ramucirumab is given over 60 minutes. The first time you receive cetuximab it will be over 120 minutes to minimize any possible allergic reactions to the drug. If there is no reaction to the drug all future doses may be given over 60 minutes. Irinotecan is given over 60-90 minutes.

For each of the treatment arms, blood will be drawn (about 1 tablespoon or 15mL) prior to treatment to check blood counts, liver and kidney function (every two weeks), and a urine test (every six weeks). Based on the side effects you experience and the results of the blood and urine tests, the doses of the drugs may be changed to make sure you receive the dose of therapy you are able to tolerate.

Arm B: (Removed in Addendum #5)

How long will I be in the study?

We think you will be in the study for at least eight weeks before the status of the tumor is checked to see if the therapy is helping. If the status at that time shows that the tumor is either shrinking or not growing, and you tolerate the therapy, then you can continue on the same treatment every two weeks as long as the tumor is controlled and you wish to continue. If the tumor shows definite growth at any point, then the therapy will be stopped.

Can I stop being in the study?

Yes. You can decide to stop anytime. However, we encourage you to talk to your doctor before you decide to withdraw, to explain your reasons and to ask you what effect your decision may have on your cancer.

Your doctor may decide to take you off this study for the following reasons, even if you wish to stay on the study: growth of the cancer; you cannot tolerate treatment; your doctors feel that the risks of continuing on the study therapy are too great; you are unable to comply with the study guidelines for treatment and follow-up; if you become pregnant or start to breast-feed; or if the study is being stopped.
Study Chart

Medicines used in this study
Irinotecan, Cetuximab and Ramucirumab by vein - given once every 14 days

Randomize
(You will be in one Group or the other)

Arm A
Cetuximab & Irinotecan by vein every 14 days

Arm C
Ramucirumab, Cetuximab & Irinotecan by vein every 14 days
WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don’t know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. There may also be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and less uncomfortable. Many side effects go away shortly after the protocol therapy is stopped, but in some cases side effects can be serious, long-lasting, permanent or life-threatening. Death is rare, but possible.

Ramucirumab has not been given previously with either irinotecan or cetuximab. This combination may magnify the known side effects of these agents, or cause unexpected side effects. For that reason, this study includes careful monitoring.

Your doctor will check you closely to see if any of these side effects are occurring and routine blood tests will be done to monitor the effects of treatment. You should talk to your doctor about any side effects that you have while taking part in the study, and you should alert your care team upon experiencing high fever, altered mental status, or problems breathing after receiving your treatment.

Risks and side effects related to the drugs and procedures we are studying include:

**Irinotecan**

**More Likely**

- Diarrhea
- Nausea
- Vomiting
- Loss of appetite
- Decreased white blood cell count that increases your risk of infection
- Anemia
- Decreased number of platelets (that may cause easy bruising or bleeding)
- Hair loss
- Fatigue (feeling weak or tired)

**Less Likely**

- Constipation (trouble having bowel movements)
- Pain in the abdomen
• Runny nose and eyes
• Flushing (reddenning of the face)
• Sweating
• Stomach cramping and early diarrhea occurring during or right after the irinotecan*

* These early symptoms respond quickly to a medicine called atropine. If these immediate side effects occur, then you will get this medicine to prevent these symptoms with each following cycle.

Rare
• Skin rash
• Changes in certain blood tests that suggest irritation or inflammation of the liver
• Trouble sleeping
• Fever
• Shortness of breath

Cetuximab:

Likely:
• Diarrhea
• Nausea or the urge to vomit
• Fatigue or tiredness
• Fever
• Headache or head pain
• Dry skin
• Acne
• Skin rash that can affect the face, scalp, and neck, but sometimes can affect much of the rest of your body

Less Likely:
• Lack of enough red blood cells (anemia)
• Inflammation (swelling and redness) of the skin of outer ear and canal
• Noise in the ears, such as ringing, buzzing, roaring, clicking
• Swelling and redness of the the outermost layer of the eye and the inner surface of the eyelids commonly called "pink eye".
• Dry eyes
• Swelling and redness of the middle layer of the eye (uvea)
• Excessive tearing in the eyes
• Belly pain
• Swelling and redness of the lips
• Constipation (trouble having bowel movements)
• Dry mouth
• Heartburn
• Irritation or sores in the lining of the mouth
• Vomiting
• Chills
• Swelling of the arms and/or legs
• Flu-type symptoms (including body aches, fever, chills, tiredness, loss of appetite, cough)
• Allergic reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, swelling of the throat, and difficulty breathing.
• Chest pain not heart-related
• Infection
• Decreased white blood cell count that may increase your risk of infection
• Weight loss
• Loss of appetite
• Dehydration (when your body does not have as much water and fluid as it should)
• Decreased blood levels of certain body minerals such as calcium and magnesium which may cause muscle cramping or a sensation of tingling and numbness of your fingers and around your mouth area.
• Decreased blood level of magnesium
• Joint pain
• Back pain
• Muscle pain
• Fainting
• Stuffy or runny nose, sneezing
• Sudden tightening of the small airways of the lung that can cause wheezing and shortness of breath
• Cough
• Hoarseness (raspy or strained voice)
• Hair loss
• Loss of some or all of the finger or toenails
• Increased skin sensitivity to sunlight
• Itching
• Area of bleeding within the skin causing a reddish purple discoloration
• Sore or destruction of skin
• Hives
• Low blood pressure
• Formation of a blood clot within a blood vessel that can block the flow of blood through a vessel or break loose and travel through the blood stream and block the flow in the small vessel of another organ, such as the lung

Rare but Serious:
• Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.
• Inflammation of the lining of the brain and spinal cord
• Inflammation of the lungs that may cause difficulty breathing and can be life-threatening
• Fluid build-up in the lungs that is not due to a heart problem that can be life-threatening
• Swelling and redness of the skin on the palms of the hands and soles of the feet

Ramucirumab

Very Common Side Effects
• Lack of energy
• High blood pressure
• Headache
• Nosebleeds
• Nausea
• Diarrhea
• Vomiting
• Decrease or loss of appetite
• High level of protein in the urine
Common Side Effects

- Bleeding gums
- Coughing up blood
- Blood in the urine
- Low platelet count
- Swelling in the arms, legs, hands, or feet
- Infusion-related reactions. Symptoms include shaking, back pain or spasms, feeling cold, red skin, trouble breathing, rash, fever, headache, body aches, stomach pain, nausea, vomiting, blurry vision, chest pain and/or tightness, very fast heartbeat, low blood pressure, and tingling or burning in the hands or feet.
- Low or severely low red blood cell count.
- Weakness or weak muscles
- Feeling cold
- Bad taste in the mouth
- Skin problems such as rash, itching, acne, dry skin, or red skin
- Redness, tenderness, and peeling skin on the palms of the hands and soles of the feet
- Hair loss
- Skin condition resembling acne
- Trouble breathing
- Fever
- Pain in the joints, muscles (with or without cramping), back, chest, arms, or legs.
- Swelling and redness in the mouth, sometimes with pain
- Dry mouth
- Throat pain
- Feeling dizzy
- Weight loss
- Damage to your liver
- Upset stomach
- Stomach pain
- Blood clots in the veins, including veins in the lung or deep veins in the legs
- Tingling, burning, prickling, or numbness, usually in the hands, arms, legs or feet
- Some loss in the sense of touch
• Trouble speaking
• Coughing
• High blood sugar
• Damage to your kidneys
• Dehydration or, too little water in the body
• Low levels of potassium, magnesium, and phosphorus in the blood
• Trouble sleeping
• Heart damage
• Cardiac arrest or cardiorespiratory arrest
• Blurry vision
• Low blood pressure
• Bruising
• Decreased levels of albumin
  Hot flash

**Uncommon Side Effects**

• Liver failure
• Collapsed lung
• Infection throughout the body
• Damage to the walls of the stomach, intestines, or rectum (causing intestinal perforation – a hole in the wall)
• More acid than normal in the blood
• Multi-organ failure
• Difficulty forming blood clots
• Changes in how the brain functions that can cause confusion, headache, nausea, vomiting, and feeling wobbly.
• Severe intestinal bleeding and life-threatening bleeding ulcer
• Abnormal vaginal bleeding
• Bruising or bleeding under the skin
• Bleeding in the mouth, ear, eye, brain, or lung, or at the site of injection
• Tumor bleeding
• Bleeding after a procedure or surgery
• Blood in the stool

• Leukoencephalopathy, a loss of white matter of the brain, which may results in brain dysfunction, and can cause forgetfulness, confusion, headache, delirium, and total or partial blindness.
Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect a fetus. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. An appropriate method of birth control must be maintained for at least 3 months after treatment with ramucirumab. This applies to both men and women. Check with your doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

Risks in Children and Elderly Patients: The safety of ramucirumab in children and elderly patients has not been established.

Based on the initial 35 patients enrolled in the study, the combination with ramucirumab resulted in lower blood counts and more diarrhea and mouth sores (mucositis) compared with the standard arm of irinotecan and cetuximab. Additionally, there were a few more GI perforation events including peri-rectal abscess formation. Because of these findings, doses were reduced in the ramucirumab arm (Arm C) to the doses tolerated by the patients treated in Arm B.

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

**ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

Taking part in this study may or may not be direct medical benefits to you. Possible benefits are shrinkage of your tumor, improvement in your symptoms related to your cancer, and prolonged survival. We hope the information learned from this study will benefit other patients with colorectal cancer in the future.

**WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?**

Your other choices may include:

- Standard chemotherapy at this medical center and at other medical centers without being in a study
- Taking part in another study
- No treatment
- Supportive or comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.
WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

The Eastern Cooperative Oncology Group (ECOG) is conducting this study. ECOG is a cancer research group that conducts studies for the National Cancer Institute. Your doctor is a member of ECOG or another group that is participating in this study. To help protect your privacy, ECOG has obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS).

With this Certificate, ECOG cannot be forced (for example, by court subpoena) to disclose information that may identify you in any federal, state or local civil, criminal, administrative, legislative or other proceeding. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes.

You should know that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about you or your involvement in this research. If an insurer or employer learns about your participation and obtains your consent to receive research information, then ECOG may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your privacy.

You should also understand that your doctor and ECOG may take steps, including reporting to authorities, to prevent you from seriously harming yourself or others.

Finally, the Certificate allows the review of your research records under some circumstances by certain organizations for an internal program audit or evaluation. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:

- Eastern Cooperative Oncology Group (ECOG)
- National Cancer Institute (NCI)
- Food and Drug Administration (FDA)
- Other regulatory agencies and/or their designated representatives
- Drug manufacturers and/or their representatives
- Central laboratories, banks and/or reviewers
- Cancer Trials Support Unit (CTSU), a service provided by the National Cancer Institute (NCI) to provide greater access to cancer trials.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.
WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment. Additional tests, such as those required to monitor blood pressure, may not be covered by your insurance company.

If randomized to Arm C, the drug Ramucirumab will be provided free of charge for the duration of the study.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute’s Web site at:

http://www.cancer.gov/clinicaltrials/learningabout/payingfor

You can print a copy of the “Clinical Trials and Insurance Coverage” information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

In the event of injury or illness as a result of the study medications or procedures, you should seek medical treatment through your physician or treatment center of choice. You should promptly notify the study doctor in the event of any illness or injury. Payment for this treatment will be your responsibility.

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

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

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

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

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

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

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

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

For questions about your rights while taking part in this study, call the __________________ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at __________________ [telephone number]. [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). [*Only applies to sites using the CIRB.]

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in any of these additional studies.

You can say “yes” or “no” to each of the following studies. Please mark your choice for each study.
ABOUT USING SPECIMENS FOR RESEARCH

Please read this form and ask about anything that is not clear to you. This is part of the informed consent process for research. This is to inform you of the possible risks, benefits, and limits of giving your samples for research.

You are being asked to give some of your samples (called specimens) and related information to be stored (banked) for future research. This may help researchers learn more about how to prevent, find and treat cancer and other diseases.

The choice to have your samples used for research is up to you. No matter what you decide, it will not affect your medical care.

Below is some general information you should know before agreeing to allow the use of your specimens for research. After the general information there are descriptions of the research projects. Each project is described separately, including the types of samples requested and how they are collected. Each description is followed by questions concerning your participation in the project. Your samples will be used only for the projects in which you agree to participate.

What are samples and where are they stored?

A sample is any material taken from your body such as tissue, blood, urine and other fluids.

If you agree, your samples will be sent to laboratories to be used in research or will be stored for research in a Cooperative Group bank. These banks are supported by the National Cancer Institute. Cooperative Group banks contain samples and information. Your samples are kept along with those from other people in the banks. Researchers then ask for samples from the banks to study them.

What information will be collected?

When your samples are sent to any bank, some personal information will be sent with the samples. Any personal information sent with the samples is not given to other researchers. The personal information is used only by the bank to identify your samples. Your privacy will be protected to the fullest extent possible. This will be discussed later in the section “How will information related to my samples be protected?”

Examples of other information that might be used for research include:

- Dates of medical procedures
- Any diagnosis and stage of your disease (if you have cancer)
- Your age and race
- Medical and family history
- Treatments you had
- How you responded to treatments
What will happen to my samples if I agree to give them for research?

If you agree to let your samples be kept for future research (research not yet defined), your samples will be stored in a Cooperative Group bank. The samples will be kept until they are used up or destroyed. The samples are given a code to protect your privacy before they are used. Any related information given to researchers will also be coded. Researchers will receive the code instead of any information that might directly identify you.

You or your doctor will not be given reports or other information about the research that uses your samples. This information will not be put into your health record. Results may be used for future research.

You will not be named or identified by other personal information if any results are published. Most publications contain results from many patients.

Your samples and related information will be used only for research and will not be sold. It is possible that research may help to create new products or treatments. If this should happen, you will not be paid.

Coded data from some research studies that use samples could be put into secure Internet databases that can be shared by other approved researchers. This could include genetic data. Current safety rules are followed to safeguard your privacy. Your name or contact information will not be put in the database.

What kind of research will be done with my samples?

Many types of research use normal or diseased (cancerous) samples. Researchers can study proteins, RNA and DNA (genes). The study of genes (DNA) is often called genetic research.

For example, your samples may be looked at:

- To see if a trait is passed down in families from one generation to the next (inherited). This type of research may help to explain why some cancers run in families or why some people have side effects from treatment while others do not. This is often studied through blood cells and DNA (genes).
- To learn about changes in the body that happen after you were born (non-inherited). For example, being in the sun too much can cause changes in cells that lead to skin cancer.

Will it help me if I give my samples for research?

Using your samples for research will probably not help you. We do hope the research results will help people in the future. The best way to prevent, find or treat cancer and other diseases is by studying human samples and data.

What are the risks of giving my samples for research?

There is a risk that your information could be misused. The chance of this happening is very small. We have many protections in place to lower this risk. See the next section, “How will the information related to your samples be protected?” Your privacy will be protected to the fullest extent possible.
There can be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Even though your genes are unique, you share some of the same genes with your blood relatives. Very rarely health or genetic information could be misused by employers, insurance companies, and others. For example, life insurance companies may charge a higher rate based on this information.

Some states have laws to protect against genetic discrimination [list appropriate state information if your state has such laws]. A new federal law called the Genetic Information Non-Discrimination Act, or GINA is in effect. This law helps to lower the risk of health insurance or employment discrimination. The law does not include other types of misuse by life insurance or long term care insurance. To learn more about the GINA Law, please check the Internet or ask the study staff.

Although we are not able to know all of the risks from taking part in research on inherited traits, we believe that the risks to you and your family are very low, because research results will not be returned to you or your doctor.

How will information related to my samples be protected?

We have many ways to protect the information related to your samples:

Your samples and information receive a unique code. Researchers only receive coded samples and information, and will not be able to link the code to you. Only approved people in the Eastern Cooperative Oncology Group can match you to the code on your samples and related information.

Strict security safeguards are in place to reduce the chance of misuse or unplanned release of information. Steps we take include password protected access to databases and restricted access to freezers or rooms that contain samples.

Before samples are given to researchers, studies are reviewed for the quality of the science and for patient protection. Records from research studies can be reviewed by the Cooperative Group, by the sponsor, and by government agencies. This is to make sure the research follows the rules of the Cooperative Group and state or federal laws.

Research results will not be returned to you or your doctor. If research results are published, your name and other personal information will not be given.

ECOG also has a Certificate of Confidentiality from the U.S. Department of Health and Human Services. The Certificate protects against the forced release of personal information from the Cooperative Group bank or database.

What this means is that ECOG cannot be forced to disclose your identity to any third party. It is possible that for some legal proceedings, the Certificate of Confidentiality could be over-ridden by a court of law.
Making your choice

The choice to take part is up to you. You may choose not to let us store and use your samples. If you decide not to let us store and use your samples, you will still receive the same medical care and you may still participate in the treatment part of this clinical trial. You may also take part in other research studies.

If you decide that your samples can be kept, you may change your mind at any time. Contact the study staff at your hospital and let them know that you do not want your samples used for research [Insert contact number]. Then, any sample that remains in the bank will no longer be used. Samples that have already been given to or used by researchers cannot be returned or destroyed.

To learn more, ask the study staff for the booklet called “Providing Your Tissue for Research: What You Need to Know” and it can be found at https://pubs.cancer.gov/ncipl/detail.aspx?prodid=P067. The web version of the information is located at: http://www.cancer.gov/clinicaltrials/learningabout/providingtissue. You may want to read the section “Why do people do research with tissue?”

Please read the research study descriptions below, review the questions carefully and circle “Yes” or “No”. If you have any questions, please talk to your doctor or nurse, or call the institution’s research review board at [IRB's phone number].

USING SPECIMENS FOR FUTURE RESEARCH

May we have some of your tissue from a previous biopsy or surgery for use in research in the future. Although most future research studies will focus on cancer, some research projects may also include other diseases, such as heart disease, diabetes or Alzheimer’s disease.

As indicated above, the specimens will only be given to researchers approved by scientific reviewers appointed by the Eastern Cooperative Oncology Group. Any research done on the specimens must also be reviewed by the researcher's Institutional Review Board.
Please review the points listed in the “Voluntary Participation” and the risks associated with allowing your specimens to be used for research (including genetic research) outlined in the section above. Then read the questions below carefully and circle “Yes” or “No”.

May your coded samples and related coded information be kept for use in research to learn about, prevent, find or treat cancer? This may also include research on inherited traits (genes passed on in families).

Yes  No

May your coded samples and related coded information be kept for use in research to learn about, prevent, find or treat other health problems (for example: diabetes, Alzheimer’s disease, or heart disease)? This may also include research on inherited traits (genes passed on in families).

Yes  No

PERMISSION TO CONTACT YOU IN THE FUTURE

We request your permission to contact you in the future about taking part in more research studies. If you agree and we decide to contact you in the future, we will first contact your doctor or someone at your hospital. They will tell you why we would like to contact you and, if you agree, they will send us your contact information. We will not attempt any direct contact without obtaining this second permission from you.

Someone from my hospital or the Eastern Cooperative Oncology Group may contact me in the future to ask me to take part in more research.

Yes  No
WHERE CAN I GET MORE INFORMATION?

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

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

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

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

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

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

SIGNATURE

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

Participant __________________________________________

Date ________________________________________________

**PLEASE READ IMPORTANT INSTRUCTIONS**

This Registration Worksheet must be completed by the institution prior to patient registration. ECOG-ACRIN institutions are responsible for assuring patient eligibility at study entry, therefore the eligibility checklist found in Section 3.0 of the protocol must also be completed prior to patient registration. The eligibility checklist may be used as source documentation for certain eligibility criteria only if it is signed and dated by the treating physician. Do not submit these forms to the ECOG-ACRIN Operations Office - Boston.

2. Only US sites may participate in this study.

5. Pt initials

   Enter first initial: _______________________
   Enter last initial: _______________________

10. Has the eligibility checklist been completed?

   1. No [INELIGIBLE]
   2. Yes [next question]

20. In the opinion of the investigator, is the patient eligible?

   1. No [INELIGIBLE]
   2. Yes [next question]

30. Has written informed consent been obtained?

   1. No [INELIGIBLE]
   2. Yes [next question]

40. Date informed consent signed.

   enter date (mm/dd/yyyy): __________

50. Calculate: the number of days from the value of question 40 to TODAY

   enter result: __________
   -less than 0, INELIGIBLE
   -greater than or equal to 0, next question.
   -unknown, INELIGIBLE

60. Has HIPAA authorization been obtained?

   1. No [INELIGIBLE]
   2. Yes [next question]
   3. Exempt - non-USA participant [question 90]

70. HIPAA Authorization Date

   enter date (mm/dd/yyyy): __________

80. Calculate: the number of days from the value of question 70 to TODAY

   enter result: __________
   -less than 0, INELIGIBLE
   -greater than or equal to 0, next question.
   -unknown, INELIGIBLE

90. ECOG performance status.

   enter value: __________
   -equal to 0, next question.
   -equal to 1, next question.

100. Discontinuation of oxaliplatin first line therapy before disease progression

   1. No [next question]
   2. Yes [next question]

115. Time frame of progression

   1. Within 6 months of last treatment [next question]
   2. Greater than 6 months since last treatment [next question]

120. Patient’s simplified disease code.

   1. Adenocarcinoma of the colon [next question]
   2. Colorectal cancer, NOS [next question]
   3. Adenocarcinoma of the rectum [next question]

600. Patient previously enrolled in an ECOG-ACRIN study?

   1. No [question 770]
   2. Yes [next question]

610. NOTE: Prior ECOG-ACRIN protocol information should only be entered for one ECOG-ACRIN protocol. If there is no prior ECOG-ACRIN protocol, fields should be left blank.
   enter response:

630. Prior protocol patient’s ECOG-ACRIN ID.  
   enter response:

770. May your coded samples and related coded information be kept for use in research to learn about, prevent, find or treat cancer? This may also include research on inherited traits (genes passed on in families). 
   1. No [next question]
   2. Yes [next question]

780. May your coded samples and related coded information be kept for use in research to learn about, prevent, find or treat other health problems (for example: diabetes, Alzheimer’s disease, or heart disease)? This may also include research on inherited traits (genes passed on in families).
   1. No [next question]
   2. Yes [next question]

790. Someone from my hospital or the ECOG-ACRIN Cancer Research Group may contact me in the future to ask me to take part in more research. 
   1. No [ELIGIBLE]
   2. Yes [ELIGIBLE]

Demographic Data Required For Patient Registration:

Patient’s Gender (m/f) __ Birthdate (mm/dd/yy) ______
Patient’s Race ________________ Zip Code __________
Patient’s Ethnicity __________________________
Patient’s Hospital No. ________________________
Patient’s Social Security Number ______________
Method of Payment ___________________________
A Randomized Phase II Study of Irinotecan and Cetuximab with or without the Anti-Angiogenic Antibody, Ramucirumab, in Advanced, K-ras Wild-type Colorectal Cancer Following Progression on Bevacizumab-Containing Chemotherapy

Version Date: April 22, 2014

Informed Consent for Cancer Treatment Trials
(English Language)

You are being asked voluntarily to take part in this study because you have colon or rectal cancer that has spread to other organs or has come back locally with the first choice of treatment and your tumor is now progressing while being treated with standard first-line therapy. This research is being done because current treatment does not help everyone with your disease.

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

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to determine what good or bad effects the drug, ramucirumab, may have and to determine whether it is safe and effective for patients to receive in this setting. Irinotecan and cetuximab are standard treatments for patients who have metastatic colon or rectal cancer, who have already received one previous chemotherapy that is no longer working, and do not have a specific type of mutation (alteration) of the K-ras gene in their tumor. Ramucirumab is an experimental (not yet FDA-approved) drug that has been found to block a pathway that allows tumors to grow in animals and humans. It is unknown if adding a drug of this type to a standard second line therapy for colorectal cancer is beneficial. You will receive either the chemotherapy with the experimental drug or the chemotherapy alone, but you will not get both.

Because there were more side effects at higher doses of the ramucirumab regimen, a new arm (Arm C) was added to replace Arm B. In the first 17 patients enrolled on Arm B, there were two deaths due to gastrointestinal perforation (a hole in the intestinal wall). Arm C was revised to include lower starting doses of all three drugs (irinotecan, cetuximab and ramucirumab) reflecting the tolerated doses previously, and also greater dose reductions for toxicity. In addition, some patients at greater risk for developing perforations will no longer be allowed to participate in the study.

You and your doctors will know what treatment you are receiving. The chemotherapy with ramucirumab is considered experimental in this study.
HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 135 patients in the United States and Canada will take part in this study (including those previously enrolled in the study with Arm B).

BEFORE YOU BEGIN THE STUDY

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

- A physical examination including your vital signs (body temperature, pulse rate, breathing and blood pressure), height and weight, questions about your medical history, and a list of medicines you are taking.
- Samples of your blood and urine will be collected.
- Female subjects of childbearing potential will have a pregnancy test.
- Imaging studies to assess your disease, which may include CT scans (a type of computerized x-ray) of your chest, abdomen, and pelvis to evaluate your tumor status.
- EKG

You will be evaluated based on the results of these tests in order to determine if you are eligible to participate in this study. If your physician finds that you are not eligible, then you will not receive this treatment as part of the study.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will be "randomized" into one of the study groups (Arm A or Arm C) described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in either of the two treatment arms. You and your study doctor will not be able to choose which study treatment you receive.

Arm A:

You will receive irinotecan and cetuximab every 14 days and it will take approximately 3 hours in the clinic for each treatment. Medications are given before chemotherapy to prevent nausea, vomiting and allergic reaction to the drugs given. Both of the chemotherapy drugs will be given intravenously (through a vein). The first time you receive cetuximab it will be over 120 minutes to
minimize any possible allergic reactions to the drug. If there is no reaction to the drug all future doses may be given over 60 minutes. Irinotecan is given over 60-90 minutes.

**Arm C:**

You will receive Irinotecan, Cetuximab and the study drug Ramucirumab every 14 days and it will take approximately 4 hours in the clinic for each treatment. Medications are given before chemotherapy to prevent nausea, vomiting and allergic reaction to the drugs given. All of the chemotherapy drugs will be given intravenously (through a vein). Ramucirumab is given over 60 minutes. The first time you receive cetuximab it will be over 120 minutes to minimize any possible allergic reactions to the drug. If there is no reaction to the drug all future doses may be given over 60 minutes. Irinotecan is given over 60-90 minutes.

For each of the treatment arms, blood will be drawn (about 1 tablespoon or 15mL) prior to treatment to check blood counts, liver and kidney function (every two weeks), and a urine test (every six weeks). Based on the side effects you experience and the results of the blood and urine tests, the doses of the drugs may be changed to make sure you receive the dose of therapy you are able to tolerate.

**Arm B:** (Removed in Addendum #5)

**HOW LONG WILL I BE IN THE STUDY?**

We think you will be in the study for at least eight weeks before the status of the tumor is checked to see if the therapy is helping. If the status at that time shows that the tumor is either shrinking or not growing, and you tolerate the therapy, then you can continue on the same treatment every two weeks as long as the tumor is controlled and you wish to continue. If the tumor shows definite growth at any point, then the therapy will be stopped.

**CAN I STOP BEING IN THE STUDY?**

Yes. You can decide to stop anytime. However, we encourage you to talk to your doctor before you decide to withdraw, to explain your reasons and to ask you what effect your decision may have on your cancer.

Your doctor may decide to take you off this study for the following reasons, even if you wish to stay on the study: growth of the cancer; you cannot tolerate treatment; your doctors feel that the risks of continuing on the study therapy are too great; you are unable to comply with the study guidelines for treatment and follow-up; if you become pregnant or start to breast-feed; or if the study is being stopped.
Study Chart

Medicines used in this study
Irinotecan, Cetuximab and Ramucirumab by vein - given once every 14 days

Randomize
(You will be in one Group or the other)

Arm A
Cetuximab & Irinotecan by vein every 14 days

Arm C
Ramucirumab, Cetuximab & Irinotecan by vein every 14 days
WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don’t know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. There may also be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and less uncomfortable. Many side effects go away shortly after the protocol therapy is stopped, but in some cases side effects can be serious, long-lasting, permanent or life-threatening. Death is rare, but possible.

Ramucirumab has not been given previously with either irinotecan or cetuximab. This combination may magnify the known side effects of these agents, or cause unexpected side effects. For that reason, this study includes careful monitoring.

Your doctor will check you closely to see if any of these side effects are occurring and routine blood tests will be done to monitor the effects of treatment. You should talk to your doctor about any side effects that you have while taking part in the study, and you should alert your care team upon experiencing high fever, altered mental status, or problems breathing after receiving your treatment.

Risks and side effects related to the drugs and procedures we are studying include:

Irinotecan

More Likely

- Diarrhea
- Nausea
- Vomiting
- Loss of appetite
- Decreased white blood cell count that increases your risk of infection
- Anemia
- Decreased number of platelets (that may cause easy bruising or bleeding)
- Hair loss
- Fatigue (feeling weak or tired)

Less Likely

- Constipation (trouble having bowel movements)
- Pain in the abdomen
- Runny nose and eyes
- Flushing (reddening of the face)
- Sweating
- Stomach cramping and early diarrhea occurring during or right after the irinotecan*

* These early symptoms respond quickly to a medicine called atropine. If these immediate side effects occur, then you will get this medicine to prevent these symptoms with each following cycle.

**Rare**

- Skin rash
- Changes in certain blood tests that suggest irritation or inflammation of the liver
- Trouble sleeping
- Fever
- Shortness of breath

**Cetuximab:**

**Likely:**

- Diarrhea
- Nausea or the urge to vomit
- Fatigue or tiredness
- Fever
- Headache or head pain
- Dry skin
- Acne
- Skin rash that can affect the face, scalp, and neck, but sometimes can affect much of the rest of your body

**Less Likely:**

- Lack of enough red blood cells (anemia)
- Inflammation (swelling and redness) of the skin of outer ear and canal
- Noise in the ears, such as ringing, buzzing, roaring, clicking
- Swelling and redness of the outermost layer of the eye and the inner surface of the eyelids commonly called "pink eye".
- Dry eyes
- Swelling and redness of the middle layer of the eye (uvea)
- Excessive tearing in the eyes
- Belly pain
- Swelling and redness of the lips
- Constipation (trouble having bowel movements)
- Dry mouth
- Heartburn
- Irritation or sores in the lining of the mouth
- Vomiting
- Chills
- Swelling of the arms and/or legs
- Flu-type symptoms (including body aches, fever, chills, tiredness, loss of appetite, cough)
- Allergic reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, swelling of the threat, and difficulty breathing.
- Chest pain not heart-related
- Infection
- Decreased white blood cell count that may increase your risk of infection
- Weight loss
- Loss of appetite
- Dehydration (when your body does not have as much water and fluid as it should)
- Decreased blood levels of certain body minerals such as calcium and magnesium which may cause muscle cramping or a sensation of tingling and numbness of your fingers and around your mouth area.
- Decreased blood level of magnesium
- Joint pain
- Back pain
- Muscle pain
- Fainting
- Stuffy or runny nose, sneezing
- Sudden tightening of the small airways of the lung that can cause wheezing and shortness of breath
- Cough
- Hoarseness (raspy or strained voice)
- Hair loss
• Loss of some or all of the finger or toenails
• Increased skin sensitivity to sunlight
• Itching
• Area of bleeding within the skin causing a reddish purple discoloration
• Sore or destruction of skin
• Hives
• Low blood pressure
• Formation of a blood clot within a blood vessel that can block the flow of blood through a vessel or break loose and travel through the blood stream and block the flow in the small vessel of another organ, such as the lung

**Rare but Serious:**
• Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.
• Inflammation of the lining of the brain and spinal cord
• Inflammation of the lungs that may cause difficulty breathing and can be life-threatening
• Fluid build-up in the lungs that is not due to a heart problem that can be life-threatening
• Swelling and redness of the skin on the palms of the hands and soles of the feet

**Ramucirumab**

**Very Common Side Effects**
• Lack of energy
• High blood pressure
• Headache
• Nosebleeds
• Nausea
• Diarrhea
• Vomiting
• Decrease or loss of appetite
• High level of protein in the urine
Common Side Effects

- Bleeding gums
- Coughing up blood
- Blood in the urine
- Low platelet count
- Swelling in the arms, legs, hands, or feet
- Infusion-related reactions. Symptoms include shaking, back pain or spasms, feeling cold, red skin, trouble breathing, rash, fever, headache, body aches, stomach pain, nausea, vomiting, blurry vision, chest pain and/or tightness, very fast heartbeat, low blood pressure, and tingling or burning in the hands or feet.
- Low or severely low red blood cell count.
- Weakness or weak muscles
- Feeling cold
- Bad taste in the mouth
- Skin problems such as rash, itching, acne, dry skin, or red skin
- Redness, tenderness, and peeling skin on the palms of the hands and soles of the feet
- Hair loss
- Skin condition resembling acne
- Trouble breathing
- Fever
- Pain in the joints, muscles (with or without cramping), back, chest, arms, or legs.
- Swelling and redness in the mouth, sometimes with pain
- Dry mouth
- Throat pain
- Feeling dizzy
- Weight loss
- Damage to your liver
- Upset stomach
- Stomach pain
- Blood clots in the veins, including veins in the lung or deep veins in the legs
- Tingling, burning, prickling, or numbness, usually in the hands, arms, legs or feet
- Some loss in the sense of touch
• Trouble speaking
• Coughing
• High blood sugar
• Damage to your kidneys
• Dehydration or, too little water in the body
• Low levels of potassium, magnesium, and phosphorus in the blood
• Trouble sleeping
• Heart damage
• Cardiac arrest or cardiorespiratory arrest
• Blurry vision
• Low blood pressure
• Bruising
• Decreased levels of albumin

Hot flash

Uncommon Side Effects

• Liver failure
• Collapsed lung
• Infection throughout the body
• Damage to the walls of the stomach, intestines, or rectum (causing intestinal perforation – a hole in the wall)
• More acid than normal in the blood
• Multi-organ failure
• Difficulty forming blood clots
• Changes in how the brain functions that can cause confusion, headache, nausea, vomiting, and feeling wobbly.
• Severe intestinal bleeding and life-threatening bleeding ulcer
• Abnormal vaginal bleeding
• Bruising or bleeding under the skin
• Bleeding in the mouth, ear, eye, brain, or lung, or at the site of injection
• Tumor bleeding
• Bleeding after a procedure or surgery
• Blood in the stool
• Leukoencephalopathy, a loss of white matter of the brain, which may results in brain dysfunction, and can cause forgetfulness, confusion, headache, delirium, and total or partial blindness.
Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect a fetus. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. An appropriate method of birth control must be maintained for at least 3 months after treatment with ramucirumab. This applies to both men and women. Check with your doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

Risks in Children and Elderly Patients: The safety of ramucirumab in children and elderly patients has not been established.

Based on the initial 35 patients enrolled in the study, the combination with ramucirumab resulted in lower blood counts and more diarrhea and mouth sores (mucositis) compared with the standard arm of irinotecan and cetuximab. Additionally, there were a few more GI perforation events including peri-rectal abscess formation. Because of these findings, doses were reduced in the ramucirumab arm (Arm C) to the doses tolerated by the patients treated in Arm B.

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

**ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

Taking part in this study may or may not be direct medical benefits to you. Possible benefits are shrinkage of your tumor, improvement in your symptoms related to your cancer and prolonged survival. We hope the information learned from this study will benefit other patients with colorectal cancer in the future.

**WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?**

Your other choices may include:

- **Standard chemotherapy at this medical center and at other medical centers without being in a study**
- **Taking part in another study**
- **No treatment**
- **Supportive or comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.**

Talk to your doctor about your choices before you decide if you will take part in this study.
WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

The ECOG-ACRIN Cancer Research Group (ECOG-ACRIN) is conducting this study. ECOG-ACRIN is a cancer research group that conducts studies for the National Cancer Institute. Your doctor is a member of ECOG-ACRIN or another group that is participating in this study. To help protect your privacy, ECOG-ACRIN has obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS).

With this Certificate, ECOG-ACRIN cannot be forced (for example, by court subpoena) to disclose information that may identify you in any federal, state or local civil, criminal, administrative, legislative or other proceeding. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes.

You should know that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about you or your involvement in this research. If an insurer or employer learns about your participation and obtains your consent to receive research information, then ECOG-ACRIN may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your privacy.

You should also understand that your doctor and ECOG-ACRIN may take steps, including reporting to authorities, to prevent you from seriously harming yourself or others.

Finally, the Certificate allows the review of your research records under some circumstances by certain organizations for an internal program audit or evaluation. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:

- ECOG-ACRIN Cancer Research Group (ECOG-ACRIN)
- National Cancer Institute (NCI)
- Food and Drug Administration (FDA)
- Other regulatory agencies and/or their designated representatives
- Drug manufacturers and/or their representatives
- Central laboratories, banks and/or reviewers
- Cancer Trials Support Unit (CTSU), a service provided by the National Cancer Institute (NCI) to provide greater access to cancer trials.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.
WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment. Additional tests, such as those required to monitor blood pressure, may not be covered by your insurance company.

If randomized to Arm C, the drug Ramucirumab will be provided free of charge for the duration of the study.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute’s Web site at:

http://www.cancer.gov/clinicaltrials/learningabout/payingfor

You can print a copy of the “Clinical Trials and Insurance Coverage” information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

In the event of injury or illness as a result of the study medications or procedures, you should seek medical treatment through your physician or treatment center of choice. You should promptly notify the study doctor in the event of any illness or injury. Payment for this treatment will be your responsibility.

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

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

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

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

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

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

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

**WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?**

You can talk to your doctor about any questions or concerns you have about this study. Contact your doctor Martin Hyzinski, M.D. at (570) 558-3020.

For questions about your rights while taking part in this study, call Mark White, M.D., Chairman of the Wright Center for Graduate Medical Education Institutional Review Board (a group of people who review the research to protect your rights) at (570) 687-9706.

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in any of these additional studies.

You can say “yes” or “no” to each of the following studies. Please mark your choice for each study.
ABOUT USING SPECIMENS FOR RESEARCH

Please read this form and ask about anything that is not clear to you. This is part of the informed consent process for research. This is to inform you of the possible risks, benefits, and limits of giving your samples for research.

You are being asked to give some of your samples (called specimens) and related information to be stored (banked) for future research. This may help researchers learn more about how to prevent, find and treat cancer and other diseases.

The choice to have your samples used for research is up to you. No matter what you decide, it will not affect your medical care.

Below is some general information you should know before agreeing to allow the use of your specimens for research. After the general information there are descriptions of the research projects. Each project is described separately, including the types of samples requested and how they are collected. Each description is followed by questions concerning your participation in the project. Your samples will be used only for the projects in which you agree to participate.

What are samples and where are they stored?

A sample is any material taken from your body such as tissue, blood, urine and other fluids.

If you agree, your samples will be sent to laboratories to be used in research or will be stored for research in a Cooperative Group bank. These banks are supported by the National Cancer Institute. Cooperative Group banks contain samples and information. Your samples are kept along with those from other people in the banks. Researchers then ask for samples from the banks to study them.

What information will be collected?

When your samples are sent to any bank, some personal information will be sent with the samples. Any personal information sent with the samples is not given to other researchers. The personal information is used only by the bank to identify your samples. Your privacy will be protected to the fullest extent possible. This will be discussed later in the section “How will information related to my samples be protected?”

Examples of other information that might be used for research include:

- Dates of medical procedures
- Any diagnosis and stage of your disease (if you have cancer)
- Your age and race
- Medical and family history
- Treatments you had
- How you responded to treatments
What will happen to my samples if I agree to give them for research?

If you agree to let your samples be kept for future research (research not yet defined), your samples will be stored in a Cooperative Group bank. The samples will be kept until they are used up or destroyed. The samples are given a code to protect your privacy before they are used. Any related information given to researchers will also be coded. Researchers will receive the code instead of any information that might directly identify you.

You or your doctor will not be given reports or other information about the research that uses your samples. This information will not be put into your health record. Results may be used for future research.

You will not be named or identified by other personal information if any results are published. Most publications contain results from many patients.

Your samples and related information will be used only for research and will not be sold. It is possible that research may help to create new products or treatments. If this should happen, you will not be paid.

Coded data from some research studies that use samples could be put into secure Internet databases that can be shared by other approved researchers. This could include genetic data. Current safety rules are followed to safeguard your privacy. Your name or contact information will not be put in the database.

What kind of research will be done with my samples?

Many types of research use normal or diseased (cancerous) samples. Researchers can study proteins, RNA and DNA (genes). The study of genes (DNA) is often called genetic research.

For example, your samples may be looked at:

- To see if a trait is passed down in families from one generation to the next (inherited). This type of research may help to explain why some cancers run in families or why some people have side effects from treatment while others do not. This is often studied through blood cells and DNA (genes).
- To learn about changes in the body that happen after you were born (non-inherited). For example, being in the sun too much can cause changes in cells that lead to skin cancer.

Will it help me if I give my samples for research?

Using your samples for research will probably not help you. We do hope the research results will help people in the future. The best way to prevent, find or treat cancer and other diseases is by studying human samples and data.

What are the risks of giving my samples for research?

There is a risk that your information could be misused. The chance of this happening is very small. We have many protections in place to lower this risk. See the next section, “How will the information related to your samples be protected?” Your privacy will be protected to the fullest extent possible.
There can be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Even though your genes are unique, you share some of the same genes with your blood relatives. Very rarely health or genetic information could be misused by employers, insurance companies, and others. For example, life insurance companies may charge a higher rate based on this information.

Some states have laws to protect against genetic discrimination. A new federal law called the Genetic Information Non-Discrimination Act, or GINA is in effect. This law helps to lower the risk of health insurance or employment discrimination. The law does not include other types of misuse by life insurance or long term care insurance. To learn more about the GINA Law, please check the Internet or ask the study staff.

Although we are not able to know all of the risks from taking part in research on inherited traits, we believe that the risks to you and your family are very low, because research results will not be returned to you or your doctor.

**How will information related to my samples be protected?**

We have many ways to protect the information related to your samples:

Your samples and information receive a unique code. Researchers only receive coded samples and information, and will not be able to link the code to you. Only approved people in the ECOG-ACRIN Cancer Research Group can match you to the code on your samples and related information.

Strict security safeguards are in place to reduce the chance of misuse or unplanned release of information. Steps we take include password protected access to databases and restricted access to freezers or rooms that contain samples.

Before samples are given to researchers, studies are reviewed for the quality of the science and for patient protection. Records from research studies can be reviewed by the Cooperative Group, by the sponsor, and by government agencies. This is to make sure the research follows the rules of the Cooperative Group and state or federal laws.

Research results will not be returned to you or your doctor. If research results are published, your name and other personal information will not be given.

ECOG-ACRIN also has a Certificate of Confidentiality from the U.S. Department of Health and Human Services. The Certificate protects against the forced release of personal information from the Cooperative Group bank or database.

What this means is that ECOG-ACRIN cannot be forced to disclose your identity to any third party. It is possible that for some legal proceedings, the Certificate of Confidentiality could be over-ridden by a court of law.

**Making your choice**

The choice to take part is up to you. You may choose not to let us store and use
your samples. If you decide not to let us store and use your samples, you will still receive the same medical care and you may still participate in the treatment part of this clinical trial. You may also take part in other research studies.

If you decide that your samples can be kept, you may change your mind at any time. Contact the study staff at your hospital and let them know that you do not want your samples used for research. Then, any sample that remains in the bank will no longer be used. Samples that have already been given to or used by researchers cannot be returned or destroyed.

To learn more, ask the study staff for the booklet called “Providing Your Tissue for Research: What You Need to Know” and it can be found at https://pubs.cancer.gov/ncipl/detail.aspx?prodid=P067. The web version of the information is located at: http://www.cancer.gov/clinicaltrials/learningabout/providingtissue. You may want to read the section “Why do people do research with tissue?”

Please read the research study descriptions below, review the questions carefully and circle “Yes” or “No”. If you have any questions, please talk to your doctor or nurse, or call the institution’s research review board at (570) 687-9706.

**USING SPECIMENS FOR FUTURE RESEARCH**

May we have some of your tissue from a previous biopsy or surgery for use in research in the future. Although most future research studies will focus on cancer, some research projects may also include other diseases, such as heart disease, diabetes or Alzheimer’s disease.

As indicated above, the specimens will only be given to researchers approved by scientific reviewers appointed by the ECOG-ACRIN Cancer Research Group. Any research done on the specimens must also be reviewed by the researcher’s Institutional Review Board.
Please review the points listed in the “Voluntary Participation” and the risks associated with allowing your specimens to be used for research (including genetic research) outlined in the section above. Then read the questions below carefully and circle “Yes” or “No”.

**May your coded samples and related coded information be kept for use in research to learn about, prevent, find or treat cancer? This may also include research on inherited traits (genes passed on in families).**

Yes  No

**May your coded samples and related coded information be kept for use in research to learn about, prevent, find or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease)? This may also include research on inherited traits (genes passed on in families).**

Yes  No

**PERMISSION TO CONTACT YOU IN THE FUTURE**

We request your permission to contact you in the future about taking part in more research studies. If you agree and we decide to contact you in the future, we will first contact your doctor or someone at your hospital. They will tell you why we would like to contact you and, if you agree, they will send us your contact information. We will not attempt any direct contact without obtaining this second permission from you.

**Someone from my hospital or the ECOG-ACRIN Cancer Research Group may contact me in the future to ask me to take part in more research.**

Yes  No
WHERE CAN I GET MORE INFORMATION?

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

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

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

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

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

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

SIGNATURE

I have been given a copy of all 20 pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant ________________________________

Date ________________________________

Person Obtaining Consent__________________________

Date____________________________
E7208
A Randomized Phase II Study of Irinotecan and Cetuximab with or without the Anti-Angiogenic Antibody, Ramucirumab (IMC-1121B), in Advanced, K-ras Wild-type Colorectal Cancer Following Progression on Bevacizumab-Containing Chemotherapy

IS REOPENED- EFFECTIVE JUNE 6, 2014

E7208 was closed to accrual on June 14, 2012 after 35 registrations were accrued as per pre-planned toxicity review. 18 patients (17 received treatment) were accrued to Arm A (IC) and 17 (16 received treatment) to Arm B (ICR). AdEERS reporting was reviewed and real time data were obtained on all treated patients. It was clear that more toxicity was seen in Arm B. (The toxicity per patient is summarized in Section 1.6 of the protocol.) The overall grade 3-5 toxicity rates were 17% for Arm A and 75% for Arm B. There were 2 toxic deaths in Arm B. Toxicities of higher incidence in Arm B included neutropenia, mucositis, diarrhea and GI perforation (including peri-anal abscess). In addition mean dose given in Arm B (mean % RDI) was considerably lower in Arm B: 65% for irinotecan, 85% for cetuximab and 92% for ramucirumab (even though no dose reductions were allowed in the protocol). This compares to 99% irinotecan and 98% cetuximab average %RDI in Arm A. Furthermore, only 3/17 patients in Arm A required dose reduction, compared to 15/16 in Arm B.

An analysis of the accrued patients at the time of the suspension found that those patients treated at reduced doses tolerated the ICR regimen, were treated longer, and had fewer disease progression events than those treated at fuller doses. Based on these findings we have modified the study by closing Arm B to further accrual, and replacing it with Arm C that employs reduced starting doses of the agents.

The amended protocol is modified in three ways: 1) A reduced dose regimen in Arm C (modified ICR) with irinotecan 150 mg/m², cetuximab 400 mg/m² and ramucirumab 6 mg/m² as starting doses, 2) Changes to the eligibility criteria (including no prior abscesses, obstruction or perforation within 6 months and more normal LFTs and albumin); and 3) Changes to the dose modifications for toxicity.

Patients currently on study should be followed according to the protocol.