Randomized Phase II Study of Weekly Irinotecan/Carboplatin (ICb) with or without Cetuximab (Erbitux) in Patients with Metastatic Breast Cancer

PROTOCOL 04-070

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ABBREVIATIONS

Abbreviation	Term
5-FU	fluorouracil
ALT	alanine transaminase (also referred to as SGPT)
ANC	absolute neutrophil count
AST	aspartate transaminase (also referred to as SGOT)
AUC	area under curve
BMS	Bristol-Myers Squibb
BUN	blood urea nitrogen
Cmax	maximum mean serum concentration
CO_2	total carbon dioxide
CBC	complete blood count
CR	complete response
ClCr	creatinine clearance
(CR+PR)	objective responses
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Score
eCRF	electronic case report form
EGF	Epidermal growth factor
EGFR	epidermal growth factor receptor
IRC	independent review committee
ILD	Interstitial lung disease
IRB	Institutional Review Board
MBC	metastatic breast cancer
NCI	National Cancer Institute
ICb	irinotecan and carboplatin
PD	progressive disease
Pfizer	Pfizer, Inc.
PFS	progression-free survival
PR	partial response
SD	stable disease
SI	Study Investigator
TGF-α	transforming growth factor-alpha
TTP	time to progression
ULN	upper limits of normal
USON	US Oncology, Inc.
USOR	US Oncology Research, Inc.
WNL	within normal limits

SYNOPSIS

Summary:

Irinotecan and carboplatin (ICb) is a synergistic antineoplastic combination in several cancers. Weekly irinotecan is highly active in MBC.[27] Epidermal growth factor receptor (EGFR) inhibition enhances antitumor activity of both irinotecan and cisplatin in breast cancer preclinical models.[28, 29] We hypothesize that the addition of Erbitux to ICb will increase the overall response rate of the ICb combination and will prolong the median time to progression for patients with metastatic breast cancer.

Objectives:

Primary objectives:

- To determine the objective response rates produced by irinotecan and carboplatin therapy with or without Erbitux

Secondary objectives:

- To calculate the duration of response and stable disease
- To determine the median progression-free survival (PFS) and time to progression (TTP – only for those who progress)
- To determine the median overall survival (OS)
- To determine toxicities for individuals with metastatic breast cancer treated with these study regimens
- To determine EGFR expression for individuals with metastatic breast cancer enrolled on this study

Number of patients: A total of 154 patients with MBC will be enrolled in this trial. Patients will be randomized 1:1 to either ICb + Erbitux or ICb alone followed by Erbitux at progression. One third of the patients in each treatment arm will have hormone receptor negative (ER- and PR-) and HER2 negative (-) breast cancer (triple negative).

Inclusion Criteria:

Note: Please see Section 8.1 for the necessary "Prestudy Assessments".

Male and female patients will be eligible for inclusion in this study if they meet all of the following criteria:

1. Has cytologically or pathologically confirmed breast cancer with documented HER2+ (positive) (3+ by IHC or FISH+) or HER2- (negative) disease. ER, PR, and HER2 status must be documented in the electronic Case Report Form (eCRF).

Note: Patients whose breast cancers are HER2 (2+) by IHC must undergo FISH testing to confirm HER2+ (positive) status.

2. Has clinically confirmed Stage IV metastatic breast cancer (MBC)
3. Has undergone prior Herceptin therapy if breast cancer is HER2+ (positive)

Note: Ascites, pleural effusion, and bone metastases are **not** considered measurable.

4. Has measurable MBC as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) Criteria in Section 10.
5. Has had up to 1 prior chemotherapy regimens for metastatic disease. Previously untreated disease is permitted.
6. Has had no prior treatment with irinotecan, carboplatin, or cisplatin
7. Has an ECOG Performance Status (PS) 0-2 (Appendix I)
8. Is ≥18 years of age
9. Has laboratory values of:

Absolute neutrophil count (ANC)	≥1000 x 10^6/L
Hemoglobin	≥9 g/dL
Total bilirubin	≤1.5 mg/dL
AST and ALT	≤2.5 x upper limit of normal (ULN) unless liver metastases present, then ≤5 x ULN allowed
Serum creatinine	≤2.0 mg/dL
Platelet count	≥75,000 x 10^6/L

10. Any prior radiation therapy has been completed >2 weeks prior to the start of study treatment.

Note: Previously irradiated lesions will **not** be evaluable; however, these patients will still be eligible. Patients must have at least 1 measurable lesion at baseline.

11. Has had a negative serum pregnancy test within 7 days prior to registration (female patients of childbearing potential). A pregnancy test is **also required** within 7 days of Dose 1.
12. If fertile, patient (male or female) has agreed to use an acceptable method of birth control to avoid pregnancy for the duration of the study and for a period of 6 months thereafter
13. Has signed a Patient Informed Consent Form
14. Has signed a Patient Authorization Form (HIPAA)
15. Has paraffin-embedded breast cancer tissue (either paraffin blocks or 20 unstained slides) available for analysis of EGFR, cytokeratin, and other biological markers. These samples will be sent to the Molecular Profiling Institute (MPI; see Appendix VII).

Note: Availability of samples should be confirmed prior to randomization (at latest, prior to first dose).

Exclusion Criteria:

Patients will be excluded from this study if they meet **any** of the following criteria:

1. Has Stage I-III breast cancer or nonmeasurable metastatic breast cancer, or any disease other than that described in inclusion criterion #1
2. Has received prior treatment with irinotecan, carboplatin, or cisplatin
3. Is receiving any concurrent chemotherapy not indicated in the study protocol or any other investigational agent(s)
4. Has received prior therapy, which specifically and directly targets the EGFR pathway. Prior Herceptin **is required for HER2+ patients.**
5. Has had prior severe infusion reaction to a monoclonal antibody
6. Has received organ allograft(s) other than corneal, bone, or skin
7. Has clinically significant uncontrolled cardiac disease (eg, congestive heart failure, symptomatic coronary artery disease or cardiac arrhythmias not well-controlled with medication) or has had a myocardial infarction <12 months
8. Has ongoing peripheral neuropathy >Grade 1
9. Has evidence of symptomatic or untreated central nervous system (CNS) metastases (unless CNS metastases have been irradiated). Chronic steroid treatment for the treatment of CNS metastases must have been discontinued for ≥4 weeks prior to study enrollment.
10. Has any other significant comorbidity that, in the opinion of the clinical Investigator, might compromise any aspect of the study
11. Has active or uncontrolled infection
12. Has acute hepatitis or is known to be HIV positive
13. Has a history of other malignancy within the last 5 years which could affect the diagnosis or assessment of MBC, with the exception of carcinoma of the cervix in situ, carcinoma of the bladder in situ, and basal cell carcinoma
14. Has previously completed a chemotherapy regimen within 3 weeks prior to the start of study treatment, or has related toxicities unresolved prior to the start of study treatment.

Note: If patient was receiving prior weekly or daily chemotherapy, he/she may begin study therapy 2 weeks after stopping prior therapy provided all toxicities have resolved; peripheral neuropathy must be ≤Grade 1 as per exclusion criterion #8 above.

15. Has had major surgery within 3 weeks from the start of study treatment, without complete recovery
16. Has participated in any investigational drug study within 4 weeks preceding the start of study treatment
17. Has received a concurrent immunotherapy or hormonal anticancer agent within 2 weeks prior to the start of the study treatment
18. Is receiving a tyrosine kinase inhibitor (ie, Iressa™)
19. Has had any prior stem cell or bone marrow transplant for any prior hematologic malignancy
20. Is pregnant or lactating
21. Is unable to comply with requirements of study

Medication and Doses:

Table 8. Treatment Schema

Cycle	Week	Day	Arm 1 90 mg/m^2 IV irinotecan AUC=2.0 IV carboplatin	Arm 2 Erbitux 250 mg/m^2 IV 90 mg/m^2 IV irinotecan AUC=2.0 IV carboplatin
1	1	1	✔	✔ (400 mg/m^2 for 1st Erbitux dose only)
	2	8	✔	✔
	3	15	Rest	Erbitux only

*Day 22 is Day 1 of the next cycle

Note: The first dose (Day 1 of Cycle 1 only) is 400 mg/m^2. All other doses of Erbitux are 250 mg/m^2. Patients whose disease progresses on ICb alone (Arm 1) or whose disease progresses after an ICb drug holiday, provided that they have not had any intervening nonprotocol therapy, will cross over to receive single-agent weekly Erbitux at the same dosage as described in Arm 2 of the study until disease progression.

Duration: Subsequent cycles will be initiated every 3 weeks, and will be continued until a patient shows evidence of disease progression or intolerable toxicity. Patients will participate in this study until disease progression.

Efficacy Assessments:

- Response rates
- Duration of response and stable disease
- Median progression-free survival
- Time to progression
- Median overall survival

Safety Assessments:

- Toxicities (graded as per NCI CTCAE v3)
- EGFR expression of tumor tissue

PART I – CLINICAL TRIAL PROTOCOL

1 INTRODUCTION

1.2 BACKGROUND ON BREAST CANCER

Breast cancer is the most common type of noncutaneous cancer among women in the United States, and it is estimated that in 2005, about 211,240 new cases of invasive breast cancer will be diagnosed.[1] Moreover, breast cancer is second only to lung cancer in cancer deaths in women, and by the end of this year, over 40,000 women will lose their lives to this disease.[1] The risk of breast cancer increases gradually with age. Most breast cancers occur in women over age 50, and after age 60, the risk is especially high (median age of patients with breast cancer is between 60-65 years). Despite successful initial treatment, breast cancer will recur in approximately 50% of patients. The 5-year relative survival rate for localized breast cancer (cancer that has not spread to lymph nodes or other locations outside the breast) has increased from 80% in the 1950s to 98% today. In cases of metastatic breast cancer (where the cancer has spread regionally), however, the 5-year survival rate is 80%, and for women with distant metastases, the rate is 26%.[1] Breast cancer is staged according to the American Joint Committee on Cancer Breast TNM Staging Tool (Appendix II).

1.1.1 Chemotherapy in Breast Cancer

Adjuvant chemotherapy has been shown to substantially improve the long-term, relapse-free survival, and overall survival in both premenopausal and postmenopausal women ≤70 years of age with both node-positive and node-negative disease.[2] Furthermore, the use of polychemotherapy (>2 agents) is superior to single agents. Four to 6 cycles of therapy have been shown to provide the most robust results as additional cycles of therapy usually magnify the toxicity profile without any evident benefit. In the 1970s, anthracyclines (ie, doxorubicin and epirubicin) were on the forefront and were used as adjuvant polychemotherapy for breast cancer. Research showed that threshold dose effects for 2 of the most active chemotherapeutic agents, doxorubicin (A) and cyclophosphamide (C), which are frequently given together (AC), appeared to result in a small, but statistically significant improvement versus non-anthracycline containing compounds.[2] In the 1980s, the platinum agents gained popularity as carboplatin and cisplatin showed promising improvements in cancer treatment. In the 1990s, the taxanes (docetaxel and paclitaxel) were found to be active agents in the treatment of metastatic breast cancer (MBC). Despite the regular use of a number of cytotoxic drugs for the treatment of MBC and polychemotherapy regimens derived from them, the median survival for patients with MBC has not been dramatically improved over the last 2 decades.

1.2 BACKGROUND ON IRINOTECAN

Note: Since Camptosar goes off patent in 2007 (during the course of this study) the generic drug (irinotecan) is used throughout the document.

Irinotecan is approved for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy. The approval was based on 3 studies; the studies showed an overall response rate of 12.8% (95% CI: 9.1%-16.6%; 0.7% CR, 12.2% PR) in 304 patients.[3] Among the 193 patients treated at the 125 mg/m^2 starting dose, the overall response rate was 15.0% (95% CI: 10.0%, 20.1%[2 CR, 27 PR]). The median duration of response was 6 months (range, 2.6-15.1 months). The median duration of response for patients beginning therapy at 125 mg/m^2 was 5.8 months (range, 2.6-15.1). Dose limiting toxicities included severe delayed diarrhea and myelosuppression.

Irinotecan itself is a relatively inactive prodrug; however, once it is converted by carboxylesterases to SN-38 (Figure 1), it becomes 2- to 2000-fold more potent as an inhibitor of the nuclear enzyme topoisomerases I.

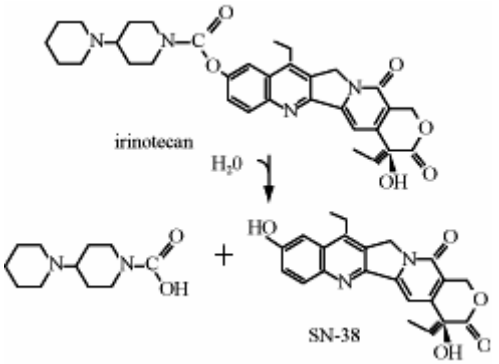

Figure 1. Conversion of irinotecan to SN-38 by de-esterification[4]

Irinotecan and its active metabolite SN-38 bind to the topoisomerase/DNA complex. Since topoisomerase I complexes with DNA only during DNA synthesis, the cytotoxic action of the irinotecan metabolite likely takes place during S-phase. The formation of a topoisomerase I/camptothecin/DNA–cleavable complex results in cell injury or death. Cleavable complexes affect DNA damage through interference with DNA metabolism and damage to the DNA replication fork. After exposure to irinotecan hydrochloride and SN-38 during DNA replication, DNA contains double-strand breaks in the replication forks, unlike the typical single-strand breaks associated with topoisomerase I. It is postulated that topoisomerase I inhibitors kill cells by stabilizing topoisomerase I DNA breaks, causing irreversible double-strand breaks through interference with the process of replication.

Factors that help determine antitumor cytotoxic effects are outlined in Figure 2. Cells with higher levels of topoisomerase are likely more sensitive to topoisomerase inhibition. Resistant cells generally have low levels of topoisomerase and fewer cleavable complexes. Because irinotecan has a unique mechanism of action, clinical response can

be achieved with single-agent therapy in patients who have developed resistance to 5-FU-based regimens.

It has been reported that human colon tumors express high levels of the multiple-drug-resistance 1 (MDR1) gene product, which in cultured cells may limit access of certain drugs to cells.[5] In vitro data have demonstrated that camptothecin and its noncharged derivatives such as irinotecan overcome MDR1-mediated resistance.

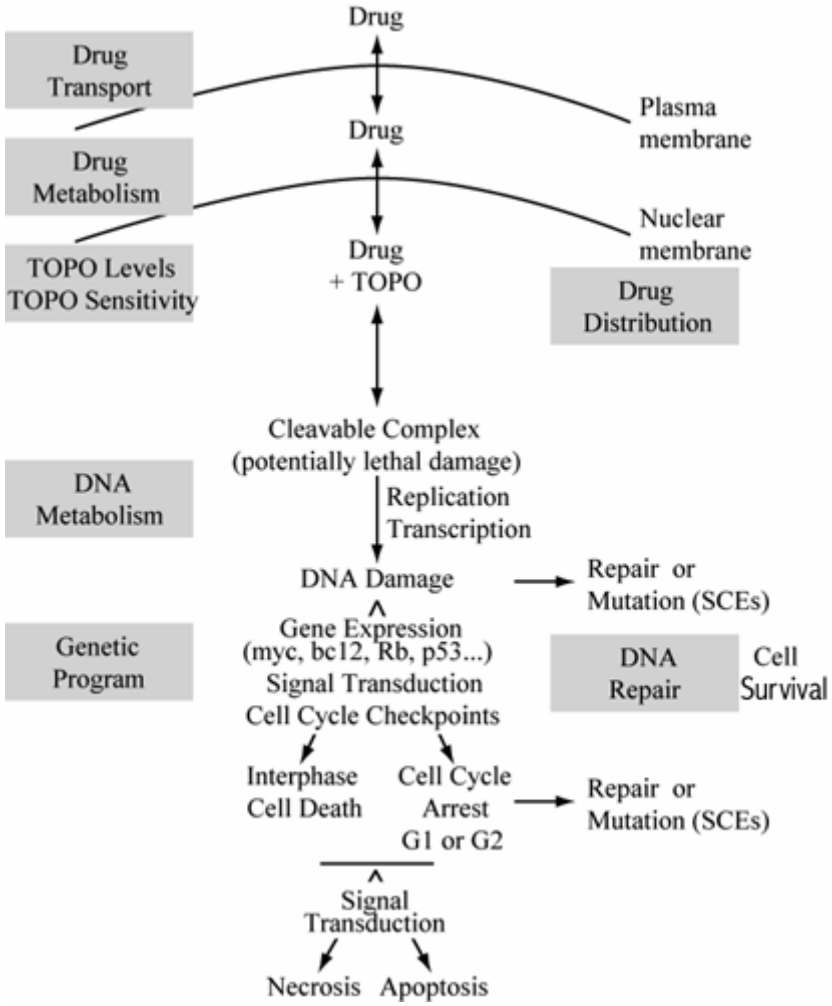

Figure 2. Schematic representation of cellular sensitivity and resistance to topoisomerase inhibitors [5]

The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes and occurs primarily in the liver. SN-38 subsequently undergoes conjugation to form a glucuronide metabolite (SN-38 glucuronide). SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using 2 cell lines in vitro. The disposition of irinotecan has not been fully elucidated in humans.

1.3 BACKGROUND ON CARBOPLATIN

Carboplatin is an analog of cisplatin. Like cisplatin, it contains a platinum atom surrounded in a plane by 2 ammonia groups and 2 other ligands in the *cis* position. The other 2 ligands in carboplatin are present in a ring structure rather than as 2 chloride atoms in cisplatin. This difference makes carboplatin more stable and has less nephrotoxicity, neurotoxicity, ototoxicity and emetogenesis.[7,8] The exact mechanism of action of carboplatin is not known. Carboplatin undergoes intracellular activation to form reactive platinum complexes, which are believed to inhibit DNA synthesis by forming interstrand and intrastrand cross-linking of DNA molecules. Carboplatin is a radiation-sensitizing agent.[9,10] It is cell cycle-phase nonspecific.[8]

1.3.1 Carboplatin in the Treatment of Metastatic Breast Cancer

In 1991, Kolaric and colleagues conducted a Phase II study to determine if carboplatin had any activity against untreated metastatic breast cancer.[11] A total of 20 patients were entered in the study and all were evaluable. Carboplatin was administered IV at a dose of 400 mg/m^2 on day 1, with a 3-week rest period. Carboplatin activity was observed in 4 patients [2 complete remissions (CRs) and 2 partial responses (PRs), for a response rate of 20% (4/20). Remission lasted 2-10 months (mean, 4 months). Toxicity was moderate, producing no drug-related deaths.[11] These results were later confirmed by a similar study conducted by Martin et al. on patients with advanced metastatic breast cancer. In this study 400 mg/m^2 of carboplatin were administered IV every 4 weeks. In this study, patients without prior chemotherapy achieved a 35% response rate. Interestingly, patients with prior exposure to chemotherapy did not respond to carboplatin therapy.[12] A current study by Robert et al. also shows the benefits of carboplatin combination therapy women with HER2 overexpressing MBC. In this study 196 women with HER2 overexpressing MBC received either trastuzumab (4 mg/kg loading dose, 2 mg/kg weekly thereafter), with paclitaxel (175 mg/m^2), and carboplatin (AUC 6) every 3 weeks followed by weekly trastuzumab, or 6 cycles of trastuzumab (4 mg/kg loading dose, 2 mg/kg) weekly thereafter with paclitaxel (175 mg/m^2) every 3 weeks. Overall response was 52% for the trastuzumab + paclitaxel + carboplatin (TPC) arm of the study versus 36% for the trastuzumab + paclitaxel (TP) arm. Median time to progression was 10.7 months for TPC and 7.0 months for TP. Both regimens were well tolerated, though
Grade 3 thrombocytopenia and Grade 4 neutropenia occurred more frequently with TPC.[13]

1.4 BACKGROUND ON IRINOTECAN AND CARBOPLATIN

Currently irinotecan and carboplatin are not used in combination for metastatic breast cancer. The combination, however, is commonly used to treat NSCLC. Wild et al reported their results for a Phase I trial of irinotecan and carboplatin in NSCLC.[13a] In their study 74 subjects were treated with escalating doses of irinotecan and carboplatin. The most common toxicity observed was neutropenia and subjects had a 40% RR to the therapy. They determined the population minimum tolerated dose (pMTD) for irinotecan/carboplatin to be 200 mg/m^2/ AUC=4 for chemo-naïve patients, and 150 mg/m^2/AUC=5 for individuals previously treated with chemotherapy. Fukuda et al

expanded on these findings in 2004 in their Phase II study of irinotecan and carboplatin to treat NSCLC. [14] Their study treated 61 patients with Stage IV disease. Subjects were dosed with irinotecan 50 mg/m^2 (Days 1, 8, and 15) and carboplatin AUC=5 on Day 1 of each 4-week cycle with an AUC of 5 mg min/mL. Of the 61 subjects, 59 were evaluable for toxicity. The most common Grade 3-4 toxicity was neutropenia. Median survival was 10 months. Twenty subjects had a partial response and 26 had stable disease. The overall response rate was 34%.

While the combination of irinotecan with other therapeutic agents has not been studied in the treatment of metastatic breast cancer, there is mounting evidence that irinotecan would serve as an effective agent to treat MBC. Irinotecan has been used to treat advanced recurrent breast cancer. In 2003 Okubo et al. reported on the use of irinotecan on 35 patients with advanced or recurrent breast cancer.[14a] In this study, patients received a weekly dose of irinotecan of 40-160 mg/body. An objective response rate of 6% and a clinical benefit rate of 23% were observed.

Perez et al conducted a Phase II study comparing 2 different irinotecan schedules for patients with MBC resistant to anthracyclines or taxanes.[14b] In this study, 52 patients with MBC were treated with 6-week cycles comprising 100 mg/m^2 weekly for 4 weeks, then a 2-week rest; 51 patients were treated with 240 mg/m^2 every 3 weeks. Patients receiving weekly irinotecan had an objective response of 23%. Patients receiving therapy every 3 weeks had an objective response of 14%. Median response of duration for weekly therapy was 4.9 months versus 4.2 months for the every-3-week schedule. Median overall survival was 9.7 months with weekly therapy versus 8.6 months for every-3-week therapy.

1.5 BACKGROUND ON ERBITUX (CETUXIMAB)

The epidermal growth factor receptor (EGFR) is a member of the erb B receptor tyrosine kinase family that includes erb B-2, erb B-3, and erb B-4.[15] It consists of an extracellular ligand-binding domain, a transmembrane region that anchors the receptor to the plasma membrane, and a cytoplasmic region containing a tyrosine kinase domain. The known natural ligands of EGFR include epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-α), which both activate the receptor by binding to the extracellular domain and inducing the formation of receptor homodimers or heterodimers, followed by internalization of the receptor/ligand complex and auto-phosphorylation. It is now accepted that the EGFR signal transduction network plays an important role in multiple tumorigenic processes, including cell cycle progression, angiogenesis, and metastasis, as well as protection from apoptosis.[15,16] In this signal network, erb B-2 is the major partner of EGFR because activated heterodimer complexes containing erb B-2 are more stable at the cell surface than complexes containing other EGFR family members.[17,18] In addition erb B-2 can decrease the rate of ligand dissociation from the cognate receptor EGFR.[19]

The effects of EGFR blockade on cell cycle progression have been investigated in several human cell types, including DiFi colon adenocarcinoma cells, non-transformed breast epithelial MCF10A cells, A431 squamous epithelial carcinoma cells, and DU145 prostatic cancer cells. These studies suggest that blocking EGFR with monoclonal

antibodies such as cetuximab leads to cell cycle arrest in G_1, which is accompanied by a decrease in cyclin dependent kinase (CDK) 2 activity, and an increase in the expression of CDK inhibitor $p27^{kip1}$. [20,21] In addition to inducing G_1-phase arrest, EGFR blockade was also shown to lead to cell death via apoptosis in DiFi colon adenocarcinoma cells.[22]

Cetuximab binds specifically to the epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) on both normal and tumor cells, and competitively inhibits the binding of EGF and other ligands, such as TGF-α.[23] Binding of cetuximab to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. The EGFR is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR (HER1), HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Overexpression of EGFR is also detected in many human cancers including those of the colon and rectum.

In vitro assays and in vivo animal studies have shown that cetuximab inhibits the growth and survival of tumor cells that overexpress the EGFR. No antitumor effects of cetuximab were observed in human tumor xenografts lacking EGFR expression. The addition of cetuximab to irinotecan or irinotecan plus 5-fluorouracil in animal studies resulted in an increase in antitumor effects compared to chemotherapy alone.

1.5.1 Human Pharmacokinetics

Cetuximab administered as monotherapy or in combination with concomitant chemotherapy or radiotherapy exhibits nonlinear pharmacokinetics.[24] The area under the concentration time curve (AUC) increased in a greater than dose proportional manner as the dose increased from 20 to 400 mg/m^2. Cetuximab clearance (CL) decreased from 0.08 to 0.02 L/h/m^2 as the dose increased from 20 to 200 mg/m^2, and at doses >200 mg/m^2, it appeared to plateau. The volume of distribution (Vd) for cetuximab appeared to be independent of dose and approximated the vascular space of 2-3 L/m^2.

Following a 2-hour infusion of 400 mg/m^2 of cetuximab, the maximum mean serum concentration (C_{max}) was 184 μg/mL (range, 92-327 μg/mL) and the mean elimination half-life was 97 hours (range, 41-213 hours). A 1-hour infusion of 250 mg/m^2 produced a mean C_{max} of 140 μg/mL (range, 120-170 μg/mL). Following the recommended dose regimen (400 mg/m^2 initial dose/250 mg/m^2 weekly dose), cetuximab concentrations reached steady-state levels by the third weekly infusion with mean peak and trough concentrations across studies ranging from 168 to 235 and 41 to 85 μg/mL, respectively. The mean half-life was 114 hours (range, 75-188 hours).

1.5.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Potential immunogenic responses to cetuximab were assessed using either a double antigen radiometric assay or an enzyme-linked immunosorbant assay. Due to limitations in assay performance and sampling timing, the incidence of antibody development in patients

receiving cetuximab has not been adequately determined. The incidence of antibodies to cetuximab was measured by collecting and analyzing serum prestudy, prior to selected infusions and during treatment follow-up. Patients were considered evaluable if they had a negative pretreatment sample and a post-treatment sample. Non-neutralizing anticetuximab antibodies were detected in 5% (28 of 530) of evaluable patients.[24] In patients positive for anticetuximab antibody, the median time to onset was 44 days (range, 8-281 days). Although the number of seropositive patients is limited, there does not appear to be any relationship between the appearance of antibodies to cetuximab and the safety or antitumor activity of the molecule.

The observed incidence of anticetuximab antibody responses may be influenced by the low sensitivity of available assays, inadequate to reliably detect lower antibody titers. Other factors, which might influence the incidence of anticetuximab antibody response, include sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cetuximab with the incidence of antibodies to other products may be misleading.

1.5.3 Clinical Studies of Cetuximab in Colorectal Cancer: Efficacy

The efficacy and safety of cetuximab alone or in combination with irinotecan were studied in a randomized, controlled trial (329 patients) and in combination with irinotecan in an open-label, single-arm trial (138 patients). Cetuximab was further evaluated as a single agent in a third clinical trial (57 patients). Safety data from 111 patients treated with single agent cetuximab was also evaluated. All trials studied patients with EGFR-expressing metastatic colorectal cancer, whose disease had progressed after receiving an irinotecan-containing regimen.

1.5.3.1 Randomized, Controlled Trials

A multicenter, randomized, controlled clinical trial was conducted in 329 patients randomized to receive either cetuximab plus irinotecan (218 patients) or cetuximab monotherapy (111 patients).[24] In both arms of the study, cetuximab was administered as a 400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly until disease progression or unacceptable toxicity. All patients received a 20-mg test dose on Day 1. In the cetuximab plus irinotecan arm, irinotecan was added to cetuximab using the same dose and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan schedules were 350 mg/m^2 every 3 weeks, 180 mg/m^2 every 2 weeks, or 125 mg/m^2 weekly times 4 doses every 6 weeks. An Independent Radiographic Review Committee (IRC), blinded to the treatment arms, assessed both the progression on prior irinotecan and the response to protocol treatment for all patients.

Of the 329 randomized patients, 206 (63%) were male. The median age was 59 years (range, 26-84), and the majority were Caucasian (n=323, 98%). Eighty-eight percent of patients had baseline Karnofsky Performance Status ≥80. Fifty-eight percent of patients had colon cancer and 40% rectal cancer. Approximately two-thirds (63%) of patients had previously failed oxaliplatin treatment.

The efficacy of cetuximab plus irinotecan or cetuximab monotherapy was evaluated in all randomized patients.

Analyses were also conducted in 2 prespecified subpopulations: irinotecan refractory and irinotecan and oxaliplatin failures. The irinotecan refractory population was defined as randomized patients who had received at least 2 cycles of irinotecan-based chemotherapy prior to treatment with cetuximab, and had independent confirmation of disease progression within 30 days of completion of the last cycle of irinotecan-based chemotherapy.

The irinotecan and oxaliplatin failure population was defined as irinotecan refractory patients who had previously been treated with and failed an oxaliplatin-containing regimen. The objective response rates (ORR) in these populations are presented in Table 1.

Table 1. Objective Response Rates per Independent Review

Populations	Cetuximab + Irinotecan		Cetuximab Monotherapy		Difference (95% CI[a])	
	n	ORR (%)	n	ORR (%)	n	ORR (%)
All Patients	218	22.9	111	10.8	12.1 (4.1 - 20.2)	0.007
Irinotecan-Oxaliplatin Failure	80	23.8	44	11.4	12.4 (-0.8 - 25.6)	0.09
Irinotecan Refractory	132	25.8	69	14.5	11.3 (0.1 - 22.4)	0.07

[a]95% confidence interval for the difference in objective response rates.
[b]Cochran-Mantel-Haenszel test

The median duration of response in the overall population was 5.7 months in the combination arm and 4.2 months in the monotherapy arm. Compared with patients randomized to cetuximab alone, patients randomized to cetuximab and irinotecan experienced a significantly longer median time to disease progression (see Table 2).

Table 2. Time to Progression per Independent Review

Populations	Cetuximab + Irinotecan (median)	Cetuximab Monotherapy (median)	Hazard Ratio (95% CI[a])	Log-rank p-value
All Patients	4.1 mo	1.5 mo	0.54 (0.42 – 0.71)	<0.001
Irinotecan-Oxaliplatin Failure	2.9 mo	1.5 mo	0.48 (0.31 - 0.72)	<0.001
Irinotecan Refractory	4.0 mo	1.5 mo	0.52 (0.37 - 0.73)	<0.001

[a]Hazard ratio of cetuximab + irinotecan: cetuximab monotherapy with 95% confidence interval.

1.5.3.2 Single-Arm Trials

Cetuximab, in combination with irinotecan, was studied in a single-arm, multicenter, open-label clinical trial in 138 patients with EGFR-expressing metastatic colorectal cancer who had progressed following an irinotecan containing regimen.[25] Patients received a 20-mg test dose of cetuximab on Day 1, followed by a 400-mg/m^2 initial dose,

and 250 mg/m^2 weekly until disease progression or unacceptable toxicity. Patients received the same dose and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan schedules were 350 mg/m^2 every 3 weeks or 125 mg/m^2 weekly times four doses every 6 weeks. Of 138 patients enrolled, 74 patients had documented progression to irinotecan as determined by an independent review committee (IRC). This IRC used an identical charter to the IRC, which reviewed the randomized trial. The study was initially reported using a different IRC and charter. The overall response rate was 15% for the overall population and 12% for the irinotecan failure population. The median duration of response was 6.5 and 6.7 months, respectively.[23]

Cetuximab was studied as a single agent in a multicenter, open-label, single-arm clinical trial in patients with EGFR-expressing metastatic colorectal cancer who progressed following an irinotecan-containing regimen.[25] Of 57 patients enrolled, 28 patients had documented progression on irinotecan. The overall response rate was 9% for the all treated group and 14% for the irinotecan failure group. The median times to progression were 1.4 and 1.3 months, respectively. The median duration of response was 4.2 months for both groups.

1.5.3.3 EGFR Expression and Response

Patients enrolled in the clinical studies were required to have immunohistochemical evidence of positive EGFR expression. Primary tumor or tumor from a metastatic site was tested with the DakoCytomation EGFR pharmDx™ test kit.[23] Specimens were scored based on the percentage of cells expressing EGFR and intensity (barely/faint, weak to moderate, and strong). Response rate did not correlate with either the percentage of positive cells or the intensity of EGFR expression.

1.5.4 Safety of Cetuximab in Clinical Studies

1.5.4.1 Anticipated Adverse Events

Except where indicated, the data described below reflect exposure to cetuximab in 774 patients with advanced metastatic colorectal cancer. Cetuximab was studied in combination with irinotecan (n=354) or as monotherapy (n=420). 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 36/420 (9%) treated for over 6 months]. The population had a median age of 59 years and was 59% 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 (0.4%)
- 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 patients (10%) receiving cetuximab plus irinotecan and 17 patients (4%) receiving cetuximab monotherapy discontinued treatment primarily because of adverse events.

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

The most common adverse events seen in 420 patients receiving cetuximab monotherapy were acneform rash (90%); asthenia/malaise (48%); nausea (29%); fever (27%); constipation, abdominal pain, and headache (26% each), and diarrhea (25%).

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 Table 3 are based on the experience of 354 patients treated with cetuximab plus irinotecan and 420 patients treated with cetuximab monotherapy.

Table 3. Incidence of Adverse Events (≥10%) in Patients with Advanced Colorectal Carcinoma

	Cetuximab plus Irinotecan (n=354)		Cetuximab Monotherapy (n=420)	
Body System Preferred Term[1]	**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	48	10
Abdominal pain	45	8	26	9
Fever[3]	34	4	27	<1
Pain	23	6	17	5
Infusion reaction[4]	19	3	21	2
Infection	16	1	14	1
Back pain	16	3	10	2
Headache	14	2	26	2
Digestive				
Diarrhea	72	22	25	2
Nausea	55	6	29	2
Vomiting	41	7	25	3
Anorexia	36	4	23	2
Constipation	30	2	26	2
Stomatitis	26	2	10	<1
Dyspepsia	14	0	6	0
Hematic/Lymphatic				
Leukopenia	25	17	<1	0
Anemia	16	5	9	3
Metabolic/Nutritional				
Weight loss	21	0	7	1
Peripheral edema	16	1	10	1
Dehydration	15	6	10	3
Nervous				
Insomnia	12	0	10	<1
Depression	10	0	7	0
Respiratory				
Dyspnea[3]	23	2	17	7
Cough increased	20	0	11	1
Skin/Appendages				
Acneform rash[5]	88	14	90	8
Alopecia	21	0	4	0
Skin disorder	15	1	4	0
Nail disorder	12	<1	16	<1
Pruritus	10	1	11	<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 cetuximab plus irinotecan or in ≥10% of patients with refractory colorectal carcinoma treated with cetuximab 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] Acneform rash is defined as any event described as “acne”, “rash”, “maculopapular rash”, “postural rash”, “dry skin”, or “exfoliative dermatitis”.

1.5.4.2 Infusion Reactions

In clinical trials, severe, potentially fatal infusion reactions were reported. These events include the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. In studies in advanced colorectal cancer, severe infusion reactions were observed in 3% of patients receiving cetuximab plus irinotecan and 2% of patients receiving cetuximab monotherapy. Grade 1 and 2 infusion reactions, including chills, fever, and dyspnea usually occurring on the first day of initial dosing, were observed in 16% of patients receiving cetuximab plus irinotecan and 19% of patients receiving cetuximab monotherapy.

A 20-mg test dose of cetuximab was administered intravenously over 10 minutes prior to the initial dose to all patients in earlier studies. The test dose did not reliably identify patients at risk for severe allergic reactions.

Severe infusion reactions occurred with the administration of cetuximab in approximately 3% of patients, rarely with fatal outcome (<1 in 1000). 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.

1.5.4.3 Pulmonary Toxicity

Interstitial lung disease (ILD) was reported in 3 of 774 (<0.5%) patients with advanced colorectal cancer receiving cetuximab. Interstitial pneumonitis with non-cardiogenic pulmonary edema resulting in death was reported in one case. Two patients had pre-existing fibrotic lung disease and experienced an acute exacerbation of their disease while receiving cetuximab in combination with irinotecan. In the clinical investigational program, an additional case of interstitial pneumonitis was reported in a patient with head and neck cancer treated with cetuximab and cisplatin. The onset of symptoms occurred between the fourth and eleventh doses of treatment in all reported cases.

1.5.4.4 Dermatologic Toxicity

In cynomolgus monkeys, cetuximab, when administered at doses of approximately 0.4 to 4 times the weekly human exposure (based on total body surface area), resulted in dermatologic findings, including inflammation at the injection site and desquamation of the external integument.[23] At the highest dose level, the epithelial mucosa of the nasal passage, esophagus, and tongue were similarly affected, and degenerative changes in the renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of the animals at the highest dose level beginning after approximately 13 weeks of treatment.

In clinical studies of cetuximab, dermatologic toxicities, including acneform rash, skin drying and fissuring, and inflammatory and infectious sequelae (eg, blepharitis, cheilitis, cellulitis, cyst) were reported. In patients with advanced colorectal cancer, acneform rash was reported in 89% (686/774) of all treated patients, and was severe (Grade 3 or 4) in 11% (84/774) of these patients. Subsequent to the development of severe dermatologic

toxicities, complications including *S. aureus* sepsis and abscesses requiring incision and drainage were reported.

Non-suppurative acneform rash described as "acne", "rash", "maculopapular rash", "pustular rash", "dry skin", or "exfoliative dermatitis" was observed in patients receiving cetuximab plus irinotecan or cetuximab monotherapy. One or more of the dermatological adverse events were reported in 88% (14% Grade 3) of patients receiving cetuximab plus irinotecan and in 90% (8% Grade 3) of patients receiving cetuximab monotherapy. Acneform rash most commonly occurred on the face, upper chest, and back, but could extend to the extremities and was characterized by multiple follicular- or pustular-appearing lesions. Skin drying and fissuring were common in some instances, and were associated with inflammatory and infectious sequelae (eg, blepharitis, cellulitis, cyst). Two cases of *S. aureus* sepsis were reported. The onset of acneform rash was generally within the first 2 weeks of therapy. Although in a majority of the patients the event resolved following cessation of treatment, in nearly half of the cases, the event continued beyond 28 days.

A related nail disorder, occurring in 14% of patients (0.4% Grade 3), was characterized as a paronychial inflammation with associated swelling of the lateral nail folds of the toes and fingers, with the great toes and thumbs as the most commonly affected digits.

1.6 RATIONALE

Irinotecan and carboplatin (ICb) is a synergistic antineoplastic combination in several cancers. Weekly irinotecan is highly active in MBC.[27] Epidermal growth factor receptor (EGFR) inhibition enhances antitumor activity of both irinotecan and cisplatin in breast cancer preclinical models.[28, 29] We hypothesize that the addition of Erbitux to ICb will increase the overall response rate of the ICb combination and will prolong the median time to progression for patients with metastatic breast cancer.

2 TRIAL OBJECTIVES

2.1 PRIMARY OBJECTIVES

- To determine the objective response rates produced by irinotecan and carboplatin therapy with or without Erbitux

2.2 SECONDARY OBJECTIVES

- To calculate the duration of response and stable disease
- To determine the median progression-free survival (PFS) and time to progression (TTP – only for those who progress)
- To determine the median overall survival (OS)
- To determine toxicities for individuals with metastatic breast cancer treated with these study regimens

- To determine EGFR expression for individuals with metastatic breast cancer enrolled on this study

3 STUDY DESIGN

This is a Phase II, noncomparative, randomized study. Patients will receive either irinotecan **90** mg/m^2 and carboplatin AUC=**2.0** on Days 1 and 8 of each 21-day cycle (Arm 1, ICb) **or** irinotecan **90**mg/m^2, carboplatin AUC=**2.0** on Days 1 and 8 of each 21-day cycle plus Erbitux 400 mg/m^2 Week 1 and then 250 mg/m^2 weekly thereafter, (Arm 2, ICb+Erbitux). Cycles will be repeated every 3 weeks. Therapy will continue until disease progression or unacceptable toxicity.

Note: Crossover is one way; only Arm 1 crosses over.

Patients who progress on Arm 1 will cross over to receive Erbitux alone. Patients on Arm 1 who stopped taking ICb for toxicity and who have not received intervening nonprotocol therapy should also cross over to receive Erbitux alone at the time of disease progression. Single-agent Erbitux will be given at a loading dose of 400 mg/m^2 for Week 1 followed by 250 mg/m^2 weekly thereafter, until the further development of PD (patient's PD on ICb is baseline disease on Erbitux as single agent; additional criteria for PD must be met to qualify as PD on single-agent Erbitux) or unacceptable toxicity.

Note: Arm 1 patients on ICb drug holiday who are not receiving intervening nonprotocol therapy should receive all regularly scheduled on-study assessments and tests at each cycle, including laboratory tests.

Patients will be assessed for response, progression, and survival. In addition, the toxicity and safety profiles of the 2 treatment arms will be evaluated.

4 SELECTION OF PATIENTS

4.1 SAMPLE SIZE

A total of 154 patients with MBC will be enrolled in this trial. Patients will be randomized 1:1 to either ICb + Erbitux or ICb alone followed by Erbitux at progression. One-third of the patients (24 patients) in each treatment arm will have hormone receptor negative (ER- and PR-) and HER2 negative (-) breast cancer (triple negative).

4.2 INCLUSION CRITERIA

Note: Please see Section 8.1 for the necessary "Prestudy Assessments".

Male and female patients will be eligible for inclusion in this study if they meet **all** of the following criteria:

1. Has cytologically or pathologically confirmed breast cancer with documented HER2+ (positive) (3+ by IHC or FISH+) or HER2- (negative) disease. ER, PR, and HER2 status must be documented in the electronic Case Report Form (eCRF).

Note: Patients whose breast cancers are HER2 (2+) by IHC must undergo FISH testing to confirm HER2+ (positive) status.

2. Has clinically confirmed Stage IV metastatic breast cancer (MBC)

3. Has undergone prior Herceptin therapy if breast cancer is HER2+ (positive)

4. Has measurable MBC as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) Criteria in Section 10.

Note: Ascites, pleural effusion, and bone metastases are **not** considered measurable.

5. Has had up to 1 prior chemotherapy regimens for metastatic disease. Previously untreated disease is permitted.

6. Has had no prior treatment with irinotecan, carboplatin, or cisplatin

7. Has an ECOG Performance Status (PS) 0-2 (Appendix I)

8. Is ≥18 years of age

9. Has laboratory values of:

Absolute neutrophil count (ANC)	≥1000 x 10^6/L
Hemoglobin	≥9 g/dL
Total bilirubin	≤1.5 mg/dL
AST and ALT	≤2.5 x upper limit of normal (ULN) unless liver metastases present, then ≤5 x ULN allowed
Serum creatinine	≤2.0 mg/dL
Platelet count	≥75,000 x 10^6/L

10. Any prior radiation therapy has been completed >2 weeks prior to the start of study treatment.

Note: Previously irradiated lesions will **not** be evaluable; however, these patients will still be eligible. Patients must have at least 1 measurable lesion at baseline.

11. Has had a negative serum pregnancy test within 7 days prior to registration (female patients of childbearing potential). A pregnancy test is **also required** within 7 days of Dose 1.

12. If fertile, patient (male or female) has agreed to use an acceptable method of birth control to avoid pregnancy for the duration of the study and for a period of 6 months thereafter

13. Has signed a Patient Informed Consent Form

14. Has signed a Patient Authorization Form (HIPAA)

15. Has paraffin-embedded breast cancer tissue (either paraffin blocks or 20 unstained slides) available for analysis of EGFR, cytokeratin, and other biological markers. These samples will be sent to the Molecular Profiling Institute (MPI; see Appendix VII).

Note: Availability of samples should be confirmed prior to randomization (at latest, prior to first dose).

4.3 EXCLUSION CRITERIA

Patients will be excluded from this study if they meet **any** of the following criteria:

1. Has Stage I-III breast cancer or nonmeasurable metastatic breast cancer, or any disease other than that described in inclusion criterion #1

2. Has received prior treatment with irinotecan, carboplatin, or cisplatin

3. Is receiving any concurrent chemotherapy not indicated in the study protocol or any other investigational agent(s)

4. Has received prior therapy, which specifically and directly targets the EGFR pathway. Prior Herceptin **is required for HER2+ patients.**

5. Has had prior severe infusion reaction to a monoclonal antibody

6. Has received organ allograft(s) other than corneal, bone, or skin

7. Has clinically significant uncontrolled cardiac disease (eg, congestive heart failure, symptomatic coronary artery disease or cardiac arrhythmias not well-controlled with medication) or has had a myocardial infarction <12 months

8. Has ongoing peripheral neuropathy >Grade 1

9. Has evidence of symptomatic or untreated central nervous system (CNS) metastases (unless CNS metastases have been irradiated). Chronic steroid treatment for the treatment of CNS metastases must have been discontinued for $\geq$4 weeks prior to study enrollment.

10. Has any other significant comorbidity that, in the opinion of the clinical Investigator, might compromise any aspect of the study

11. Has active or uncontrolled infection

12. Has acute hepatitis or is known to be HIV positive

13. Has a history of other malignancy within the last 5 years which could affect the diagnosis or assessment of MBC, with the exception of carcinoma of the cervix in situ, carcinoma of the bladder in situ, and basal cell carcinoma

14. Has previously completed a chemotherapy regimen within 3 weeks prior to the start of study treatment, or has related toxicities unresolved prior to the start of study treatment.

> **Note:** If patient was receiving prior weekly or daily chemotherapy, he/she may begin study therapy 2 weeks after stopping prior therapy provided all toxicities have resolved; peripheral neuropathy must be ≤Grade 1 as per exclusion criterion #8 above.

15. Has had major surgery within 3 weeks from the start of study treatment, without complete recovery

16. Has participated in any investigational drug study within 4 weeks preceding the start of study treatment

17. Has received a concurrent immunotherapy or hormonal anticancer agent within 2 weeks prior to the start of the study treatment

18. Is receiving a tyrosine kinase inhibitor (ie, Iressa™)

19. Has had any prior stem cell or bone marrow transplant for any prior hematologic malignancy

20. Is pregnant or lactating

21. Is unable to comply with requirements of study

4.4 REASONS OFF TREATMENT

Patients will be taken **off treatment** if any of the following occur: off treatment assessments (Section 8.3) should be completed within 7 days following the last dose of study drug.

1. Disease progression Arm 2 only (follow as per Section 8.4.1). Arm 1 patients who progress will cross over to Erbitux as a single-agent as per Section 7.2.2.

2. Intolerable toxicity **Arm 2** only (follow as per Section 8.4.1). However, if a patient on Arm 2 experiences intolerable toxicity to the ICb portion of the treatment and is CR, PR, or SD, the patient may continue treatment with Erbitux alone after discussion of the individual case with the Study Investigator. **Arm 1** patients who discontinued ICb due to toxicity and who progress will cross over to Erbitux as a single-agent as per Section 7.2.2, provided that they have not received any intervening nonprotocol therapy.

3. Treatment is interrupted for more than 3 weeks on **Arm 2** for any reason (follow as per Section 8.4.1). If treatment is interrupted for >3 weeks on the ICb portion of **Arm 1**, the patient should discontinue ICb but remain on study, provided that no intervening nonprotocol therapy is received, until disease progression when the patient will cross over to Erbitux alone as stated in No. 2 above.

4. For patients who have crossed over to single-agent Erbitux, any treatment interruption for more than 3 weeks (follow as per Section 8.4.1)

5. An intercurrent illness that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree or require discontinuation of study treatment (follow as per Section 8.4.1)

6. Nonprotocol therapy (chemotherapy, radiotherapy, hormonal therapy, immunotherapy, or surgery) is administered during study treatment (follow as per Section 8.4.1)

7. Noncompliance with protocol or treatment (follow as per Section 8.4.1)

8. The patient becomes pregnant (follow as per Section 8.4.1)

9. The patient refuses to continue treatment (follow as per Section 8.4.1)

10. Patient completes the treatment portion of the protocol (follow as per Section 8.4.2.)

11. Physician decision (follow as per Section 8.4.1)

The date of and reason for discontinuation must be noted on the Change of Status page of the electronic Case Report Form (eCRF). Every effort should be made to complete the appropriate assessments.

4.5 REASONS OFF STUDY

Patients will be considered **off study** if any of the following occur:

1. Termination of study by USOR and/or BMS

2. Patient is lost to follow-up. If a patient does not return for scheduled visits, every effort should be made to re-establish contact. In any circumstance, every effort should be made to document patient outcome, if possible.

3. Withdrawal of consent (patient will not be contacted and no further information will be collected)

4. Death

The appropriate information must be completed on the Change of Status page of the eCRF.

5 CONCOMITANT THERAPY

Administration of other chemotherapy or immunotherapy, or hormonal therapy, or experimental medications during the study is not allowed. Patients cannot receive radiation therapy while receiving study therapy without previous discussion with the SI.

Supportive care may be administered at the discretion of the Investigator. Replacement steroids are permitted. All concomitant treatments, including blood and blood products, must be reported on the source documentation (not necessarily in the eCRF). The following concomitant medications **must** be documented on the Con Meds page of the eCRF:

- Blood and blood products
- Prophylactic antibiotics
- Premedications
- All con meds at baseline
- Antifungals
- Hematopoietic growth factors
- Antibiotics

Herbal therapies or alternative therapies are permitted but discouraged.

5.1 DRUG-DRUG INTERACTIONS

5.1.1 Irinotecan

The adverse effects of irinotecan, such as myelosuppression and diarrhea, would be expected to be exacerbated by other antineoplastic agents having similar adverse effects.

Patients who have previously received pelvic and/or abdominal irradiation are at increased risk of severe myelosuppression following the administration of irinotecan. The concurrent administration of irinotecan with irradiation has not been adequately studied and is not recommended.

Lymphocytopenia has been reported in patients receiving irinotecan, and it is possible that the administration of dexamethasone as antiemetic prophylaxis may increase the likelihood of this effect. However, serious opportunistic infections have not been observed, and no complications have specifically been attributed to lymphocytopenia. **The use of dexamethasone as an antiemetic is allowed.**

Hyperglycemia has also been reported in patients receiving irinotecan. Usually, this has been observed in patients with a history of diabetes mellitus or evidence of glucose intolerance prior to administration of irinotecan. It is probable that dexamethasone, given as antiemetic prophylaxis, contributed to hyperglycemia in some patients.

The incidence of akathisia in clinical trials was greater (8.5%, 4/47 patients) when prochlorperazine was administered on the same day as irinotecan than when these drugs were given on separate days (1.3%, 1/80 patients). The 8.5% incidence of akathisia,

however, is within the range reported for use of prochlorperazine when given as a premedication for other chemotherapies.

It would be expected that laxative use during therapy with irinotecan would worsen the incidence or severity of diarrhea, but this has not been studied.

In view of the potential risk of dehydration, secondary to vomiting and/or diarrhea induced by irinotecan, the physician may wish to withhold diuretics during dosing with irinotecan and certainly during periods of active vomiting or diarrhea.

5.1.2 Carboplatin

The renal effects of nephrotoxic compounds may be potentiated by carboplatin.

5.1.3 Erbitux

A drug interaction study was performed in which Erbitux was administered in combination with irinotecan. There was no evidence of any pharmacokinetic interactions between Erbitux and irinotecan.

6 THERAPEUTIC AGENTS

6.1 IRINOTECAN (CAMPTOSAR®, IRINOTECAN HCL, CPT-11 PI 5/02)

Note: since Camptosar goes off patent in 2007 (during the course of this study) the generic drug (irinotecan) is used in the dosing schema; CPT-11 is used for pharmacokinetics and drug substance discussions.

Irinotecan (CPT-11, irinotecan HCl, Camptosar®) is a topoisomerase I inhibitor that exhibits antitumor activity by inducing irreversible double-strand DNA damage and apoptosis. This drug is commercially available. Irinotecan is indicated as a component of first line therapy in combination with 5-FU and LV in patients with metastatic cancer of the colon or rectum. It is also indicated for patients whose metastatic colon or rectal cancer has recurred or progressed following initial 5-FU therapy.

6.1.1 Formulation

Irinotecan is being supplied for this study by Pfizer, Inc.

Irinotecan is supplied as a sterile, pale yellow, clear, aqueous solution. It is available in 2 single-dose sizes: 2 mL vials containing 40 mg irinotecan and 5 mL vials containing 100 mg irinotecan. Each milliliter of solution contains 20 mg of irinotecan (on the basis of the trihydrate salt), 45 mg of sorbitol NF powder, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.5 (range, 3.0-3.8) with sodium hydroxide or hydrochloric acid.

6.1.2 Storage and Stability

Vials of irinotecan injection should be stored at a controlled room temperature (15° to 30°C, 59° to 86°F) and protected from light. It is recommended that the vial (and backing/plastic blister) remain in the carton until the time of use.

Once diluted, the solution is physically and chemically stable for up to 24 hours at room temperature (approximately 25°C) and in ambient fluorescent lighting. Diluted solutions stored at refrigerated temperatures (approximately 2° to 8°C, 36° to 46°F) and protected from light are physically and chemically stable for 48 hours if prepared in a certified sterile hood. If the diluted solutions are prepared at the counter, it is advisable to use the refrigerated solution within 24 hours due to possible microbial contamination. Freezing irinotecan and admixtures of irinotecan may result in precipitation of the drug and should be avoided. Diluted solutions should be used within 6 hours if kept at room temperature (15° to 30°C, 59° to 86°F). Other drugs should not be added to the infusion solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration when solution and container permit.

6.1.3 Preparation and Administration

Care should be exercised in the handling and preparation of infusion solutions prepared from irinotecan injection. The use of gloves is recommended. If a solution of irinotecan contacts the skin, wash the skin immediately and thoroughly with soap and water. If irinotecan contacts the mucous membranes, flush thoroughly with water.

If possible, irinotecan diluted solution should be prepared in a certified sterile hood. Vial contents should be inspected for particulate matter and when drug product is withdrawn from vial into syringe. Irinotecan injection must be diluted prior to infusion. Irinotecan should be diluted in 5% Dextrose injection, USP, to a final concentration range of 0.12 to 2.8 mg/mL. In most clinical trials, irinotecan was administered in 250 mL to 500 mL of 5% Dextrose injection, USP.

Irinotecan should be administered by intravenous infusion over 90 minutes.

6.1.4 Pharmacokinetics

Pharmacokinetic parameters for irinotecan (CPT-11) and its active metabolite SN38 following a 90-minute infusion of CPT-11 at dose levels of 125 and 340 mg/m^2 were determined in 2 clinical studies in patients with solid tumors. Pharmacokinetic data are summarized in Table 4.

Table 4. Summary of Mean (±SD) CPT-11 and SN38 Pharmacokinetic Parameters in Patients with Solid Tumors

	CPT-11					SN38		
Dose (mg/m^2)	**C_{max} (ng/mL)**	**AUC_{0-24} (ng·h/mL)**	**$T_{1/2}$ (h)**	**V_z (L/m^2)**	**CL ($L/h/m^2$)**	**C_{max} (ng/mL)**	**AUC_{0-24} (ng·h/mL)**	**$T_{1/2}$ (h)**
125 (N=64)	1,660 ± 797	10,200 ± 6,027	5.8[a] ± 0.7	110 ± 48.5	13.3 ± 6.01	26.3 ± 11.9	229 ± 108	10.4[a] ± 3.1
340 (N=6)	3,392 ± 874	20,604 ± 6,027	11.7[b] ± 1.0	234 ± 69.6	13.9 ± 4.00	56.0 ± 28.2	474 ± 245	21.0[b] ± 4.3

C_{max} Maximum plasma concentration
AUC_{0-24} Area under the plasma concentration-time curve from time 0 to 24 hours after the end of the 90-minute infusion
$T_{1/2}$ Terminal elimination half-life
V_z Volume of distribution of terminal elimination phase
CL Total systemic clearance
a Plasma specimens collected for 24 hours following the end of the 90-minute infusion.
b Plasma specimens collected for 48 hours following the end of the 90-minute infusion. Because of the longer collection period, these values provide a more accurate reflection of the terminal elimination half-lives of CPT-11 and SN38.

6.1.5 Adverse Effects

A Phase III study investigated the addition of irinotecan to a 5-FU + LV regimen versus administration of irinotecan alone in patients with metastatic colorectal cancer. Table 5 lists the adverse events that were reported with irinotecan treatment alone.

Death

Thirteen patients (5.8%) died. Two of these deaths (0.9%) were treatment-related (neutropenic fever).

Hematologic

Patients with baseline serum total bilirubin levels of 1.0 mg/dL or more also had a significantly greater likelihood of experiencing first-course Grade 3 or 4 neutropenia than those with bilirubin levels less than 1.0 mg/dL (50% vs. 18%). In addition, neutropenic fever (concurrent Grade 4 neutropenia and Grade 2 or greater fever) occurred in 3% of the patients.

Table 5. Adverse Events Attributed to CPT-11 (Irinotecan) in Patients with Metastatic Colorectal Cancer

	Grade 1-4	Grade 3-4
Total: Adverse Events	**99.6**	**45.7**
Gastrointestinal		
Diarrhea		
Late	83.0	31.0
Grade 3	0	18.4
Grade 4	0	12.6
Early	43.0	6.7
Nausea	81.6	16.1
Abdominal Pain	67.7	13.0
Vomiting	62.8	12.1
Anorexia	43.9	7.2
Constipation	32.3	0.4
Mucositis	29.6	2.2
Hematologic		
Neutropenia	96.4	31.4
Grade 3	0	19.3
Grade 4	0	12.1
Leukopenia	96.4	21.5
Anemia	96.9	4.5
Neutropenic Fever	0	5.8
Thrombocytopenia	96.0	1.7
Neutropenic Infection	0	2.2
Body as a Whole		
Asthenia	69.1	13.9
Pain	22.9	2.2
Fever	43.5	0.4
Infection	13.9	0.4
Metabolic and Nutritional		
Increased Bilirubin	83.9	7.2
Dermatologic		
Exfoliative Dermatitis	0	0
Rash	14.3	0.4
Alopecia	46.1	0
Respiratory		
Dyspnea	22.0	2.2
Cough	20.2	0.4
Pneumonia	3.6	1.3
Neurologic		
Dizziness	21.1	1.8
Somnolence	9.4	1.3
Confusion	2.7	0
Cardiovascular		
Vasodilation	9.0	0
Hypotension	5.8	1.7
Thromboembolic Events	5.4	0
Grading based on CTC Version 1.0		

Teratogenic

Irinotecan may cause fetal harm when administered to a pregnant woman. Radioactivity related to ^{14}C-irinotecan (CPT-11) crosses the placenta of rats following IV administration of 10 mg/kg (which in separate studies produces a CPT-11 C_{max} and AUC about 3 and 0.5 times, respectively, the corresponding values in patients administered 125 mg/m^2). Administration of 6 mg/kg/day intravenous CPT-11 to rats and rabbits during the period of organogenesis was embryotoxic, as characterized by increased post-implantation loss and decreased numbers of live fetuses. CPT-11 was teratogenic in rats at doses greater than 1.2 mg/kg/day and in rabbits at 6.0 mg/kg/day. Teratogenic effects included a variety of external, visceral, and skeletal abnormalities. CPT-11 administration to rat dams for the period following organogenesis through weaning at doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights in the offspring.

Pregnancy

There are no adequate and well-controlled studies of irinotecan in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with irinotecan.

Nursing Mothers

Radioactivity appeared in rat milk within 5 minutes of intravenous administration of radiolabeled CPT-11 and was concentrated up to 65-fold at 4 hours after administration relative to plasma concentrations. It is recommended that nursing be discontinued while receiving therapy with CPT-11.

Please see the package insert for additional adverse events.

6.2 CARBOPLATIN (PARAPLATIN® OR EQUIVALENT PI 6/2001)

Carboplatin (Paraplatin for injection) is a platinum coordination compound that is used as a cancer chemotherapeutic agent. Carboplatin is indicated for the treatment of advanced ovarian cancer. Carboplatin is commercially available from Bristol-Myers Squibb.

6.2.1 Formulation

Carboplatin (Paraplatin for injection) is a platinum coordination compound; the chemical name is platinum, diammine [1,1-cyclobutanedicarboxylato (2-)-0, 0']-,(SP-4-2). Carboplatin is a crystalline powder with the molecular formulation $C_6H_{12}N_2O_4Pt$ and a molecular weight of 371.25.

6.2.2 Storage and Stability

Unopened vials of carboplatin should be stored at 25°C (77°F); excursions are permitted to 15° - 30°C (59°-86°F). Unopened vials should be protected from light. Solutions for infusion should be discarded 8 hours after preparation.

Unopened vials of carboplatin are stable for the life indicated on the package. When stored at the temperatures indicated above and protected from light. When prepared as directed, carboplatin solutions are stable for 8 hours at room temperature (25°C). Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded 8 hours after dilution. Parenteral drugs should be inspected visually for particulate matter and discoloration prior to administration.

6.2.3 Preparation and Administration

Immediately before use, the content of each vial must be reconstituted with either Sterile Water for Injection, USP; 5% Dextrose in Water (D_5W); or 0.9% Sodium Chloride Injection, USP, according to the following schedule:

Vial Strength	Diluent Volume
50 mg	5 mL
150 mg	15 mL
450 mg	45 mL

These dilutions all produce a carboplatin concentration of 10 mg/mL. Carboplatin can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D_5W) or 0.9% Sodium Chloride Injection, USP

6.2.4 Pharmacokinetics

Carboplatin, like cisplatin, produces predominantly interstrand DNA cross-links rather than DNA-protein cross-links. This effect is apparently cell-cycle nonspecific. The aquation of carboplatin, which is thought to produce the active species, occurs at a slower rate than in the case of cisplatin. Despite this difference, it appears that both carboplatin and cisplatin induce equal numbers of drug-DNA cross-links, causing equivalent lesions and biological effects. The differences in potencies for carboplatin and cisplatin appear to be directly related to the difference in aquation rates.

In patients with creatinine clearances of about 60 mL/min or greater, plasma levels of intact carboplatin decay in a biphasic manner after a 30-minute intravenous infusion of 300 to 500 mg/m^2 of carboplatin. The initial plasma half-life (alpha) was found to be 1.1 to 2 hours (N = 6), and the post distribution plasma half-life (beta) was found to be 2.6 to 5.9 hours (N = 6). The total body clearance, apparent volume of distribution and mean residence time for carboplatin are 4.4 L/ hour, 16 L and 3.5 hours, respectively. The C_{max} values and areas under the plasma concentration vs. time curves from 0 to infinity ($AUC_{0-\infty}$) increase linearly with dose, although the increase was slightly more than dose proportional. Carboplatin, therefore, exhibits linear pharmacokinetics over the dosing range studied (300-500 mg/m^2).

Carboplatin is not bound to plasma proteins. No significant quantities of protein-free, ultrafilterable platinum-containing species other than carboplatin are present in plasma. However, platinum from carboplatin becomes irreversibly bound to plasma proteins and is slowly eliminated with a minimum half-life of 5 days.

The major route of elimination of carboplatin is renal excretion. Patients with creatinine clearances of approximately 60 mL/min or greater excrete 65% of the dose in the urine within 12 hours and 71% of the dose within 24 hours. All of the platinum in the 24-hour urine is present as carboplatin. Only 3 to 5% of the administered platinum is excreted in the urine between 24 and 96 hours. There are insufficient data to determine whether biliary excretion occurs.

In patients with creatinine clearances below 60 mL/min the total body and renal clearances of carboplatin decrease as the creatinine clearance decreases. Carboplatin dosages should therefore be reduced in these patients.

6.2.5 Adverse Effects

Adverse event information was compiled from studies of patients with ovarian cancer and compared 2 cisplatin combinations (NCIC study and SWOG study).[30] The pattern of toxicity exerted by the carboplatin-containing regimen was significantly different from that of the cisplatin-containing combinations. Differences between the 2 studies may be explained by different cisplatin dosages and by different supportive care. The carboplatin-containing regimen induced significantly more thrombocytopenia and, in 1 study, significantly more leukopenia and more need for transfusional support. The cisplatin-containing regimen produced significantly more anemia in 1 study. However, no significant differences occurred in incidences of infections and hemorrhagic episodes.

Nonhematologic toxicities (emesis, neurotoxicity, ototoxicity, renal toxicity, hypomagnesemia, and alopecia) were significantly more frequent in the cisplatin-containing arms.

Data from a single-agent study is summarized in Table 6.

Table 6. Adverse Experiences in Ovarian Cancer Patients Treated with Carboplatin	
Event	**Percent**
Bone marrow	
Thrombocytopenia (<100,000/mm^3)	62
Thrombocytopenia (<50,000/mm^3)	35
Neutropenia (<2,000 cells/mm^3)	67
Neutropenia (<1,000 cells/mm^3)	21
Leukopenia (<4,000/mm^3)	85
Leukopenia (<2,000/mm^3)	26
Anemia (<11 g/dL)	90
Anemia (<8 g/dL)	21
Infections	5
Bleeding	5
Transfusions	44
Gastrointestinal	
Nausea and vomiting	92
Vomiting	81
Other GI side effects	21
Neurologic	
Peripheral neuropathies	6
Ototoxicity	1
Other sensory side effects	1
Central neurotoxicity	5
Renal	
Serum creatinine elevations	10
Blood urea elevations	22
Hepatic	
Bilirubin elevations	5
SGOT elevations	19
Alkaline phosphatase elevations	37
Electrolyte loss	
Sodium	47
Potassium	28
Calcium	31
Magnesium	43
Other side effects	
Pain	23
Asthenia	11
Cardiovascular	6
Respiratory	6
Allergic	2
Genitourinary	2
Alopecia	2
Mucositis	1

Please see the package insert for additional adverse events.

6.3 CETUXIMAB (ERBITUX™ PI 2/04)

Cetuximab is an antiEGFR 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.

6.3.1 Supplier/How Supplied

Bristol-Myers Squibb (BMS) will supply Erbitux (cetuximab) free of charge to the patient. The product is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous cetuximab particulates. Each single-use 50-mL vial contains 100 mg of cetuximab at a concentration of 2 mg/mL and is formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.42mg/mL sodium phosphate monobasic monohydrate, and Water for injection, USP.

6.3.2 Packaging and Labeling

Cetuximab for injection will be supplied by BMS in single-use, ready-to-use 50-mL vials containing 2 mg/mL of product.

6.3.3 Handling and Dispensing of Erbitux

Erbitux must be dispensed only from official study sites by authorized personnel according to local regulations. Erbitux should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that study drug is only dispensed to study patients.

6.3.4 Storage Requirement/Stability

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 Erbitux in infusion containers are chemically and physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) or 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° to 8° C. Discard any unused portion of the vial.

6.3.5 Preparation and Administration

Erbitux must not be administered as an IV push or bolus.

Erbitux must be administered with the use of a low protein binding 0.22-micrometer in-line filter.

Erbitux 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**.

Erbitux can be administered via infusion pump or syringe pump.

Infusion Pump:

- 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).
- Fill Erbitux into a sterile evacuated container or bag such as glass containers, polyolefin bags (eg, Baxter Intravia ®), ethylene vinyl acetate bags (eg, Baxter Clintec®), DEHP plasticized PVC bags (eg, Abbott Lifecare®), or PVC bags.
- Repeat procedure until the calculated volume has been put in to the container. Use a new needle for each vial.
- Administer through a low protein binding 0.22-micrometer in-line filter (placed as proximal to the patient as practical).
- Affix the infusion line and prime it with Erbitux before starting the infusion.
- Maximum infusion rate should not exceed 5 mL/min.
- Use 0.9% saline solution to flush line at the end of infusion.

Syringe Pump:

- Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike may be used).
- Place the syringe into the syringe driver of a syringe pump and set the rate.
- Administer through a low protein binding 0.22-micrometer in-line filter rated for syringe pump use (placed as proximal to the patient as practical).
- Connect up the infusion line and start the infusion after priming the line with Erbitux.
- Repeat procedure until the calculated volume has been infused.
- Use a new needle and filter for each vial.
- Maximum infusion rate should not exceed 5 mL/min.
- Use 0.9% saline solution to flush line at the end of infusion.
- Erbitux should be piggybacked to the patient's infusion line.

Following the Erbitux infusion, a 1-hour observation period is recommended.

6.3.6 Safety Precautions

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

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

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

6.3.7 Adverse Effects

Adverse effects are summarized in Section 1.5.4

Anaphylaxis-like infusion reactions

There have been reports of rare episodes of anaphylactic-like infusion reactions to Erbitux. If patients experience such reactions the following procedures should be followed:

Severe infusion reactions require the immediate interruption of Erbitux therapy and permanent discontinuation from further treatment. 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.

In clinical trials, mild to moderate infusion reactions were managed by slowing the infusion rate of Erbitux and by continued use of antihistamine premedications (eg, diphenhydramine) in subsequent doses**.** If the patient experiences a mild or moderate (Grade 1 or 2) infusion reaction, the infusion rate should be permanently reduced (slowed) by 50%. For grade 1 or 2 reactions manifesting only as delayed drug fever, maintain the Erbitux dose and infusion rate. Consideration should be given to administration of acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) prior to the subsequent Erbitux infusion if not contraindicated in subjects. Dose and schedule of these agents is entirely at the Investigator's discretion.

Emergency medication and oxygen (and note any specifics in BMS protocol) must be available in the infusion room during the time that patients are receiving Erbitux dosing.

N**ote:** Erbitux should be immediately and permanently discontinued in patients who experience severe (Grade 3 or 4) infusion reactions.

Symptomatic Hypomagnesemia

There have been reports of patients treated with cetuximab occasionally developing a magnesium-wasting syndrome with inappropriate urinary excretion. A 34-year-old male patient with metastatic colon cancer developed profound fatigue and symptomatic hypocalcemia and hypomagnesemia while receiving cetuximab and irinotecan, but no other agents with the potential to cause magnesium wasting. The patient required intravenous magnesium supplementation for the duration of cetuximab therapy, but electrolyte abnormalities resolved upon discontinuation of treatment. This case prompted investigators to review serum chemistry reports for a consecutive case series of 154 colorectal cancer patients treated with cetuximab.[30a] During cetuximab treatment, 34 (22%) patients had at least 1 serum magnesium measurement during cetuximab treatment, and 6 had Grade 3 (<0.9 mg/dL) and 2 had Grade 4 (<0.7 mg/dL. The investigators suggest that because EGFR is strongly expressed in the kidney that the EGFR blockage exerted by cetuximab may interfere with magnesium transport. They

recommend that serum magnesium levels be measured and replenished as necessary during cetuximab therapy whenever fatigue or hypocalcemia is encountered.

Please see the package insert for additional adverse events.

7 INVESTIGATIONAL PLAN

7.1 REGISTRATION PROCEDURES

Written documentation of full, noncontingent IRB approval must be on file before a patient can be registered. The registration process begins when the coordinator has obtained a signed informed consent. Before calling the Central Research office please enter patient demographics into the Clinical Trial Management System (CTMS); this is the Web-based intranet system for the delivery of trial information across USOR. Entering a patient into CTMS does not signify that you have registered the patient in the study. If you have any difficulty with CTMS please contact the Research Information Technology office at (832) 348-5184.

Secondly, the coordinator must fax the signed consent form and current registration form (make sure to use the latest version of the registration form, check the footer at the bottom of the page of the registration form) to the Central Research Office at (832) 601-6462. If within 30 minutes an e-mail confirming registration is not received, then the Coordinator will call the Registration Coordinator at (832) 348-5964 (please note new number) to confirm receipt. An accession number is directly assigned once the patient is found eligible. **Treatment must begin within 5 working days after the patient's registration on the study.**

Lastly, the Registration Coordinator will enter the accession number into the CTMS/eRT databases. This will constitute your registration confirmation. The Registration Coordinator will send a confirmation of registration via e-mail. Please make a copy and attach to your file.

The complete form will provide the following information:

1. Protocol Number
2. Study Investigator Identification
   - Institutional Name and/or Affiliate
   - Study Investigator's Name
3. Patient Identification
   - Initials
   - Patient Identification Number, obtained from the CTMS
   - Patient Accession Number, given verbally over the telephone by the Registration Coordinator, and/or via e-mail.
4. Demographics, including date of birth, performance status, and race
5. Eligibility Verification
   - Patients must meet all of the eligibility requirements
6. Date of planned Start of Treatment

It is the policy of the USOR Research Office to allow the SI of Investigator-Initiated studies the opportunity to review and grant exceptions for minor deviations in eligibility, in order to maximize patient accrual without jeopardizing patient safety or scientific integrity of these studies. Examples might include minor deviations of baseline labs, timing of prior treatment or tests, etc. It is recognized that these questions arise frequently. The procedure to be followed is for the Investigator or his/her representative (eg, research nurse) to e-mail the request to the SI for an exception. The SI would then make a determination, which is binding. In no instance should this exception constitute a safety issue for the patient or a significant deviation from the scientific purpose of the study. All requests for exceptions and the decision of the SI will be recorded by the USOR Research Office and then be reviewed on a regular basis by the appropriate disease committee chair and any other interested committees.

7.2 STUDY TREATMENT ADMINISTRATION

7.2.1 Premedications

Irinotecan

There is no required premedication for the administration of irinotecan. Premedication for irinotecan is at the discretion of the Treating Physician.

Erbitux

All patients should be premedicated with diphenhydramine hydrochloride 50 mg (or an equivalent antihistamine) and 10 mg dexamethasone by IV given 30-60 minutes prior to the first dose of Erbitux. Premedication may be administered prior to subsequent doses, at the Investigator's discretion; the dose of diphenhydramine (or a similar agent) may be reduced.

Carboplatin

No premedication is required prior to the administration of carboplatin.

7.2.2 Chemotherapy and Erbitux

The initial dose of Erbitux is 400 mg/m^2 intravenously administered over 120 minutes, followed by weekly infusions at 250 mg/m^2 IV over 60 minutes. **The infusion rate of Erbitux must never exceed 5 mL/min.** Patients must be continuously observed during the infusion for signs of anaphylaxis-like infusion reactions.

Note: Should anaphylaxis occur, all emergency medications and supplies necessary to treat the patient should be kept in the infusion room.

Dose levels for Erbitux are summarized in Table 7:

Table 7. Erbitux Dose Levels	
Does Level	**Weekly Erbitux dose**
Starting dose	250 mg/m^2
Dose Level -1	200 mg/m^2
Dose Level -2	150 mg/m^2

Patients will be closely monitored for treatment-related adverse events, especially infusion reactions (see Section 5.2.1), during the infusion and the postinfusion observation hour. For the initial Erbitux infusion, vital signs should be monitored preinfusion, 1/2 hour into the infusion, at the end of the infusion and 1 hour postinfusion. For subsequent infusions, vital signs should be taken pre- and postinfusion; however, it is recommended that the patient be observed for 1 hour postinfusion.

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.

Note: Caution must be exercised with every Erbitux infusion, as there were patients who experienced their first severe infusion reaction during later infusions.

At each cycle, patients must have the following hematologic values to receive their planned dose: ANC $\geq$1000 and platelets $\geq$100,000. Treatment will be delayed until counts are at these levels. Patients can resume treatment at the previous dose if counts recover, or will be given reduced doses (see Table 10): irinotecan **70** mg/m^2 and carboplatin AUC=**1.5**. The Erbitux dose will not be reduced.

Arm 1

1. Patients will receive 90 mg/m^2 of irinotecan administered IV during a 90-minute period **followed by** carboplatin area under the curve (AUC)= 2.0 administered IV during a 30-60 minute period on Days 1, 8 of a 21 day cycle
2. One cycle of treatment is defined as 2 weeks of treatment, followed by 1 week of rest
3. Successive cycles will be initiated every 3 weeks, and will be continued until a patient shows evidence of disease progression or intolerable toxicity.

Patients whose disease progresses on ICb alone or whose disease progresses after an ICb drug holiday, provided that they have not had any intervening nonprotocol therapy, will cross over to receive single-agent weekly Erbitux at the same dosage as described in Arm 2 of the study until disease progression. Arm 1 patients may also stop either irinotecan or carboplatin due to agent-related toxicity and continue on the other agent alone after discussion with the Study Investigator.

Arm 2

1. Patients will receive Erbitux 400 mg/m^2 IV over 120 min for their first dose and 250 mg/m^2 IV over 60 min weekly thereafter. Following therapy with Erbitux,

patients will receive 90 mg/m^2 of irinotecan administered IV during a 90-minute period followed by carboplatin area under the curve (AUC)=-2.0 administered IV during a 30-60 minute period on Days 1, 8 of a 21 day cycle.

2. One cycle of treatment is defined as 2 weeks of chemotherapy treatment, followed by 1 week of rest. Erbitux is given weekly (Day 1, 8, and 15) without interruption.

3. Successive cycles will be initiated every 3 weeks, and will be continued through until a patient shows evidence of disease progression or intolerable toxicity.

An Arm 2 patient may also stop either irinotecan or carboplatin due to agent-related toxicity and continue on the other agent in combination with Erbitux after discussion with the Study Investigator.

The treatment schema is summarized in Table 8.

Table 8. Treatment Schema

Cycle	Week	Day	Arm 1 90 mg/m^2 IV irinotecan AUC=2.0 IV carboplatin	Arm 2 Erbitux 250 mg/m^2 IV 90 mg/m^2 IV irinotecan AUC=2.0 IV carboplatin
1	1	1	✔	✔ (400 mg/m^2 for 1st Erbitux dose only)
	2	8	✔	✔
	3	15	Rest	Erbitux only

*Day 22 is Day 1 of the next cycle
Note: Patients whose disease progresses on ICb alone (Arm 1) or whose disease progresses after an ICb drug holiday, provided that they have not had any intervening nonprotocol therapy, will cross over to receive single-agent weekly Erbitux at the same dosage as described in Arm 2 of the study until disease progression.

Drug order:

Arm 1: irinotecan→ carboplatin

Arm 2: Erbitux→ irinotecan→ carboplatin

Note: H1/H2 Blockers will be given with the first dose of Erbitux. Premedication may be administered prior to subsequent doses at the Treating Physician's discretion as per section 7.2.1.

7.2.3 Treatment Delay

1. Treatment may be delayed no more than 3 weeks on Arm 2 (not counting rest weeks) to allow recovery from acute toxicity. If treatment is interrupted for >3 weeks on the ICb portion of Arm 1, the patient should discontinue ICb but remain on study, provided that no intervening nonprotocol therapy is received, until disease progression when the patient will cross over to Erbitux alone.

2. Patients on Arm 2 or Arm 1 patients who have crossed over who are off study treatment for more than 3 weeks (not counting rest weeks) due to toxicities will be considered off study.

3. Administration of study drugs must be as scheduled above; anything else must be documented as a deviation (minor).

7.2.4 Dose Modification for Toxicity

Dose reductions are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 as linked in Appendix VI.

If a treatment day variation is needed for reasons other than toxicity, an attempt should be made to keep the variation within the following parameters: **±3 days for 21-day cycles.** Delays within this window are NOT a deviation.

Two dose reductions for hematological toxicities will be permitted before a patient is taken off study. Two dose reductions are allowed if the patient experiences recurrent Grade 3 nonhematologic toxicities, including neurotoxicity. A patient will be taken off study for a second occurrence of a Grade 4 nonhematologic toxicity.

7.2.4.1 Nonhematologic Toxicity

1. For nonhematologic toxicities that are ≤Grade 2, manage symptomatically if possible, and retreat without dose reduction.

2. For nonhematologic, nonneurologic Grade 3 or 4 toxicities (excluding nausea, vomiting and alopecia), the treatment should be withheld until resolution to <Grade 1 toxicity.

3. Treatment should be resumed as per the recommendations in Table 9 and Table 10. **These reductions are permanent**.

4. If the treatment was withheld for more than 3 weeks, the patient will be taken off study treatment.

Table 9 summarizes dose reductions for nonhematological, nonneurologic toxicities.

Table 9. Dose Reductions for Nonhematological Toxicities

Toxicity Grade	Irinotecan	Carboplatin
1-2	Treat symptomatically*	Treat symptomatically*
3-4 First occurrence (except nausea and vomiting)	Reduce dose to 70 mg/m^2	Reduce dose to AUC = **1.5**
3 Second occurrence** (except nausea and vomiting)	Reduce to **60** mg/m^2	Reduce dose to AUC = **1.0**

* Loperamide 1 after each loose stool up to 6 a day for Grade 1-2 diarrhea
**Remove patient from study for second occurrence Grade 4 toxicity in spite of dose reduction

Treatment for nausea and vomiting will be at the discretion of the Treating Physician.

For febrile neutropenia

If febrile neutropenia develops, treat with Neulasta on the following cycle (6 mg, subcutaneously, Day 9). If a second episode occurs despite treatment with Neulasta, decrease irinotecan to **70** mg/m^2 and carboplatin to AUC=**1.5**.

7.2.4.1.1 NONHEMATOLOGICAL TOXICITIES SPECIFIC FOR ERBITUX

Please refer to Section 7.2.4.2.1 for management of infusion reactions, pulmonary toxicity, and dermatological toxicity, which are specific to Erbitux.

7.2.4.2 Hematologic Toxicity

Treatment decisions and dose reductions should be made based on the ANC and platelet counts on the scheduled day of treatment. Patients should not be treated on Day 1 if ANC <1000/μ/L or platelets <100K. If a patient's counts are to low to treat, then either add Neulasta to the next cycle if the patient's ANC have failed to recover or reduce the dose of ICb according to Table 10 once the counts recover to treatable levels.

For patients who are responding to ICb with or without Erbitux but who develop cumulative thrombocytopenia (platelets fail to recover to 100K on Day 1 despite 2 dose reductions of carboplatin), carboplatin should be discontinued and patients should be treated with either irinotecan alone or irinotecan and Erbitux until disease progression. If doses must be reduced a third time, contact the SI.

Table 10. Dose Reductions for Hematological Toxicity Day 8 of Each Cycle*

Value on Day 8	**Irinotecan**	**Carboplatin**
ANC ≥1000/μL Platelets >100K	**90** mg/m^2	AUC=**2.0**
1000>ANC ≥750/μL** and/or 75K <platelets<100K	Reduce dose to **70** mg/m^2***	Reduce dose to AUC=**1.5****
If dose has already been reduced once	Reduce dose to **60** mg/m^2***	Reduce dose to AUC=**1.0****
ANC <750/μL and/or platelets<75K	Hold Day 8 chemotherapy. Do not make up chemotherapy.	

* The dose reductions shown in this table can also be used for Day 1.
** Neulasta can be given on Day 9.
*** Reduced doses will not be re-escalated. If a patient requires a dose reduction on Day 8 of a cycle, continue therapy with this dose reduction.

7.2.4.2.1 MANAGEMENT OF ADVERSE EVENTS SPECIFIC FOR ERBITUX

There will be no dose level reductions below a weekly dose of 150 mg/m^2.

Adverse events should be coded according to CTCAE Version 3.0. Infusion reactions should be graded according to allergic reaction/hypersensitivity.

Management of Infusion Reactions

Severe infusion reactions require the immediate interruption of Erbitux therapy and permanent discontinuation from further treatment. 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.

In clinical trials, mild to moderate infusion reactions were managed by slowing the infusion rate of Erbitux and by continued use of antihistamine premedications (eg, diphenhydramine) in subsequent doses**.** If the patient experiences a mild or moderate (Grade 1 or 2) infusion reaction, the infusion rate should be permanently reduced (slowed) by 50%. For grade 1 or 2 reactions manifesting only as delayed drug fever, maintain the Erbitux dose and infusion rate. Consideration should be given to administration of acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) prior to the subsequent Erbitux infusion if not contraindicated in subjects. Dose and schedule of these agents is entirely at the Investigator's discretion.

N**ote:** Erbitux should be immediately and permanently discontinued in patients who experience severe (Grade 3 or 4) infusion reactions.

Management of Pulmonary Toxicity

In the event of acute onset (Grade ≥2) or worsening pulmonary symptoms, which are not thought to be related to underlying cancer, Erbitux therapy should be interrupted and a prompt investigation of these symptoms should occur. Erbitux treatment should not be resumed until these symptoms have resolved to Grade 1. If interstitial lung disease is confirmed, Erbitux should be discontinued and the patient should be treated appropriately.

Treatment of Isolated 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, pretreat with acetaminophen or nonsteroidal anti-inflammatory agent (at Treating Physician's discretion), repeat antipyretic dose 6 and 12 hours after cetuximab infusion. The infusion rate will remain unchanged for future doses.

If 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.

Management of Dermatologic Toxicity

Patients developing dermatologic toxicities while receiving Erbitux should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Dose modifications of any future Erbitux infusions should be instituted in case of severe (Grade 3) acneform rash. Treatment with topical and/or oral antibiotics should be considered; topical corticosteroids are not recommended.

If a patient experiences severe acneform rash, Erbitux treatment adjustments should be made according to the following table. In patients with mild and moderate skin toxicity, treatment should continue without dose modification.

Table 11. Erbitux Dose Modification Guidelines – Dermatologic Toxicity

Grade 3 Acneform Rash	Erbitux	Outcome	Erbitux Dose Modification
1st occurrence	Delay infusion 1 to 2 weeks	Improvement	Continue at 250 mg/m^2
		No Improvement	Discontinue Erbitux
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 200 mg/m^2
		No Improvement	Discontinue Erbitux
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 150 mg/m^2
		No Improvement	Discontinue Erbitux
4th occurrence	**Discontinue Erbitux**		

7.3 TOXICITY

Toxicities will be graded and reported according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 as linked in Appendix VI. This document can also be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page <http://ctep.info.nih.gov>.

8 SCHEDULE OF ASSESSMENTS

The schedule of assessments for the trial is shown in Appendix V. If a required observation or procedure is missed, documentation is required in the source records on the Protocol Deviation Form (available on CTMS) and on the eCRF, to explain the reason for this protocol deviation.

8.1 PRESTUDY ASSESSMENTS

The following assessments will be performed **within 3 weeks prior to registration** unless otherwise specified.

1. A signed Patient Informed Consent Form must be obtained.
2. A signed Patient Authorization (HIPAA) Form has been obtained.
3. It has been confirmed that the patient meets **all** inclusion criteria and **none** of the exclusion criteria.
4. A complete medical history (review of body systems, excluding gynecological and rectal exams)
5. A complete physical examination (including height, weight, vital signs, review of body systems, and calculation of BSA).
6. Assessment of PS on the ECOG scale (Appendix I)
7. CBC with differential and platelet count
8. Complete metabolic profile (CMP), including: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO_2], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium)
9. Assessment of magnesium (baseline)

   Note: Careful monitoring of magnesium is necessary to avoid magnesium-wasting syndrome that has been reported in patients receiving cetuximab in combination with irinotecan and carboplatin.

10. Calculation of creatinine clearance (ClCr) using the Cockcroft-Gault formula (Appendix III)

    Note: Do not recalculate the carboplatin dose based on increases or decreases in ClCr of <20%.

11. Females of childbearing potential (premenopausal women and peri-menopausal women who have been amenorrheic <12 months) must have a serum pregnancy test performed **within 7 days prior to registration**. A pregnancy test must be done **within 7 days prior to the first dose** as well. Thus, results from the test done prior to registration can be used as long as it was not done more than 7 days prior to dosing.
12. Radiological assessment of tumors: patients must have a chest x-ray, a chest CT, and a pelvic/abdominal CT or MRI, as well as a bone scan **within 4 weeks** of registration unless a PET scan has been done. A PET scan is acceptable for screening of organs to establish nonmeasurable disease, but is not acceptable to document measurable disease. Measurable disease must be established on physical examination or CT scan or MRI. Please see RECIST definition of measurable disease (Section 10.1.1). The methods used for prestudy assessments (CT, MRI, or PET) should be used throughout the study. If possible, the same equipment should be used each time. Under RECIST criteria, **PET cannot be used** to assess measurable disease.

13. Assessment of HER2 status will be conducted at the local site using available archival breast cancer tissue from each patient and performing a FISH or IHC test. Patients will be considered HER2+ if their breast cancers are FISH positive or IHC3+. Patients whose breast cancers are HER2 2+ by IHC must undergo FISH testing to determine whether their breast cancer is HER2- (negative) or HER2+ (positive). This assessment does not have to be repeated if it was performed **>3 weeks prior to registration.**
14. Paraffin-embedded breast cancer tissue (either paraffin blocks or 20 unstained slides) **must be available** for analysis of EGFR, cytokeratin, and other biological markers. These samples will be sent to the Molecular Profiling Institute (MPI; see Appendix VII).

8.2 ASSESSMENTS DURING TREATMENT

The following evaluations will be performed during therapy (up to 3 days prior to the beginning of each cycle). Any delay within this window is NOT a deviation:

1. A brief physical examination, including vital signs and body weight (calculation of BSA). Doses will be recalculated only in cases of weight changes >10%.
2. Brief medical history
3. Review of concomitant medications, **prior to Cycle 1 dosing only**
4. A CBC with differential and platelet count
5. A CMP
6. Assessment of magnesium

> **Note**: Careful monitoring of magnesium is necessary to avoid magnesium-wasting syndrome that has been reported in patients receiving cetuximab in combination with irinotecan and carboplatin.

7. Calculation of ClCr using the Cockcroft-Gault formula (Appendix III)

> **Note**: Do not recalculate the carboplatin dose based on increases or decreases in ClCr of <20%.

8. Tumor response by clinical assessment of the patient's disease (ie, by physical examination) must be performed at the beginning of each cycle of therapy
9. Radiological assessment of tumors to follow known disease will be performed every **6 weeks** for **6 months** and **then every 12 weeks** thereafter. Bone scans will be repeated **every 16 weeks**. The methods used for prestudy assessments (CT, MRI, or PET) should be used throughout the study. If possible, the same equipment should be used each time. **Under RECIST criteria, PET cannot be used to assess measurable disease**.
10. Assessments of other sites of disease must be performed only to confirm a CR.

11. Paraffin-embedded breast cancer tissue (either paraffin blocks or 20 unstained slides, **must be available** for analysis of EGFR, cytokeratin, and other biological markers. These samples will be sent to the Molecular Profiling Institute (MPI; see Appendix VII).
12. A toxicity assessment must be performed.

Note: Specific grading of **alopecia** will be documented on the eCRF.

13. Review of concomitant medications prior to Cycle 1.

8.3 OFF TREATMENT ASSESSMENTS

This is a single assessment that will be performed when patient finishes treatment (off treatment because of PD or toxicity). Note that Arm 1 patients who progress on ICb or Arm 1 patients who stopped taking ICb for toxicity who progress, provided that they did not receive any intervening nonprotocol therapy, will cross over to treatment with **single-agent Erbitux** on the Arm 2 treatment schema until disease progression.

The following evaluations will be performed**, within 7 days** (unless otherwise specified), following the last treatment:

1. A complete physical examination, including vital signs, and body weight
2. Assessment of PS on the ECOG scale (Appendix I)
3. A CBC with differential and platelet count
4. A CMP
5. A tumor clinical assessment of the patient's disease (ie, by physical examination)
6. Radiological assessment of tumors follow known disease. The methods used for prestudy assessments (CT, MRI, or PET) should be used throughout the study. If possible, the same equipment should be used each time. Under RECIST criteria, PET should not be used to assess measurable disease.
7. Date and site of relapse or progression (for patients who go off due to PD)
8. A toxicity assessment
9. Survival status
10. If not already done on study, paraffin blocks or slides for the assessment of biomarkers to predict whether or not the patient will benefit from Erbitux, will be shipped to MPI (see Appendix VII).

8.4 FOLLOW-UP ASSESSMENTS

Patients will participate in this study until their disease progresses. Follow-ups will be performed every 3 months **from the date of last treatment dose**.

8.4.1 Treatment Failure Follow-up

Patients who discontinue treatment (for reasons outlined in Section 4.4) will be followed every 3 months until disease progression for the following information.

1. Subsequent therapy given following this study therapy
2. Date and site of relapse or progression
3. Survival status
4. Toxicities will be recorded for the first 30 days following the last study treatment (specific grading of alopecia is to be documented on the eCRF).
5. If not already done on study, at first follow-up visit only, ensure that paraffin blocks or slides for the assessment of biomarkers, to predict whether or not the patient will benefit from Erbitux, will be shipped to MPI (see 8.3 #10).

This information will be documented on the eCRF within 15 days of the patient's visit.

8.4.2 Response Follow-Up

For patients with a CR, PR, or SD who are no longer receiving study treatment due to toxicity or patient choice, the following assessments will be performed approximately every 3 months (unless stated otherwise) until disease progression.

1. Brief medical history
2. A physical examination including vital signs, and body weight
3. CBC with differential and platelet count
4. A CMP
5. A tumor clinical assessment of the patient's disease (ie, by physical examination) and a CT scan of known areas of disease (patients will be imaged every 3 months until progressive disease).
6. Date and site of relapse or progression
7. Toxicities will be recorded for the first 30 days following the last study treatment
8. Survival status
9. If not already done on study, at first follow-up visit only, ensure that paraffin blocks or slides for the assessment of biomarkers, to predict whether or not the patient will benefit from Erbitux, will be shipped to MPI (see 8.3 #10).

Note: Patients who experience PD after having a CR, PR, or SD, will be followed as described in Treatment Failure Follow-up (Section 8.4.1). Patients who die or withdraw consent are considered **off study** and no further information will be collected.

9 SAFETY EVALUATIONS

9.1 ADVERSE EVENTS

All Grade 2, 3, and 4 nonhematological adverse events (AEs), Grades 1 and 2 alopecia, and Grade 2, 3, and 4 hematologic toxicities will be recorded in the eCRF throughout the trial. In addition, all treatment-related Grade 1 and 2 laboratory abnormalities, which are deemed "clinically significant" by the Treating Physician, will be documented in the eCRF.

Adverse events (AEs) will be recorded throughout the trial. Toxicities and AEs will be graded and reported using the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 as linked in Appendix VI. The relationship of each event to treatment will be assessed by the Treating Physician and recorded on the eCRF. Additional information about each event, such as treatment required, eventual outcome, and whether or not therapy had to be interrupted or dosages reduced, will also be recorded on the eCRF. Adverse events will be recorded for up to 30 days following the last study treatment.

Definitions and additional reporting instructions are provided in Part II of this protocol.

9.2 LABORATORY DATA

For the treatment of the patient, laboratory data will be obtained according to the schedule of assessments. Only the laboratory data requested on the eCRF need to be recorded on the appropriate laboratory eCRF page. In addition, abnormal results that are associated with an AE will be documented on the Adverse Event page of the eCRF if the laboratory abnormality fits the definition of an AE or can potentially result in an AE.

10 EFFICACY ASSESSMENTS

10.1 DEFINITIONS

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee.[31] Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Best response will be determined based on the sequence of disease status with corresponding best response (Appendix IV).

Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

10.1.1 Measurable Disease

Lesions that can be accurately measured in at least 1 dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques (CT, MRI, X-ray) or as ≥10 mm with spiral CT scan.

Note: PET cannot provide accurate measurements and **cannot** be used for repeated measurements throughout the study. **RECIST does not include measurements by PET**.

10.1.2 Nonmeasurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan) are considered nonmeasurable disease. Lesions that are considered as truly nonmeasurable include the following:

1. bone lesions
2. leptomeningeal disease
3. ascites
4. pleural/pericardial effusion
5. inflammatory breast disease
6. lymphangitis cutis/pulmonis
7. abdominal masses that are not measurable on imaging techniques
8. cystic lesions

10.2 TUMOR RESPONSE EVALUATION

10.2.1 Evaluation of Lesions

10.2.1.1 Target Lesions

All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total representative of all involved organs should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter (LD). The baseline sum of the LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

10.2.1.2 Non-target Lesions

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, and these lesions should be followed as “present” or “absent.”

10.3 RESPONSE CRITERIA

10.3.1 Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions.
- **Partial Response (PR):** At least a 30% decrease in the sum of the longest diameter (LD) of target lesions taking as reference the baseline sum LD.
- **Progression (PD):** At least a 20% increase in the sum of LD of target lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of 1 or more new lesions.
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum LD since the treatment started.

10.3.2 Evaluation of Non-Target Lesions

- **Complete Response:** Disappearance of all non-target lesions and normalization of tumor marker level.
- **Incomplete Response/Stable Disease:** Persistence of 1 or more non-target lesions (non-CR) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease:** Appearance of 1 or more new lesions. Unequivocal progression of existing non-target lesions. Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the Treating Physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair).

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

10.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see section Evaluation of Target Lesions). See Appendix IV for sequence of disease status with corresponding best response.

Table 12. Evaluation of Best Overall Response

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

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

10.4 GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

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

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

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

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

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

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

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

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

10.5 CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

10.5.1 Confirmation

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that will be performed not less than **4 weeks** after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria (Section 10.3.1), at least once after study entry at a minimum interval (not less than 6 weeks).

10.5.2 Duration of Response

The duration of overall response is measured from the first date measurement criteria are met for CR/PR (whichever status is recorded first) 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), or last date of follow-up for patients who do not progress.

The duration of overall complete response is measured from the date measurement criteria are first met for CR until the first date that recurrent disease is objectively documented. If a patient has not progressed or died, duration of response is censored at the date of last follow-up.

10.5.3 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for disease progression are met and considering that the duration of stable disease is at least 6 weeks (2 cycles) from the start of treatment. If a patient has not progressed or died, duration of response is censored at the date of last follow-up.

10.6 PROGRESSION-FREE SURVIVAL

Progression-free survival will be measured from the treatment start date (date of first dose) to either the date the patient is first recorded as having disease progression (even if the patient went off treatment because of toxicity) as long as the patient does not start a new treatment, or the date of death if the patient dies due to any causes before progression. Patients who start a new treatment before they progress will be censored as of the date of start of the new treatment. If a patient has not progressed or died, time to progression is censored at the date of last follow-up.

10.7 TIME TO PROGRESSION

For patients who progress, time to progression (TTP) will be measured from the treatment start date (date of first dose) to the date the patient is first recorded as having disease progression (even if the patient went off treatment because of toxicity). Patients who start a new treatment before they progress will be censored as of the date of start of the new treatment.

10.8 SURVIVAL

Survival will be measured from the date of start of treatment to the date of death. For patients who do not die, survival will be censored at the date of the last follow-up.

10.9 TIME TO RESPONSE

For patients who achieve an objective response (CR or PR of measurable disease), the time to response will be assessed from the date of start of treatment to the date of first response.

11 STATISTICAL CONSIDERATIONS

11.1 PATIENT POPULATIONS

11.1.1 Efficacy Analysis

For the tumor response analysis, 3 patient populations will be defined: all eligible patients, evaluable patients, and patients who received study drugs.

Intent-to-treat Population

This population includes all eligible patients registered on study regardless of whether or not patients received any study drug.

Efficacy, Evaluable Population (Per-protocol Population)

Evaluable patients include all patients who received at least 2 cycles of treatment with at least 1 follow-up tumor assessment. If progressive disease occurs before 2 cycles can be administered, the patient will be considered PD. If lethal toxicity or discontinuation of treatment secondary to toxicity occurs, the patient will be considered a treatment failure.

Safety Analyses

The safety analysis will include all **eligible** patients who are registered on the study and who received at least 1 dose of any study drug. Adverse events that are unrelated to treatment and occur >30 days after the administration of treatment will not be reported or analyzed.

11.2 OBJECTIVES AND ENDPOINTS

The primary objective of this study is to determine the overall response rate when Erbitux is added to ICb in patients with metastatic breast cancer. Secondary objectives are:

- To calculate the duration of response and stable disease
- To determine the median progression-free survival (PFS) and time to progression (TTP – only for those who progress)
- To determine the median overall survival (OS)
- To determine toxicities for individuals with metastatic breast cancer treated with these study regimens
- To determine EGFR expression for individuals with metastatic breast cancer enrolled on this study

11.3 SAMPLE SIZE

124 patients will undergo a 1:1 randomization to ICb + Erbitux versus ICb alone followed by Erbitux at progression. Patients in each group will be stratified by hormone receptor negative and HER2 negative breast cancer (triple negative) until a cohort of 24 patients are registered in each arm. This is a noncomparative study; no direct statistical comparisons will be made between the 2 groups. The 2 groups will run parallel to each other. Using STPlan exact method, a total of 62 patients in each group (including 10% for early dropouts) will provide 80% power with a type I error rate of 5% to reject the null hypothesis that the ORR is less than 60% (approximately 37 response) in the ICb + Erbitux group ($H_o = 0.43$), and less than 43% (approximately 27 response) in the ICb alone group ($H_o = 0.27$). On an estimated accrual of 8 patients per month, the anticipated time to accrual is 16 months. Patients will be followed until disease progression or death (if death occurs prior to progression).

Thirty more patients will be added to the study for a total of 154 patients (from the original sample size of 124 patients). The reason for increasing the sample size (15 additional patients in each arm) is to replace the nonevaluable patients who went off-treatment early due to adverse events or withdrawal of consent.

A final report could be generated when all patients complete treatment and have been followed for at least 2 years.

11.4 STATISTICAL METHODS

Patient characteristics including race, sex, ECOG performance status, prior treatment(s) and age will be evaluated using descriptive statistics for each group in the ITT population. In the evaluable population, the objective response rates, together with the 95% confidence interval will be determined, as well as the duration of response. The median and range of cycles received per arm and for the crossover will be listed. The 1- and 2-year progression-free survival and survival will be analyzed using the Kaplan-Meier survival method.[32] For patients who progressed, median time to progression and ranges will be presented. Reasons off treatment and causes of death will be reported.

The number of patients who crossed over in Arm 1 will be listed as well as their responses to Erbitux following the crossover.

Incidence and type of adverse events will be tabulated and summarized using descriptive statistics. Toxicities will be graded and reported according to the NCI CTCAE version 3.0. The toxicity profile of the study drugs will be evaluated in the safety population. Patients who receive at least 1 dose of any study drug will be included in the safety analysis.

PART II – PROCEDURES

12 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

BMS considers the SAE reporting period to begin with signing of the informed consent.

AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious. This also applies to patients experiencing AEs that cause interruption or discontinuation of investigational product, or those experiencing AEs that are present at the end of their participation in the study. Such patients should receive post-treatment follow-up as appropriate. If an ongoing AE changes in its severity or in its perceived relationship to study drug, a new AE entry for the event should be completed.

12.1 DEFINITIONS

12.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

12.1.2 Serious Adverse Event

An AE (experience) or reaction occurring at any dose should be classified as a serious adverse event (SAE) if any of the following occur:

Death: Any death from any cause while a patient is receiving treatment on this protocol, or ≤30 days following the last dose of protocol treatment, must be reported to the SI (Dr. Joyce O'Shaughnessy, 214-370-1796), Bristol-Myers Squibb and to the IRB within 24 hours of first notification. A ***serious AE*** is any untoward medical occurrence that at **any dose**:

- results in death,
- is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalization or causes prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,

- results in the development of drug dependency or drug abuse,

- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (eg, medical, surgical) to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) **For reporting purposes, BMS also considers the occurrences of pregnancy or overdose (regardless of adverse outcome) as events, which must be reported as important medical events.**

Adverse events classified as "serious" require expeditious handling and reporting to BMS to comply with regulatory requirements.

All serious AEs whether related or unrelated to investigational product, must be immediately reported to BMS (or designee) by confirmed facsimile transmission. If only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site.

For studies conducted under an Investigator IND, any event that is both serious and unexpected must be reported to the FDA as soon as possible and, in no event, later than 7 days (death or life-threatening event) or 15 days (all other SAEs) after the Investigator's or institution's initial receipt of the information. Bristol-Myers Squibb will be provided with a simultaneous copy via facsimile of all adverse events filed with the FDA. SAEs should be reported on the MedWatch Form 3500A, which can be accessed at:

http://www.accessdata.fda.gov/scripts/MedWatch/

MedWatch forms should be sent to the FDA online at the above Internet address or at:

MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)

All SAEs should simultaneously be faxed to Bristol-Myers Squibb at:

Global Pharmacovigilance
Bristol-Myers Squibb Company
Fax Number: 609-818-3804

Collection of complete information concerning SAEs is extremely important. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (eg, hospital discharge summaries and autopsy reports), should

be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.

12.1.3 Unexpected Adverse Event

An unexpected event is any AE that is not identified in nature, severity or frequency in the Clinical Investigator's brochure or the drug package insert.

12.2 REPORTING

12.2.1 Adverse Events

Adverse events will be recorded for the duration of a patient's study treatment, and for up to 30 days following the last study treatment. All AEs, regardless of causal relationship are to be recorded in the source documentation. Only those specified in Section 9.1 are to be recorded in the eCRF.

The Treating Physician must determine and record the toxicity of AEs. Toxicities will be graded and reported according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 as linked in Appendix VI. The relationship of each event to treatment will be assessed by the Treating Physician and recorded on the eCRF. Additional information about each event, such as treatment required, whether or not therapy had to be interrupted or dosages reduced, and eventual outcome will also be recorded on the eCRF.

Pre-existing conditions will be recorded at baseline on the Medical History Form. If a pre-existing condition does not change, it does not have to be reported as an AE on subsequent cycles.

12.2.2 Serious Adverse Events

All SAEs will be reported by telephone upon becoming aware of the event to US Oncology Central Safety Department. The SAEs should be reported by facsimile within 24 hours to Bristol-Myers Squibb and to the US Oncology Central Safety Department. A copy will be sent to the FDA (if applicable) by US Oncology Central Safety Department. A facsimile cover page will be available with both Bristol-Myers Squibb and US Oncology Central Safety Department contact information.

US Oncology Central Safety Department **Regulatory Affairs - Safety** **US Oncology, Inc.** 4144 N. Central Expwy Suite 1250 Dallas, TX 75204	
Direct: (214)-584-3205	Fax: (214) 584-3403 Toll Free Fax: 1-877-571-8934

The site will supply as much information as available at the time of the initial fax to Bristol-Myers Squibb and to the US Oncology Central Safety Department (study number,

subject initials, subject study number, event), during both business and non-business hours, to:

Sponsor contact information –

Global Pharmacovigilance and Labeling
Bristol-Myers Squibb Company
Fax Number: 609-818-3804

SAEs MUST BE SENT TO (**Bristol-Myers Squibb**) and to the US Oncology Central Safety Department by fax within 24 hours of notification by the site.

All SAEs must be documented on the Serious Adverse Event Report Form and on the adverse event eCRF page. The event term used on the SAE report should match the term in the eCRF. The Coordinators should fax the completed Forms to Bristol-Myers Squibb and to the USOR Central Safety Department (see contact information below) within 24 hours of becoming aware of the event. This fax will serve as the initial report. The USOR Central Safety Department will forward the necessary information to the Study Investigator, the Institutional Review Board (via notification letter), FDA (if applicable) and the data fax line (Dallas or Houston).

Questions and concerns from the above regarding the SAE Report will be addressed directly from Bristol-Myers Squibb, who will subsequently contact the site for answers/clarification. Any follow-up/final information from the Coordinator will be faxed directly to Bristol-Myers Squibb. In addition this follow-up/final report will need to the faxed to the USOR Central Safety Department to continue with the procedure outlined above.

In the instance where a participating site utilizes a local IRB, the Treating Physician or designee will be held responsible for notification of the serious adverse event to their local IR.

12.2.3 Overdose

An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. For reporting purposes, BMS considers an overdose, regardless of adverse outcome, as an important medical event (see Serious Adverse Events).

12.2.4 Discontinuation of Patient

The Treating Physician must notify the SI at any time following discontinuation of a patient on study for the occurrence of a serious or unexpected AE associated with the use of the study medication.

12.3 PREGNANCY

Prior to study enrollment, women of childbearing potential (WOCBP) must be advised of the importance of avoiding pregnancy during trial participation and the potential risk

factors for an unintentional pregnancy. In addition, men enrolled on this study should understand the risks to any sexual partner of childbearing potential and should practice an effective method of birth control.

All WOCBP MUST have a negative pregnancy test within 7 days prior to first receiving investigational product. If the pregnancy test is positive, the patient must not receive investigational product and must not be enrolled in the study.

In addition, all WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual period) at any time during study participation.

The Investigator must immediately notify BMS in the event of a confirmed pregnancy in a patient participating in the study.

13 PROTOCOL AND DATA DEVELOPMENT

13.1 ETHICS

13.1.1 Institutional Review Board

This trial can be undertaken only after review and full approval of the protocol and a Patient Informed Consent Form has been obtained from a properly constituted IRB. This written approval must be dated and it must clearly identify the protocol, any amendments, the Patient Informed Consent Form, and any applicable recruiting materials and subject compensation programs approved.

The decision concerning the conduct of the study will be made in writing to the SI. Copies of this decision and of all IRB correspondence will be kept on file at the study site; copies will be provided to the USOR Research Office.

During the trial, the SI is required to send various documents to the IRB for review:

1. Changes to the current protocol.

2. All protocol amendments and Patient Informed Consent Form revisions.

3. Reports of AEs that are serious, unexpected, and associated with the investigational drug, and any life-threatening problems, or death.

4. Required progress reports.

If local IRB approval is acquired, the USOR Regulatory Affairs Office should be informed via research Standard Operation Procedures (SOP).

Particular attention is drawn to the FDA regulations regarding the IRB. The SI provides Bristol-Myers Squibb and Pfizer, Inc. with the necessary assurance that an IRB is responsible for the initial and continuing review and approval of the proposed clinical

study in accordance with these regulations. At least once a year, the IRB will be asked to review and re-approve the clinical trial protocol; the request must be documented in writing. At the end of the trial, the SI will notify the IRB that the trial has been completed.

13.1.2 Patient Informed Consent

The informed consent should meet the requirements of the latest version of the Declaration of Helsinki and any applicable regulations and guidelines. It must be approved by an institutional ethics committee/IRB.

Prior to entry into the trial and before any protocol-required procedures are performed, the Treating Physician must explain the nature of the trial, its intended purpose, and the implications of participation to potential patients or to their legal representatives. They will be told about the possible risks and benefits, and the possible adverse experiences. They will be informed that patients' participation is voluntary, and that they may withdraw consent to participate at any time. They will also be informed that if patients choose not to participate in the trial alternative treatments are available; such refusal will not prejudice further treatment of their disease. Potential patients or their legal representatives must be given the opportunity to ask questions about the trial protocol and the procedures involved.

Finally, each patient will be told that his or her records may be accessed by authorized personnel of USOR and other authorized individuals without violating the patient's confidentiality, to the extent permitted by the applicable laws and/or regulations. By signing the written Patient Informed Consent Form, the patient or his or her legal representative is authorizing such access. Following this explanation and prior to entry into the trial, the written, dated, and signed Patient Informed Consent Form must be obtained from each patient or his or her legal representative; a copy will be given to the person signing the form.

13.1.3 Confidentiality of Records

The Treating Physician is required to retain, in a confidential manner, sufficient information on each patient (ie, full name, current address, and social security number) so that the patient may be contacted by the FDA or by the USOR should the need arise.

13.2 STUDY RECORDS

13.2.1 Documentation

A log of all patients evaluated for this protocol must be maintained at each site. Patients excluded from admission will be provided with a clear explanation of the specific reasons why they have been excluded from the study. Patients who are included will be assigned a patient identification number.

For each patient treated with the study drug(s), the Research Coordinator is required to prepare and maintain case histories that include all observations and other data pertinent

to the investigation. This will include all source documents needed to verify the accuracy of all observations and other data contained in the eCRFs on each study patient.

The Treating Physician or his/her designee is required to retain the records related to the trial for a period of 2 years following the date a marketing application is approved for the indication being investigated. If no application is to be filed or if the application is not approved for such indication, the records must be retained until 2 years after the investigation is discontinued and the regulatory agencies are notified.

The Treating Physician shall retain study drug disposition records, copies of eCRFs (or electronic files), and source documents for the maximum period required by the country and institution in which the study will be conducted, or for the period specified by USOR, whichever is longer. The Investigator must contact USOR prior to destroying any records associated with the study.

If the Investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another Investigator, IRB). Notice of such transfer will be given in writing to USOR.

13.2.2 Electronic Case Report Form Procedures

Data will be entered at the site using eCRFs. The Treating Physician or his/her designee is responsible for recording all data relating to the trial on the eCRFs. The Treating Physician must verify that all data entries on the eCRFs are accurate and correct eCRFs must be completed **within 15 days** of the end of each cycle following the completion of study therapy.

If an item is not available or is not applicable, it should be documented as such; **no blank spaces should be left on an eCRF.**

For patients removed from study, the Clinical Research Office Project Manager must be notified by e-mail within 3 working days of the removal. eCRFs must then be completed **within 15 days** of the date of removal from the study. Long-term survival information will be collected.

13.3 MONITORING/SITE VISITS

Study sites will be monitored through regular site visits conducted at least once per year by the regional quality and compliance auditor of USOR. To ensure accuracy, a minimal data set from the eCRFs for all cases will be compared with the original patient source documents during site visits. The monitor may also review case histories, laboratory certifications, IRB records, drug accountability records, and other documentation. In addition, representatives of the FDA or of other regulatory agencies may review study records.

At all times, patients' confidentiality will be monitored.

13.4 MODIFICATION OF PROTOCOL

Any changes to this protocol that affect study objectives, study design, study procedures, patient population, or significant administrative procedures will require a formal amendment to the protocol. Any proposed protocol amendments must be sent in writing to the applicable IRB. Prior to implementation, an amendment must be agreed upon by the SI, Bristol-Myers Squibb, and Pfizer, Inc., and approved by the applicable IRB.

General administrative changes to the protocol are minor corrections and/or clarifications that do not affect the manner in which the study is to be conducted. Such administrative changes will be agreed upon by the SI and will be documented in a memorandum. The applicable IRB will be notified of administrative changes according to applicable IRB guidelines.

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Appendix I ECOG Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of light or sedentary nature—(eg, light housework or office work)
2	Ambulatory and capable of all self care, but unable to carry out any work activities; up and about > 50% of waking hours
3	Capable only of limited self-care, confined to bed or chair > 50% of waking hours
4	Completely disabled; cannot carry out any self care; totally confined to bed chair
5	Dead

Appendix II Staging

The **sixth edition** of The American Joint Committee on Cancer Staging Manual will be used to stage breast cancer in order to determine eligibility for this study. This manual may be obtained at the following link on the USOR CTMS:

https://ctms.usoncology.com/Web_Docs/AJCC%20STAGING%20FORMS/25%20Breast.pdf

Appendix III Calculations

Body Surface Area

Actual weight will be used to calculate body surface area and study drug doses for all patients, including obese patients.

Note: Computer programs, which utilize height and weight to calculate BSA and/or drug dose, are acceptable as long as they do not vary by >5% (±) from the manual dose calculation

The following formulas are recommended for the calculation of BSA:

The DuBois formula for calculating the body surface area (BSA) in squared meters (m^2) follows: BSA m^2= (Weight in kg) $^{0.425}$ (Height in cm) $^{0.725}$ x 0.007184

Lam et al and Mosteller (Lam RK, et al. NEJM. 1988;318:1130 (letter) and Mosteller RD: Simplified calculation of body surface area. NEJM. 1987;317:1098) have published the following **simplified formulas** that can be calculated using a hand-held pocket calculator:

$$m^2 = \sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3600}} \quad \text{or} \quad m^2 = \sqrt{\frac{\text{Height (in)} \times \text{Weight (lb)}}{3131}}$$

Creatinine Clearance

Creatinine Clearance (ClCr) – Cockcroft and Gault method
Cockcroft DW, Gault MH. Nephron. 1976;16:31-41

Note: It is recommended that the ideal or adjusted (non-obese) weight be used, unless you are correcting by the BSA comparison/adjustment method.

Creatinine clearance (mL/min) =

$$\frac{(140\text{-age in years}) \times (\text{actual weight in kg})}{(72 \times \text{serum creatinine in mg/dL})}$$

for female patients, multiply the result by 0.85

Note: do not use the method of Jelliffe for the calculation of creatinine clearance!

Appendix IV Sequence of Disease Status with Corresponding Best Response

1st objective status	2nd objective status	3rd objective status	Best response
3-6 week assessment interval:			
Progression	---	---	Progression
Stable, PR, CR, unk	Progression	---	Progression
Stable[1]	Stable	Progression	Stable
Stable, unk[1]	PR, CR	Progression	Stable
Stable, unk	Unknown[d]	Progression	Unknown
PR[2]	PR	Progression	PR
PR[2]	CR	Progression	PR
PR, CR	Unknown[d]	Progression	Unknown
CR[3]	CR	Progression	CR
Unknown[1]	Stable	Progression	Stable
> 6 week assessment interval:			
Progression	---	---	Progression
Stable[1]	Progression	---	Stable
PR or CR (no 4 week confirmation)[1]	Progression	---	Stable
PR (4 week confirmation)[2]	Progression	---	PR
PR[2]	PR	Progression	PR
PR[2]	CR (no 4 week confirmation)	Progression	PR
CR (4 week confirmation)[3]	Progression	---	CR
CR[3]	CR	Progression	CR
Unknown[4]	Progression	---	Unknown

1. Best response is the same if these sequences are preceded by the objective statuses of unknown or stable, or if unknowns separate the first objective status from the second.
2. Best response is the same if these sequences are preceded by the objective statuses of unknown, stable, or PR, or if unknowns separate the first objective status from the second.
3. Best response is the same if these sequences are preceded by the objective statuses of unknown, stable, PR, or CR, or if unknowns separate the first CR from the second.
4. Best response is the same if followed by additional unknowns.

Appendix V Schedule of Assessments

Assessment	**Prestudy** see 8.1	**During Treatment** *(at the beginning of each cycle, unless otherwise specified)* see 8.2	**Off Study Tx** *(within 7 days of last treatment)* see 8.3	**Follow-up** (see 8.4) *Every 3 months until PD*	
				Treatment Failure	**Response**
Informed consent	✔				
Signed patient authorization (HIPAA)	✔				
Inclusion/exclusion criteria	✔				
Complete physical examination	w/in 3 weeks prior to registration (PTR)		✔		
Brief physical exam		✔			✔
Medical history	w/in 3 weeks PTR				
Brief medical history		✔	✔		✔
Review of concomitant meds		Prior to Cycle 1			
ECOG PS Scale	w/in 3 weeks PTR	✔	✔		
CBC with differential and platelet count	w/in 3 weeks PTR	✔	✔		✔
Complete metabolic profile	w/in 3 weeks PTR	✔	✔		✔
Assessment of magnesium	w/in 3 weeks PTR	✔			
Creatinine Clearance	w/in 3 weeks PTR	✔			
Pregnancy test	w/in 7 days PTR and w/in 7 days prior to Dose 1				
Radiological assessment of disease	w/in 4 weeks PTR	every 6 weeks for 6 months then every 12 weeks. Bone Scans every 16 weeks	✔		(CT scan every 3 mos until PD)
HER2 status	✔				
Tumor response by clinical assessment		✔	✔		✔
Date and site of relapse or progression			✔ for pts who PD	✔	✔
Survival status			✔	✔	✔
Toxicity assessment (NCI CTCAE)		✔	✔	For 30 days after last tx	For 30 days after last tx
Review of concomitant meds		✔ (Prior to cycle 1)			
Samples (paraffin blocks and/or tissue slides)	Availability confirmed	Send to central lab (MPI) for EGFR testing by the end of Cycle 2	If not already done, send to MPI for biomarkers	If not already done, at first follow-up visit, make sure that paraffin blocks or slides have been sent to MPI.	
Subsequent therapy given following study therapy				✔	

Complete metabolic profile includes: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO_2], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium)

Appendix VI Terminology Criteria for Adverse Events (CTCAE), Version 3.0

MARCH 31, 2003 Publish Date: December 12, 2003

COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS
(CTCAE) Version 3.0

As of April 02, 2003 NCI has introduced version 3.0 of the Common Terminolgoy Criteria for Adverse Events. These may be obtained at the following web link http://ctep.cancer.gov/reporting/ctc.html or on the USOR CTMS.

DO NOT USE CTC VERSION 2.0 TO GRADE TOXICITIES IN THIS STUDY!

Appendix VII Pathology Submission Procedure

Investigators must submit:

- One paraffin block or 20 unstained slides from a representative area of the tumor to be used for molecular studies.
- Surgical Pathology Report
- Pathology Submission Form

Ship directly to The Molecular Profiling Institute (address and phone number below). The Pathology Submission Form must be completed and submitted even if the patient pathology specimens are not available for submission. Please make a copy of the Pathology Submission Form and file in the patient study record and submit a copy to Houston Data Research.

Please indicate on the package "Pathology Specimens Enclosed".

ADDRESS AND PHONE NUMBER

The Molecular Profiling Institute

445 N. Fifth Street

Phoenix, AZ 85004

(602) 358-8900