ECOG-ACRIN cancer research group
Reshaping the future of patient care

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

Rev. 6/14

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Rev. 7/12, 11/14

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Version Date: March 22, 2016

Irinotecan (NSC #616348) Commercially available for this study

Cetuximab (NSC #714692) Commercially available for this study

Rev.5/16 **Ramucirumab (NSC #749128) (IND 109448) Supplied by Eli Lilly & Company for this study**

Rev. 7/12, 6/14, 11/14

STUDY PARTICIPANTS

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

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
Addendum #6 – 6/14
Addendum #7 – 11/14
Addendum #8 – 12/14
Addendum #9 – 6/15
Addendum #10 – 5/16

Rev. 6/14

Table of Contents

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Rev. 7/12, 11/14

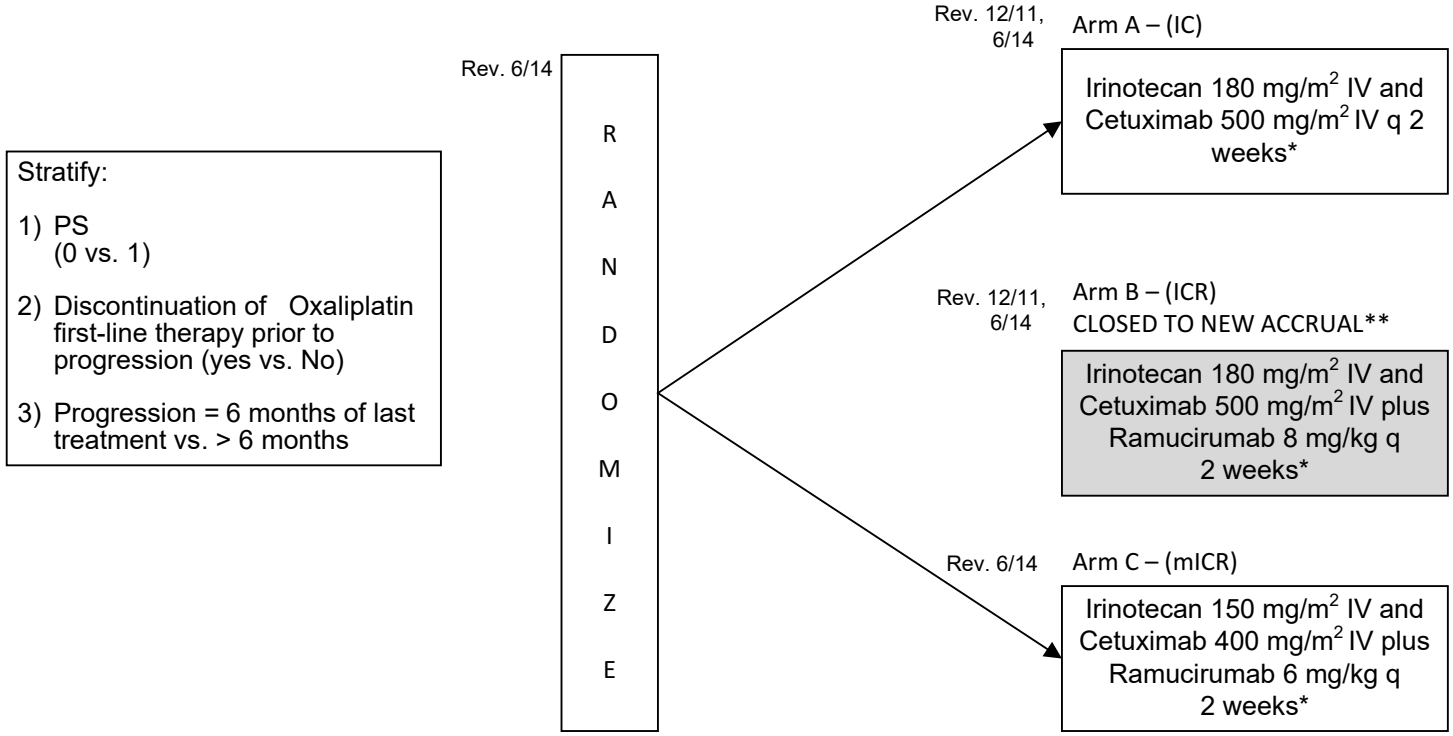
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email - CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)	Please refer to the patient enrollment section for instructions on using the Oncology Patient Enrollment (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	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.
The most current version of the **study protocol and supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

Rev.5/16

Schema

Rev. 12/11 Eligibility: metastatic or advanced CRC, K-ras wild-type, first line therapy with oxaliplatin-containing Chemotherapy and bevacizumab, now progressing.



Rev. 12/11

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

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

Rev. 6/14 ** Arm B closed to accrual in Addendum #5. New patients are randomized to Arm A or Arm C.

Rev. 6/14 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 irionotecan 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. 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/m^2 q2w safely. The study was continuing at the time of presentation.

Table 1

Schedule	C_{min} (µg/mL)	AUC (µg/mL*h)	$t_{1/2}$ (h)	CL_{ss} (L/h/m^2)
400/250 mg/m^2 q1w	47.0 (37.3)	17278 (5205)	110 (24)	0.016 (0.004)
400 mg/m^2 q2w	25.6 (11.8)	27655 (6965)	124 (25)	0.015 (0.004)
500 mg/m^2 q2w	35.2 (13.8)	34953 (6275)	134 (33)	0.015 (0.003)

Mean (SD)

This combination of irinotecan 180 mg/m^2 and cetuximab 500 mg/m^2 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 (IgG_1) 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 18 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).

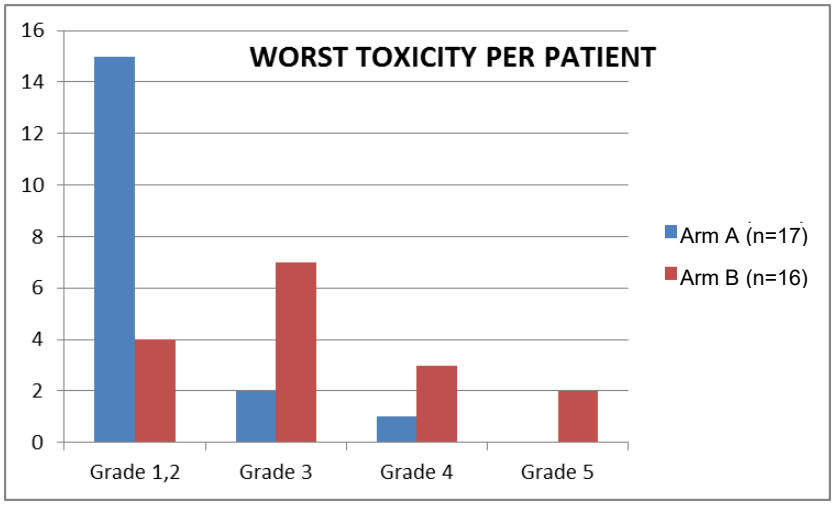
1.5 Summary and Study Rationale

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.

Rev. 6/14, 6/14

1.6 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/m^2, cetuximab 400 mg/m^2 and ramucirumab 6 mg/m^2 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.



Rev. 6/14

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.

3.1.7.1 Was oxaliplatin discontinued before date of progression?

Yes _____ No _____

Rev. 12/11, 6/14, 11/14

_____ 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 _____

Rev. 12/11

3.1.9 [Deleted in Addendum #3]

_____ 3.1.10 Performance Status 0-1.

3.1.10.1 PS 0 _____ 1_____

_____ 3.1.11 Adequate Organ Function ≤ 4 weeks prior to registration.

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

ANC: _____ Date: _____

Hemoglobin: _____ Date: _____

Platelets: _____ Date: _____

3.1.11.2 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: _____

Rev. 11/14

3.1.11.3 Proteinuria: Urine protein/creatinine (UPC) ratio < 0.5 or urine protein ≤ 1+ on dipstick or routine urinalysis (UA).

If UPC ≥ 0.5 or 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.

UPC < 0.5 (Yes / No) _____ Date: _____

Urine protein ≤ 1+ (Yes / No) _____ Date: _____

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

Rev. 6/14

3.1.11.4 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: _____

3.1.11.5 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): _____

Rev. 12/11, 6/14

_____ 3.1.12 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.

_____ 3.1.13 No clinically significant (equivalent to NCI CTCAE grade 3-4) bleeding episodes within the prior 3 months.

_____ 3.1.14 No active infection, symptomatic congestive heart failure, unstable angina pectoris, symptomatic or poorly controlled cardiac arrhythmia, uncontrolled thrombotic or hemorrhagic disorder.

_____ 3.1.15 No uncontrolled or poorly-controlled hypertension despite standard medical management (e.g. consistently SBP > 160 and DBP > 90 mmHg).

_____ 3.1.16 No major surgery within 28 days prior to randomization, or subcutaneous venous access device placement within 7 days prior to randomization

_____ 3.1.17 No history of acute arterial thrombotic events within 6 months (including CVA, TIA, MI or unstable angina).

_____ 3.1.18 No brain or CNS metastases.

_____ 3.1.19 No other cancer requiring therapy within last three years (except *in situ* carcinoma or non-melanoma skin cancer).

Rev. 6/14

_____ 3.1.20 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.

_____ 3.1.21 Patient must not have a history of inflammatory bowel disease requiring pharmacological and/or surgical intervention within the 12 months prior to randomization.

_____ 3.1.22 Patient must not have a known allergy to any of the treatment components.

4. Registration and Randomization Procedures

Rev. 11/14

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

CTSU Registration Procedures

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

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 be approved to 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. **For sites under the CIRB initiative, IRB data will automatically load to RSS.**

Downloading Site Registration Documents:

Site registration forms may be downloaded from the **E7208** protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the **ECOG-ACRIN** link to expand, then select trial protocol **E7208**
- Click on the Site Registration Documents link

Requirements for E7208 site registration:

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
FAX: (215) 569-0206

E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Required Protocol Specific Regulatory Documents

1. **CTSU Regulatory Transmittal Form.**
2. **Copy of IRB Informed Consent Document.**

   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**

Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Patient Enrollment

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.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at <https://eapps-ctep.nci.nih.gov/iam/index.jsp>) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. 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.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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.

Rev.5/16

Treatment should start within 10 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:

a. Performance Status 0 vs. 1
b. Discontinuation of oxaliplatin before disease progression: Yes vs. No
Rev. 12/11
c. Time since treatment with chemotherapy or bevacizumab ≤ 6 months vs. > 6 months.

4.5 Additional Requirements

4.5.1 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

Lilly 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:

	Baseline	Every Six Weeks	End of Treatment	30 Days After End of Treatment
EKG	**X**		**X**	
Pregnancy Test*	**X***	**X**	**X**	**X**
UPC	**X**	**X**		

*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

Rev. 12/11

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

5.1 Administration Schedule

Rev. 6/14

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

Rev. 6/14

5.1.2 Treatment/ARM B – (ICR)

CLOSED to accrual in Addendum #5

Rev. 6/14

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.

Rev. 12/11, 6/14

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 CTEP-AERS for timelier monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

Rev. 6/14

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.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is ***clearly NOT related*** to treatment
Unlikely	The AE is ***doubtfully related*** to treatment
Possible	The AE ***may be related*** to treatment
Probable	The AE is ***likely related*** to treatment
Definite	The AE is ***clearly related*** to treatment

- **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 CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

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

Rev. 6/14

- 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 ncictephelp@ctep.nci.nih.gov.

5.2.4 Determination of Reporting Requirements

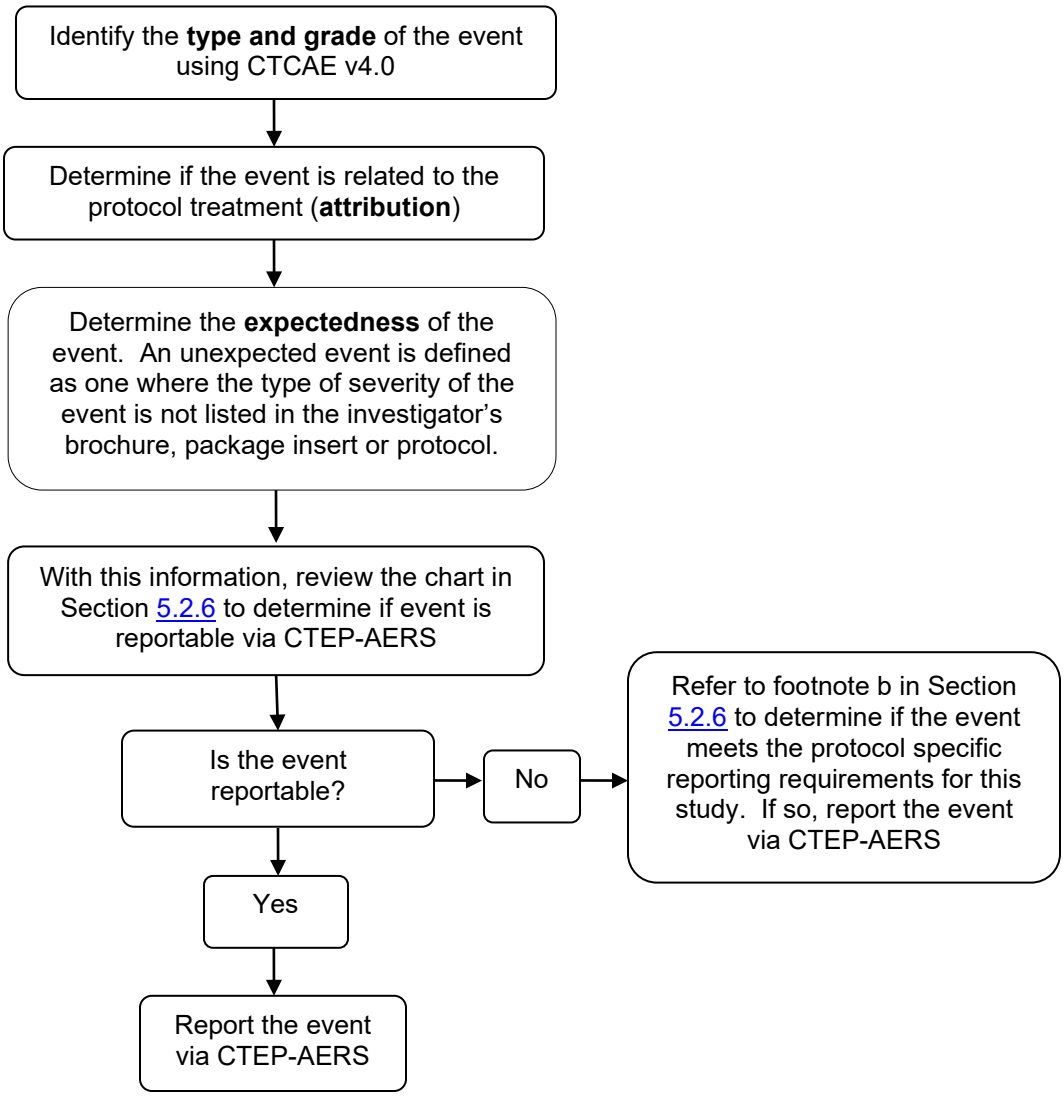
Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- 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



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					
Attribution	**Grade 4**		**Grade 5[a]**		**ECOG-ACRIN and Protocol-Specific Requirements**
	Unexpected	Expected	Unexpected	Expected	
Unrelated or Unlikely			7 calendar days	7 calendar days	See footnote (b) for special requirements.
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

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:

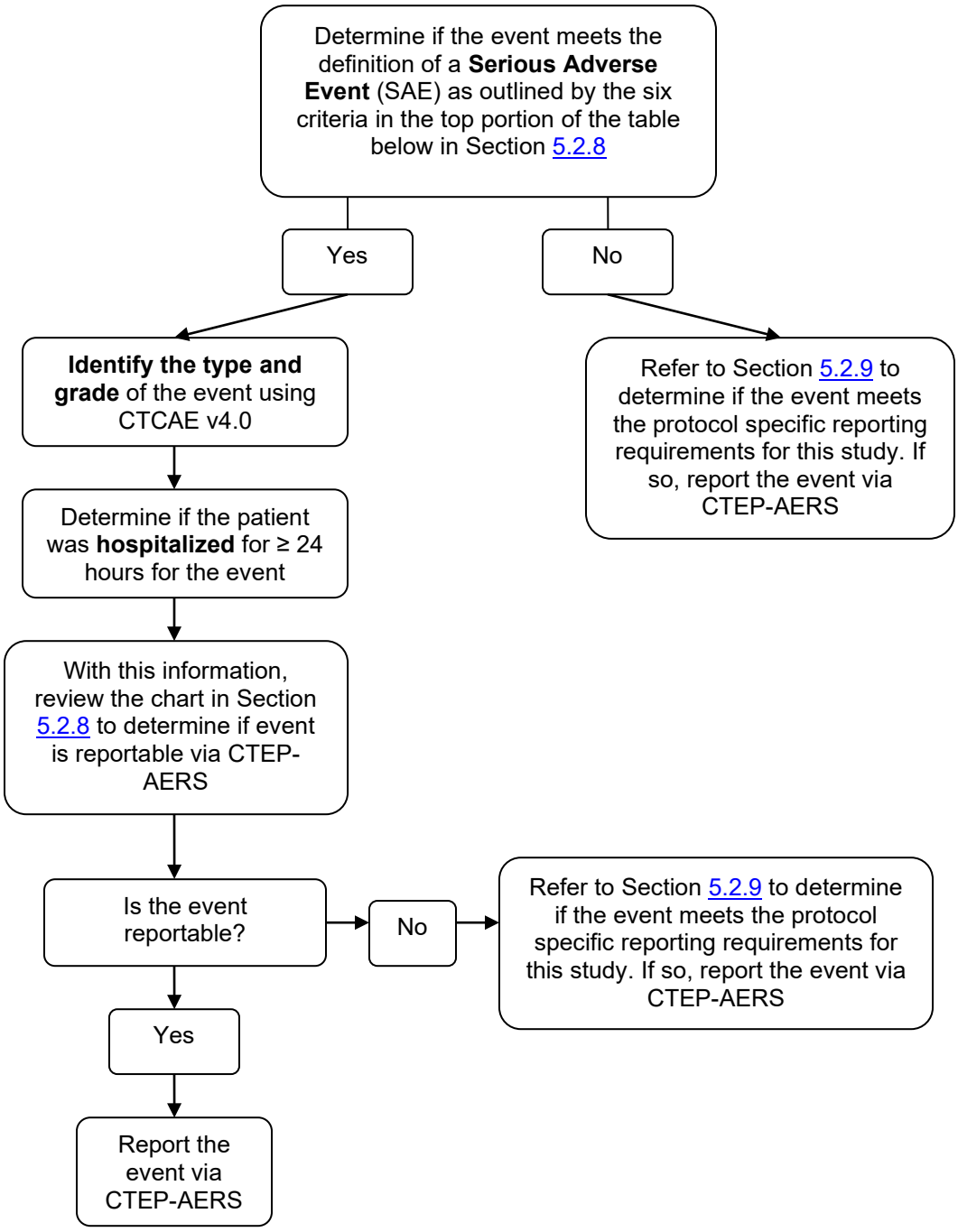
Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported via CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events via CTEP-AERS, 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.

Rev. 6/14

5.2.7 Steps to Determine if an Adverse Event is to be Reported in an Expedited Manner for Arms B and C

Rev. 6/14

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).



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

Rev. 6/14

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* [1]

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.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

Rev. 6/14

Expedited 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.

[1]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:

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

Rev. 6/14

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.

Rev. 6/14

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

2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov

   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.

Rev. 12/11

Version 2.1, March 31, 2010[1]

Adverse Events with Possible Relationship to Cetuximab (CTCAE 4.0 Term) [n= 2282]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
EAR AND LABYRINTH DISORDERS		
	External ear inflammation	
	Tinnitus	
EYE DISORDERS		
	Conjunctivitis	
	Dry eye	
	Uveitis	
	Watering eyes	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Cheilitis	
	Constipation	
Diarrhea		
	Dry mouth	
	Dyspepsia	
	Mucositis oral	
Nausea		
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
	Edema limbs	
Fatigue		
Fever		
	Flu like symptoms	
	Infusion related reaction	
	Non-cardiac chest pain	
IMMUNE SYSTEM DISORDERS		
	Allergic reaction	
		Anaphylaxis

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		
	Alopecia	
Dry skin		
	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

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 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. 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.

Rev. 12/11, 6/14

f. Dose reductions for all agents are as follows:

ARM	AGENT	INITIAL DOSE	LEVEL -1	LEVEL -2
A (IC)	Cetuximab	500 mg/m^2	400 mg/m^2	250 mg/m^2
	Irinotecan	180 mg/m^2	150 mg/m^2	120 mg/m^2
B (ICR) Closed to accrual	Ramucirumab	8 mg/kg	6 mg/kg	5 mg/kg
	Cetuximab	500 mg/m^2	400 mg/m^2	250 mg/m^2
	Irinotecan	180 mg/m^2	150 mg/m^2	120 mg/m^2
C (mICR)	Ramucirumab	6 mg/kg	5 mg/kg	4 mg/kg
	Cetuximab	400 mg/m^2	250 mg/m^2	200 mg/m^2
	Irinotecan	150 mg/m^2	120 mg/m^2	90 mg/m^2

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.

Grade	Dose Modification
2	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.
3-4	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.
Febrile neutropenia	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.

5.4.3 Diarrhea

Rev. 6/14

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.

Grade	Dose Modification
2	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.
3	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.
4	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.

Rev. 6/14

Rev. 6/14

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.

Grade	Dose Modification
3-4	Reduce *irinotecan* one dose level. For subsequent cycles, continue irinotecan at the reduced dose level from the previous cycle.

5.4.5 Mucositis

Grade	Dose Modification
2	Reduce irinotecan one dose level for subsequent cycles. No modifications (or delays) will be made for Ramucirumab or cetuximab.
3 (Rev. 6/14)	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.
4 (Rev. 6/14)	Hold ALL protocol treatment. If mucositis resolves to ≤ Grade 2, reduce all agents one dose level for all subsequent cycles.

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)

Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice	
Grade 1 (SBP 120-139 mmHg or DBP 80-89 mm Hg)	Consider increased BP monitoring; start anti-hypertensive medication if appropriate
Grade 2 asymptomatic (SBP 140-159 mmHg or DBP 90-99 mm Hg)	Begin anti-hypertensive therapy and continue agent
• Grade 2 symptomatic (SBP 140-160 mmHg or DBP 90-100 mm Hg) • Grade 3 (≥ SBP 160 mmHg or ≥ DBP 100 mmHg	• Start or adjust anti-hypertensive medication • Hold agent until symptoms resolve **AND** BP < 160/90mmHg
• Grade 4 (Hypertensive crisis or malignant hypertension)	Discontinue agent

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)

Grade 3 Rash	**Cetuximab**	**Outcome**	**Cetuximab Dose Modification**
1st occurrence	Hold infusion 1 to 2 wks	If improvement: If no improvement:	Continue at current dose Discontinue cetuximab
2nd occurrence	Hold infusion 1 to 2 wks	If improvement: If no improvement:	Reduce one dose level Discontinue cetuximab
3rd occurrence	Hold infusion 1 to 2 wks	If improvement: If no improvement:	Reduce two dose levels Discontinue cetuximab
4th occurrence	Discontinue cetuximab		
Grade 4 Rash	Discontinue cetuximab		

5.4.15 Infusion Reactions

Grade 1	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.
Grade 2	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.
Grade 3 and Grade 4	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.

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.

Rev. 6/14

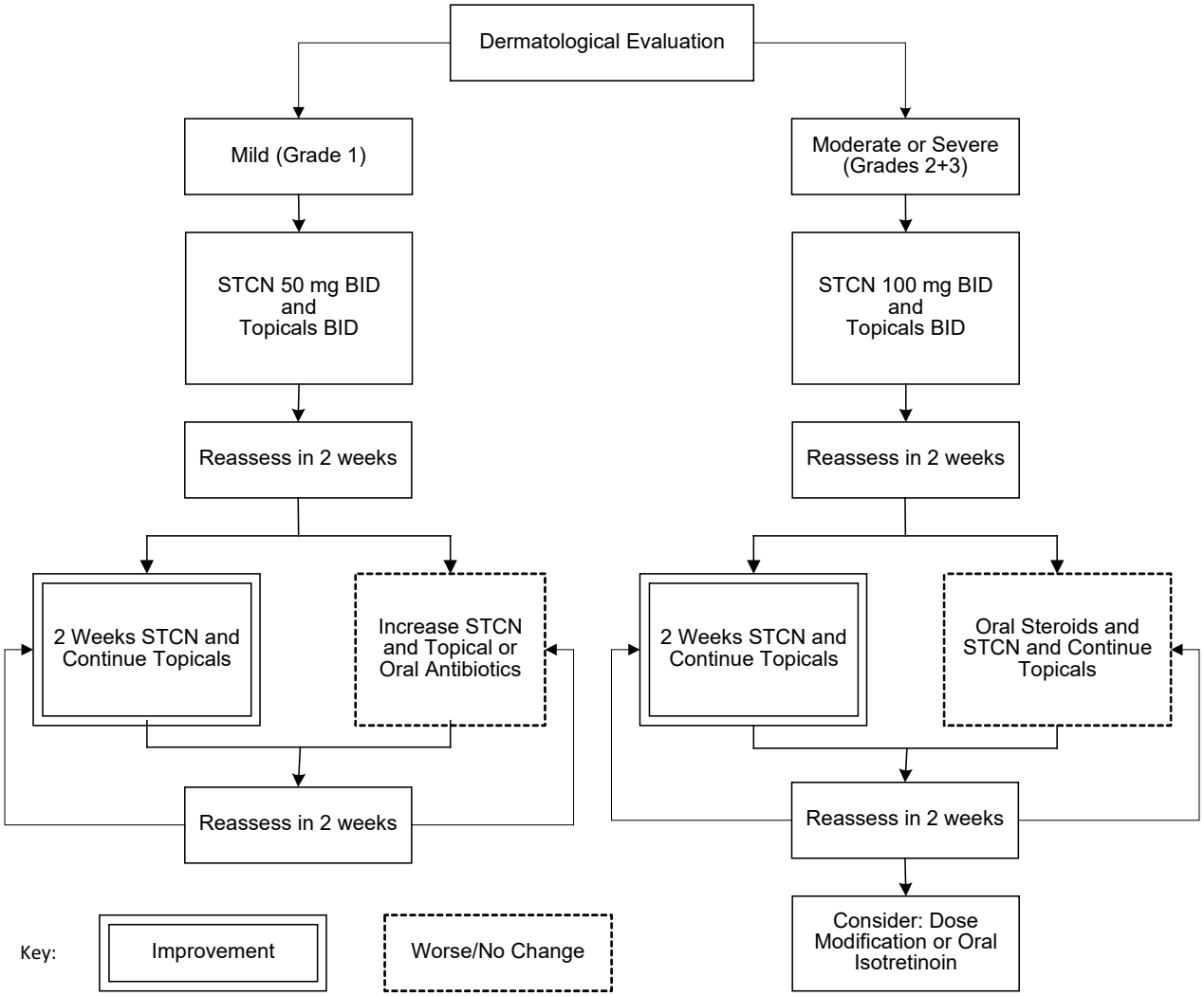
5.5.6 Dermatology Management

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).

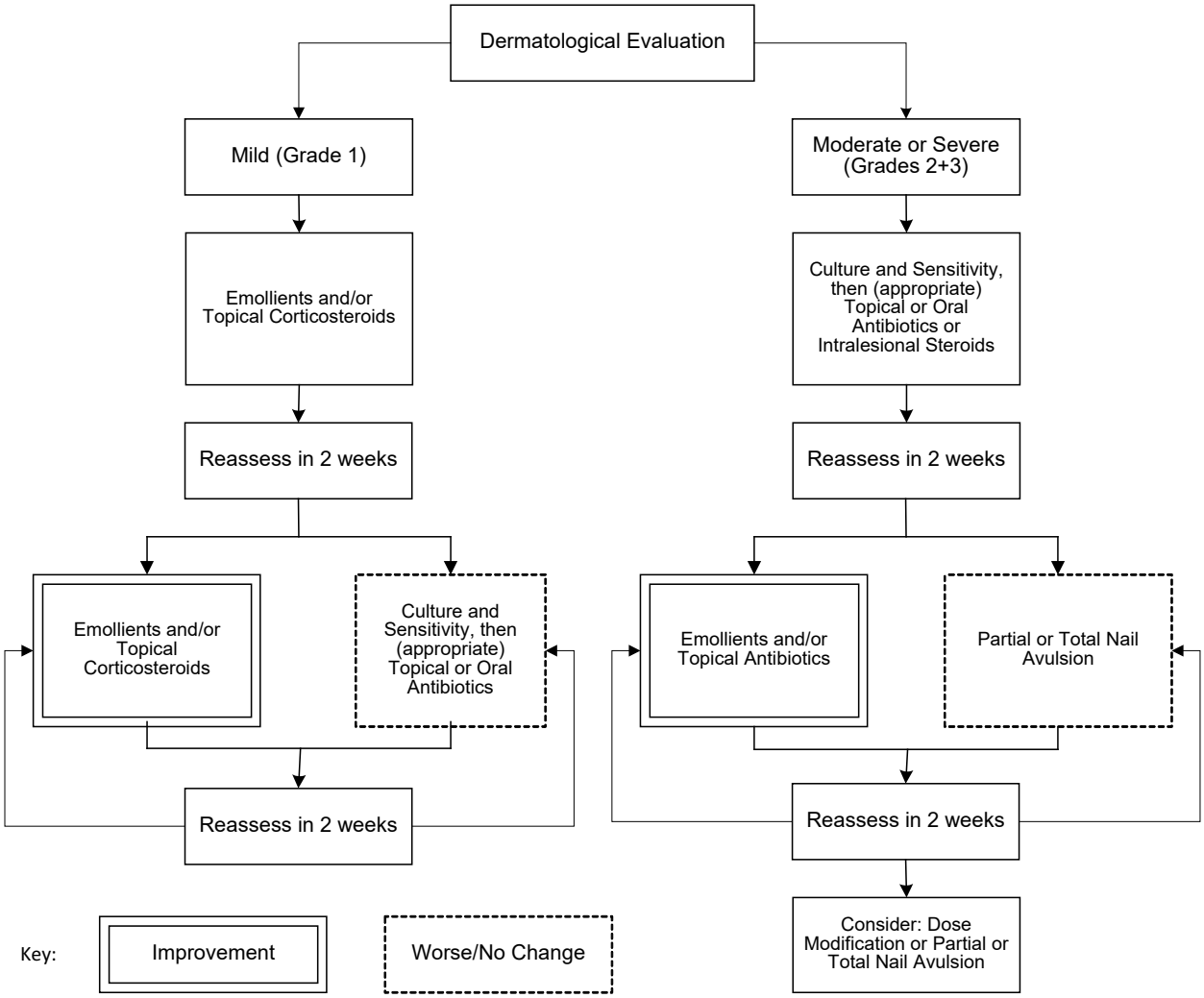
Table 1-1: Algorithm for Management of Acneiform Rash



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



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 ≥ 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 ≥ 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)

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

*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.

Rev. 6/15

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.

Test / Assessment	Pre-Study	Every 2 weeks	Every 4 weeks	Every 6 weeks	Every 8 weeks until progression	Follow-up[1]
Physical						
History and Physical	X	X				X
Weight and Performance Status	X	X				
Blood Pressure[7]	X	X				
Toxicity Assessment	X	X[6]	X[6]			
Disease Assessment	X					
EKG	X					X[5]
Laboratory						
CBC/diff/plts	X[2]	X				
Chemistry Panel (chem. 6 including creatinine)	X	X				
Calcium	X		X			
Albumin	X		X			
Magnesium	X	X				
Liver Panel (AST/ALT/Bilirubin)	X	X				
Urine Protein[8]	X			X		
Blood or Urine Pregnancy Test[3]	X			X		X[9]
K-ras mutation Status	X					
PT/INR	X[10]					
RADIOLOGIC EVALUATION						
CT scans (chest/abd/pelvis)	X				X[4]	X
Pathology Submissions[11]	X					

Rev. 6/14

Rev. 11/14

Rev. 12/14

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.

Rev. 12/14

6. Toxicity Assessment every 2 weeks 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.

Rev. 11/14

8. UPC or urine protein on dipstick or routine urinalysis (UA). However, in the occurrence of 2+ urine protein on dipstick or UA or a UPC ≥ 0.5, a 24-hour urine collection for protein must be obtained.
9. At the end of treatment with a 30 day safety followup. Repeat as clinically indicated.

Rev. 12/14

10. 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).
11. 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] -IHpyroano [3',4':6, 7I 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 toposisomerase-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.

Rev. 6/14

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/m^2 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/m^2 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 <u>not</u> 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 IgG_1 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.

Rev. 6/14

8.2.5 Dose Specifics

8.2.5.1 Arms A (IC) and B (ICR)

Cetuximab will be given as a 500 mg/m^2 dose every 2 weeks.

8.2.5.2 Arm C (mICR)

Cetuximab will be given as a 400 mg/m^2 dose every 2 weeks.

8.2.6 Preparation

The product is formulated to 2 mg protein/mL with phosphate buffered saline, pH 7.2 $\pm$ 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.

Rev. 12/14

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.

Rev. 12/11

The initial dose of cetuximab is 400 mg/m^2 or 500 mg/m^2 as assigned 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

Body System **Preferred Term**[1]	**ERBITUX plus Irinotecan (n=354)**		**ERBITUX Monotherapy (n=279)**	
	Grades 1 - 4	**Grades 3 and 4**	**Grades 1 - 4**	**Grades 3 and 4**
	% of Patients			
Body as a Whole				
Asthenia/Malaise[2]	73	16	49	10
Abdominal Pain	45	8	25	7
Fever[3]	34	4	33	0
Pain	23	6	19	5
Infusion Reaction[4]	19	3	25	2
Infection	16	1	11	1
Back Pain	16	3	11	3
Headache	14	2	25	3
Digestive				
Diarrhea	72	22	28	2
Nausea	55	6	29	2
Vomiting	41	7	25	3
Anorexia	36	4	25	3
Constipation	30	2	28	1
Stomatitis	26	2	11	<1
Dyspepsia	14	0	7	0
Hematic/Lymphatic				
Leukopenia	25	17	1	0
Anemia	16	5	10	4
Metabolic/Nutritional				
Weight Loss	21	0	9	1
Peripheral Edema	16	1	10	<1
Dehydration	15	6	9	2
Nervous				
Insomnia	12	0	10	<1
Depression	10	0	9	0
Respiratory				
Dyspnea[3]	23	2	20	7
Cough Increased	20	0	10	1
Skin/Appendages				
Acneiform Rash[5]	88	14	90	10
Alopecia	21	0	5	0
Skin Disorder	15	1	5	0
Nail Disorder	12	<1	16	<1
Pruritus	10	1	10	<1
Conjunctivitis	14	1	7	<1

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

Rev. 5/16

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. For questions regarding cetuximab destruction please contact Lilly at iits_usmail-oncology@lilly.com.

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 (36F° - 46°F). IMC-1121B should be protected from light when being stored. In the event

Rev. 12/11, 5/16

of a temperature excursion, please contact iits_usmail-oncology@lilly.com.

8.3.5 Dose Specifics

Rev. 6/14

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.

Rev. 6/14

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 (36F° - 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.

Rev. 6/15, 5/16

8.3.9 Availability

Ramucirumab is an investigational agent (IND 109448), available free of charge and distributed by Eli Lilly and Company (Lilly). 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.

Drug may be ordered following submission and approval of the required regulatory documents as outlined in Section 4. Please place an order when you have a potential patient or a consented patient. A five cycle supply (ten 50-ml vials containing 500 mg at a concentration of 10mg/ml) of Ramucirumab will be provided.

Investigators must email a completed E7208 Drug Request Form (See Appendix IV) to iits_usmail-oncology@lilly.com and data_account_usmail-sdc@lilly.com.

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.

Institutions should allow 10 business days (excluding Fridays) for shipment of drug from Lilly from receipt of the E7208 Drug Request Form. Shipments will be made from Lilly 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 ECOGACRIN 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 10 business days (excluding Fridays) for shipment of drug from Lilly from receipt of the E7208 Drug Request Form. Shipments will be made from Lilly 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-ACRIN 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 Certificate of Destruction Form located in Appendix V. A copy of this

Rev. 12/11

form should be sent to iits_usmail-oncology@lilly.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.

Rev. 5/16

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)

Rev. 7/12

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. For questions regarding IMC-1121B destruction please contact Lilly at iits_usmail-oncology@lilly.com.

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

Rev. 6/14, 6/14

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.

Rev. 6/14

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.

Rev. 6/14

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.

Rev. 6/14

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.

Rev. 12/11

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 safely 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.

Rev. 6/14

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.

Rev. 6/14

9.4 Gender and Ethnicity

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

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	4	4
Not Hispanic or Latino	50	81	131
Ethnic Category: Total of all subjects	50	85	135
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	5	7	12
Native Hawaiian or other Pacific Islander	0	0	0
White	45	78	123
Racial Category: Total of all subjects	50	85	135

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.

Rev. 12/14

10. Biological Specimen Submissions

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.

Rev. 12/14

NOTE: ECOG-ACRIN requires that all samples submitted must be entered and tracked via the online ECOG-ACRIN Sample Tracking System. See Section 10.3.

10.1 Materials Required For This Protocol

Rev. 12/14

10.1.1 Forms – Must be sent with each submission

- 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

Rev. 12/14

NOTE: If tissue blocks are not available, please contact the ECOG-ACRINCentral Biorepository and Pathology Facility (CBPF) at 1-844744-2420 or eacbpf@mdanderson.org to discuss alternative submission requirements. If pathology materials cannot be submitted, please indicate the in STSand 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:

Rev. 12/14

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

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

Rev. 12/14

Important: 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. 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-acrin.tst@jimmy.harvard.edu

Study Specific Notes

Rev. 12/14

If STS is unavailable at time of sample submission, submit the specimens using the ECOG-ACRIN Generic Specimen Submission Form (#2981) with the required documentation and retroactively enter the information when STS is available. Notify the CBPF the day of by faxing a copy of the submission form to 713-563-6506.

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

Rev. 12/14

Inventories of all samples, submitted from institutions will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of specimens forwarded and utilized for approved laboratory research studies will be submitted by the investigating laboratories to the ECOG-ACRIN Operations Office – Boston upon request in an electronic format defined by the ECOG-ACRIN Operations Office-Boston.

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

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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:

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

Rev. 12/14

4. ECOG-ACRIN Generic Specimen Submission Form (#2981)

Rev. 12/14

Guidelines for Submission of Pathology Materials

The following items should always be included when submitting pathology materials to the ECOG-ACRIN *Central Biorepository and Pathology Facility:*

- Institutional Surgical Pathology Report
- Pathology materials (see attached List of Required Material)

Instructions:

1. Provide the following information **with all specimens submitted**:

   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, The Generic Specimen Submission Form, may be used as a tool to capture information for entering information into STS.The pathologist should return the required pathology samples and surgical pathology reports, along any additional information required. If any other reports are required, they should be obtained from the appropriate department at this time.
3. Keep a copy of STS shipping manifest or Submission Form for your records. (The original should be sent to the CBPF.)
4. Double-check that ALL required forms, reports and pathology samples are included in the package to the Central Biorepository and Pathology Facility. (See appropriate List of Required Material.)

   Pathology specimens submitted WILL NOT be processed by the Biorepository and Pathology Facility until all necessary items are received.

5. Mail pathology materials to:

   ECOG-ACRIN Central Biorepository and Pathology Facility
   MD Anderson Cancer Center
   Department of Pathology, Unit 085
   Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
   1515 Holcombe Blvd
   Houston, TX 77030
   Phone: Toll Free 1-844-744-2420
   (713-745-4440 Local or International Sites)
   Fax: 713-563-6506
   Email: eacbpf@mdanderson.org

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 *Central Biorepository and Pathology Facility* by telephone 1-844-744-2420 or by email: eacbpf@mdanderson.org

Rev. 12/14

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. Institutional pathology report **(must be included with EVERY pathology submission)**.
2. 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

Rev. 12/14

NOTE: If tissue blocks are not available, please contact the ECOG-ACRIN *Central Biorepository and Pathology Facility* (CBPF) at 1-844-744-2420 to discuss alternative submission requirements.

Robert L. Comis, MD, and Mitchell D. Schnall, MD, PhD
Group Co-Chairs

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 request 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 *Central Biorepository and Pathology Facility*.

Rev. 12/14

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 *Central Biorepository and Pathology Facility* at 1-844-744-2420 or by email at eacbpf@mdanderson.org

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address:_____

Phone: _____

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time- point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

9/12/14

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 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]

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

Rev. 6/15, 5/16

Appendix IV

Rev. 12/11, 12/14

Investigational Product Shipment Request Form

Shipping Investigational Products and Related Supplies:
Investigational Product Shipment Request Form

MQS442-010-TL36-v1

Investigational Product Shipment Request Form	
Please send a completed form to: Data_account_USMAIL-SDC@lilly.com & iits_usmail-oncology@lilly.com	
Protocol Trial Alias/Study Code	I4E-IE-I004 (E7208)
Ship-to-address*	
E-mail address*	

Site Number*	Investigator Name*	Attention to, or Other Recipient, Name*	Phone Number of Recipient*
101 - _____			

*Make sure required fields match information in Drug Shipment and Site Identification information provided.

Is this an initial Lilly drug order request? ☐ Yes ☐ No
If YES, please include a copy of your IRB with your drug order - IP Shipment form.

Planned Due Date on Site	
Indicate date material must be received by: Please allow **5** Business days for non-refrigerated shipments. Please allow **10** working days for refrigerated shipments. Refrigerated shipments will not be sent on Fridays.	
Are there any restrictions to specific days or times that product cannot be received? If "Yes," please indicate restrictions below.	☐ Yes ☐ No
Delivery Restrictions:	

Internal Use Only

Item Number	Lot Number (Optional)	Product Description	Qty
NDC 0002-7678-01		Cyramza (Ramucirumab) Injection 500mg/50ml	
NDC 0002-7669-01		Cyramza (Ramucirumab) Injection 100mg/50ml	

Comment	

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

Rev. 5/16

Appendix V

Disposition Form

To Be Completed By Site Personnel and email to its usmail-oncology@lilly.com

Investigator: Site Name / No.:

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 Eli Lilly & Company

I. Reason for Return:

Is an Investigation Required? ☐ Yes ☐ No

II. Inspection:

Date Received: Quantity Received:

Shipper Container Integrity	☐ Satisfactory	☐ Unsatisfactory
Product Container Integrity	☐ Satisfactory	☐ Unsatisfactory
Temperature Indicator	☐ Satisfactory	☐ Unsatisfactory

Comments:

III. Disposition:

☐ Preclinical Inventory Quantity ☐ Destroyed Quantity

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

Rev. 5/16

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 #): _____

Date: _____
CTEP ID: _____
Name of Investigator: _____
NCI Investigator ID #: _____

Time Point	Date of Service	Type of Biopsy Performed	Amount Requested (please itemize costs) Please Note: Amount requested may not exceed $150 per EKG, $50 per UPC and $75 per Pregnancy Test.

☐ **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 the EA drug team at 900.drugorder@jimmy.harvard.edu or 617-632-3610.
Please fax the completed form along with the related test results to 617-632-2063.

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 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:**_____

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 VIII

E7208 Temperature Excursion Form

Rev. 12/11, 5/16

For a copy of the Temperature Excursion Form please contact iits_usmail-oncology@lilly.com