Phase II Study of Panitumumab, Nab-paclitaxel, and Carboplatin for Patients with Primary Inflammatory Breast Cancer (IBC) without HER2 Overexpression

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1.0 OBJECTIVES:

1.1 **Primary Objectives** is to determine the pathologic complete response (CR) rate in patients with primary inflammatory breast cancer (IBC) without HER2 overexpression by Panitumumab, Nab-paclitaxel, and Carboplatin (PNC) and FEC preoperative systemic chemotherapy.

1.2 Secondary Objectives

1.2.1 To determine the disease-free survival (DFS) produced by PNC regimens.

1.2.2 To determine the overall survival (OS) produced by PNC regimens.

1.2.3 To determine the disease-free survival (DFS) produced by PNC regimens among patients with triple negative breast cancer.

1.2.4 To determine the overall survival (OS) produced by PNC regimens patients with triple negative breast cancer.

1.2.5 To determine the safety and tolerability by PNC regimens.

1.2.6 To determine whether pathologic response rate correlates with EGFR expression level.

1.3 Exploratory

1.3.1 To identify molecular markers predictive of pathologic CR rate by analysis of multilayer immunohistochemical staining (IHC)

1.3.2 To identify molecular marker by gene profiling and proteinomics

2.0 BACKGROUND AND RATIONALE:

2.1 *Inflammatory breast cancer* (IBC) is the most aggressive form of primary breast carcinoma and has distinctive biological features. The outcome for patients with IBC is bleak despite multimodality treatment approaches; 3-overall survival (OS) rates after combined chemotherapy, surgery, and radiation are only 40% compared to 80% for non-inflammatory breast cancer (Cristofanilli *et al.*, 2007; Ueno *et al.*, 1997). Current treatment modalities are inadequate for IBC, and a better understanding of the biological features of the disease is necessary if more effective interventions are to be developed. Pathological CR rate determines the long-term outcome (DFS as well as overall survival) of inflammatory breast cancer. Thus, we will use pathological CR rate produced by preoperative chemotherapy as a primary endpoints of this study.

2.2 *Clinical Characteristics of IBC*. Inflammatory breast cancer is defined by a rapid onset of diffuse skin erythema, edema involving more than 2/3 of the breast resulting in a pitted appearance (peau d'orange), as well as tenderness, induration and warmth of the involved breast (Cristofanilli *et al.*, 2003). At the time of initial diagnosis most IBC patients have lymph node involvement and approximately 30% have distant metastases (Liauw *et al.*, 2004).

2.3 *Pathology of IBC*. This type of breast cancer frequently demonstrates dermal lymphatic invasion by tumor emboli, which contributes to the rapid engorgement of the breast and clinical features of "inflammation." However, absence of dermal lymphatic invasion does not exclude the diagnosis if the clinical signs are present (Giordano and Hortobagyi, 2003). In fact, the AJCC does not consider the presence of dermal lymphatic invasion without characteristic clinical features to be sufficient to diagnose IBC. When a retrospective analysis was performed in patients diagnosed with IBC based on clinical criteria, with or without pathologic evidence of dermal lymphatic invasion, patients with clinical symptoms had a poorer prognosis, including a shorter DFS and OS compared to patients with only pathologic findings of dermal lymphatic invasion (Amparo *et al.*, 2000). These findings support the importance of clinical features in the initial diagnosis of IBC.

2.4 *Molecular changes of IBC*. These tumors are characterized by high histologic grade, high proliferation rate (e.g., elevated MIB1 expression, high S-phase proportion, or high thymidine-labeling index), aneuploidy, and high levels of expression of p53 and MUC1, RhoC, E-cadherin, and growth factor receptors such as HER2 and EGFR. IBC is often associated with a "basal-like" phenotype, high intratumoral microvessel density, high levels of tumor angiogenesis- and lymphangiogenesis-related factors such as vascular endothelial growth factors (VEGF) -A, -C, and -D, Flt-1, KDR, Tie-1, and Tie2, and high expression of chemokines such as CCL3/MIP1A and CCL5/RANTES. We recently undertook an IHC analysis of 44 cases of IBC diagnosed between 1994 and 2002 and found HER2 overexpression in 21 patients (48%) and EGFR overexpression in 12 of 40 patients (30%). Significantly, EGFR overexpression was the only factor predictive of worse outcome: the 5-year OS rate was significantly lower for women with EGFR-positive disease than for women with EGFR-negative disease (P=0.01). Moreover, tumors that expressed EGFR, alone or in combination with CXCR4, were associated with a

relatively higher incidence of bone recurrence (Cabioglu *et al.*, 2007; Cristofanilli *et al.*, 2007). The association of EGFR overexpression and increased risk of recurrence and death indicates that EGFR may represent a potential therapeutic target in IBC.

2.5 *Treatment of IBC*. Surgery was the first therapeutic modality used to treat IBC, but produced disappointing results. The mean survival of patients treated with mastectomy alone ranged from 12-32 months (Cristofanilli *et al.*, 2003) with a 5-year OS rate <5% (Ueno *et al.*, 1997). Radiation therapy alone appears to have little impact on survival, with median overall survival rates ranging from 4 to 28 months in studies with very small patient populations (Chittoor, 1998). An extensive review of IBC data at the M.D. Anderson Cancer Center conducted by Ueno and colleagues (Ueno *et al.*, 1997) concluded that surgery plus radiotherapy as opposed to radiotherapy alone did not have an impact on DFS or OS. Cristofanilli and colleagues reported that the addition of radiotherapy improved locoregional control rate, but the combination had no significant effect on survival (Cristofanilli *et al.*, 2003). At this time, combined-modality treatment (neoadjuvant chemotherapy, mastectomy, adjuvant chemotherapy, and radiotherapy) is considered to be a standard of care for IBC (Ueno *et al.*, 1997). Further, pathological CR in surgical samples after preoperative systemic chemotherapy is the most important prognostic factors to determine the long-term outcome of IBC. Twenty-eight percent of patients using this modality remained disease-free beyond 15 years when compared with single modality treatments that yielded only 5%.

Anthracyclines (FEC; 5-FU, epirubicin, cyclophosphamide or FAC; 5-FU, adriamycin, cyclophosphamide) and taxanes (paclitaxel or docetaxel) are the most effective cytotoxic agents in the management of primary breast cancer and have demonstrated their importance in the management of early breast cancer and IBC (Cristofanilli *et al.*, 2003).

Despite improvements in survival with the implementation of aggressive multi-modality induction therapies, women with IBC still have far lower survival rates than those with non-IBC. Furthermore, the quality of life of patients with refractory or relapsed IBC is often negatively impacted by pain, erythema, edema and cosmetic appearance of uncontrolled chest wall disease. Thus, there is a need for novel treatment for primary IBC before recurrence of disease. This is why new combination chemotherapy (panitumumab, nab-paclitaxel, carboplatin) will be added to standard anthracycline regiments (FEC). New combination chemotherapy is added to standard FEC x 4 cycles which allows us to compare the pathological CR rate to the historical pathological CR rate [paclitaxel followed by FEC].

2.6 Lapatinib study in IBC (Study EGF103009). We recently completed a phase II trial testing lapatinib (TYKERB, a dual EGFR and HER2 inhibitor) in combination with paclitaxel as preoperative systemic chemotherapy for primary IBC. The results of that study indicated that lapatinib had optimal activity in HER2-overexpressing IBC but limited response in EGFR overexpressing by IBC. We recently showed that lapatinib has very limited activity against EGFR-overexpressing tumors (Zhang *et al.*, 2008). Thus, there is an urgent need for new EGFR-targeted therapy. Interestingly, panitumumab (see below for details) has been shown to be active in breast cancer preclinical model using MDA-MB-468, which overexpresses EGFR by both IHC and FISH [Amgen, preclinical study]. Further, EGFR tyrosine kinase inhibitor such as erlotinib does have an anti-tumor activity against human inflammatory breast cancer cells [Ueno's lab]. At last, in colorectal cancer, relationship between EGFR expression level and antitumor response remains controversial (Sartore-Bianchi *et al.*, 2007; Van Cutsem *et al.*, 2007). Thus, in this clinical trial, we will treat all patients with negative HER2-expressing IBC by panitumumab.

2.7 *Panitumumab*. This drug is previously known as ABX-EGF. It is a high affinity (Kd = 5 x 10-11 M) fully human IgG2 monoclonal antibody directed against human EGFR. Panitumumab blocks the ligands EGF and TGFα binding to EGFR, inhibits tumor growth, and elicits both tumor regression and eradication of established tumors in murine xenograft tumor models (Yang *et al.*, 1999). The antineoplastic effects of panitumumab *in vivo* have been demonstrated using human xenograft mouse models including breast cancer. Panitumumab has been shown to inhibit the growth of human epidermoid carcinoma A431 xenografts in athymic mice resulting in the complete regression of large (up to 1.2 cm3) established A431 tumors, regardless of initial tumor size. Lower doses of panitumumab administered twice weekly for 3 weeks inhibited growth of preexisting solid tumors. Furthermore, a single injection of panitumumab (1 mg) resulted in significant and prolonged tumor inhibition.

Preclinical Toxicology and Pharmacokinetics. Results of panitumumab toxicology studies (1- and 3-month duration) have identified diarrhea and skin rash as the principal toxicities, of which the skin rash was considered related to the pharmacological action of panitumumab. Pharmacokinetics was shown to be nonlinear, and the production of monkey anti-human antibodies (MAHA) against panitumumab in

animals caused a significant decrease in exposure over the course of the 3-month study. In a 6-month toxicology study where panitumumab was administered IV at weekly doses of 7.5, 15, and 30 mg/kg to cynomolgus monkeys, skin rash and diarrhea were observed in several animals in all dose groups; both of these toxicities were considered to be related to the pharmacological action of panitumumab. Additionally, several animals showed decreased food consumption and body weight loss (Panitumumab Toxicology Study 103419).

2.8 *Nab-paclitaxel*. In this protocol, paclitaxel will be replaced with Nab-paclitaxel for paclitaxel with carboplatin regimen**.** Nab-paclitaxel (Abraxane, ABI-007, albumin-bound paclitaxel) is a Cremophor EL-free, albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers.

Nab-paclitaxel is a novel biologically interactive albumin-bound paclitaxel combining a protein with a chemotherapeutic agent in the particle form. This composition provides a novel approach of increasing intra-tumoral concentration of the drug by a receptor-mediated transport process allowing transcytosis across the endothelial cell wall, thereby breaching the blood/tumor interface. This albumin-specific receptor mediated process involves the binding of a specific receptor (gp60) on the endothelial cell wall, resulting in activation of a protein caveolin-1, which initiates an opening in the endothelial wall with formation of a little caves or caveolae, with transport of the albumin-bound chemotherapeutic complex via these caveolae to the underlying tumor interstitium (Desai *et al.*, 2006). A protein specifically secreted by the tumor (SPARC) binds and entraps the albumin, allowing release of the hydrophobic drug to the tumor cell membrane (Desai *et al.*, 2006). Nab-paclitaxel is the first biologically interactive nanoparticle leveraging this gp-60/caveolin-1/caveolae/SPARC pathway to increase intra-tumoral concentration of the drug and reducing toxic drug in normal tissue.

Clinical Studies with nab-paclitaxel

Every 3 Weeks Schedule. A Phase III trial in patients with metastatic breast cancer compared Nab-paclitaxel 260 mg/m2 to paclitaxel 175 mg/m2 given every 3 weeks (Gradishar *et al.*, 2005). Efficacy analyses were based on the ITT population. The ORR was significantly greater for Nab-paclitaxel than for paclitaxel for all patients (33% *v* 19%, respectively; $P = 0.001$), patients who received first-line therapy (42% *v* 27%, respectively; $P = 0.029$), patients who received second-line or greater therapy (27% *v* 13%, respectively; $P = 0.006$), and patients who had received prior anthracycline therapy in either the adjuvant/metastatic setting (34% *v* 18%, respectively; $P = 0.002$) or the metastatic setting only (27% *v* 14%, respectively; $P = 0.010$). Tumor response rate was also significantly higher for Nab-paclitaxel than for paclitaxel in patients with visceral dominant lesions (34% *v* 19%, respectively; $P = 0.002$) and in patients aged younger than 65 years (34% *v* 19%, respectively; $P < 0.001$). ORR also was greater for Nab-paclitaxel compared with standard paclitaxel in patients with nonvisceral dominant lesions (34% *v* 19%, respectively) and in patients $\geq$ 65 years old (27% *v* 19%, respectively), but the results did not reach statistical significance because of the small number of patients in these subsets. Median TTP was significantly longer with Nab-paclitaxel than with paclitaxel for all patients (23.0 *v* 16.9 weeks, respectively; hazard ratio [HR] = 0.75; $P = 0.006$). At the time of these analyses (October 2004), the median censoring time for overall patient survival was 103 weeks for the Nab-paclitaxel group and 101 weeks for the paclitaxel group. There was a trend for greater median survival for all patients treated with Nab-paclitaxel than with paclitaxel (65.0 *v* 55.7 weeks, respectively; $P = 0.374$). Although no difference in survival was observed in first-line patients, the difference was statistically significant in patients who received Nab-paclitaxel, compared with paclitaxel, as second-line or greater therapy (56.4 *v* 46.7 weeks, respectively; HR = 0.73; $P = .024$).

The incidence of hypersensitivity reactions (any Gr) was low for both arms (1% for Nab-paclitaxel and 2% for paclitaxel). No severe (Gr III or IV) treatment-related hypersensitivity reactions occurred in any of the patients in the Nab-paclitaxel group despite the absence of premedication. In contrast, Gr III hypersensitivity reactions occurred in the paclitaxel group despite standard premedication (chest pain, two patients; allergic reaction, three patients). Per protocol, corticosteroids and antihistamines were not administered routinely to patients in the Nab-paclitaxel group; however, premedication was administered for emesis, myalgia/arthralgia, or anorexia in 18 patients (8%) in the Nab-paclitaxel group in 2% of the treatment cycles, whereas 224 patients (> 99%) in the paclitaxel group received premedication in 95% of the cycles.

Although the patients in the Nab-paclitaxel group received an average paclitaxel dose-intensity 49% greater than that received by patients in the paclitaxel group, the incidence of treatment-related Gr IV neutropenia was significantly lower in the Nab-paclitaxel group than in the paclitaxel group (9% v 22%,

respectively; *P* < 0.001), with a higher mean neutrophil nadir (1.67 *v* 1.31x109/L, respectively; *P* = 0.046), suggesting that polyethylated castor oil may have contributed to this toxicity in patients who received standard paclitaxel.

As expected with a higher dose of paclitaxel, treatment-related Gr III sensory neuropathy occurred more frequently in the Nab-paclitaxel arm than in the paclitaxel arm (10% *v* 2%, respectively; *P* < 0.001); however, these episodes improved with interruption of treatment to Gr II or 1 in a median 22 days and were easily managed with treatment interruption and dose reduction. By day 28 after its first occurrence, the number of patients with persistent Gr III sensory neuropathy was the same (n = 4) in both study arms. No episodes of motor neuropathy or Gr IV sensory neuropathy were reported in either group.

Subgroup analyses revealed that the safety profiles of Nab-paclitaxel and paclitaxel in patients who received the drugs as first-line therapy were similar to those in the overall study population. In subgroup analyses by age, the reported AEs were similar in patients less than 65 years old and patients ≥ 65 years old in both groups. Of the patients ≥ 65 years old, the incidences of the following AEs were notably lower in the Nab-paclitaxel group than in the paclitaxel group: neutropenia (23% *v* 59%, respectively), leukopenia (10% *v* 31%, respectively), nausea (20% *v* 38%, respectively), hyperglycemia (0% *v* 19%, respectively), and flushing (0% *v* 16%, respectively). These data indicate no additional safety concerns for Nab-paclitaxel in patients ≥ 65 years old compared with younger patients. Six patients (3%) in the Nab-paclitaxel group and eight patients (4%) in the standard paclitaxel group died during the study, all as a result of disease progression. No treatment-related deaths occurred in the Nab-paclitaxel group; one patient (< 1%) in the paclitaxel group died of multiorgan failure, which was considered by the investigator to be possibly related to treatment but may also have been a result of sepsis and/or progressive disease.

Weekly Schedule. In a phase II trial in heavily pretreated patients with taxane-refractory metastatic breast cancer, objective antitumor responses occurred in 15% of women treated with weekly nab-paclitaxel 100 mg/m2 (Blum JL, et al. J Clin Oncol 22:14S, abstract 543:2004). This regimen was well tolerated. 91% of patients were treated at the full dose of 100 mg/m2 of nab-paclitaxel without dose reductions.

Based on these favorable toxicities, another trial was conducted to determine the activity and safety profile of nab-paclitaxel followed by FEC in women with LABC. Between 7/05 and 5/06, 65 women with LABC initiated preoperative nab-paclitaxel 100 mg/m2 weekly for 12 consecutive weeks followed by (a) 4 cycles of FEC-100 q3wks (F:500 mg/m2, E:100 mg/m2, C:500 mg/m2) if their cancer was HER2 negative or (b) 4 cycles of FEC-75 q3wks (F:500 mg/m2, E:75 mg/m2, C:500 mg/m2) if their cancer was HER2+ and they received trastuzumab. Trastuzumab could be co-administered with nab-paclitaxel and FEC-75 on a standard weekly schedule at the discretion of the investigator in patients with HER2+ disease. Primary endpoint will be pathologic complete response rate following completion of FEC. Secondary endpoints include complete clinical response rate assessed at the completion of nab-paclitaxel and safety.

The median age was 47 years (range: 28-70). Stage IIB disease was present in 31%, IIIA in 46%, and IIIB in 24%. Tumors were ER+ in 54% and HER2+ in 28%. Preliminary toxicity data with nab-paclitaxel reported in the first 44 patients shows the most frequent toxicities have been diarrhea (Gr II/3-16%/7%), fatigue (Gr II/3-30%/5%), and sensory neuropathy (Gr II/3-9%/5%). No Grade 4 or 5 toxicities and only one Gr 3 neutropenia have been reported. All 12 doses of nab-paclitaxel were administered to 29 of the first 32 patients, and 28 of these completed the 12 doses in 12-14 weeks. **Thus, weekly nab-paclitaxel has minimal toxicity in chemotherapy naive patients with LABC**.

2.9 *Combination of paclitaxel with carboplatin in breast cancer*. New non-anthracycline regimens have been used for both primary and metastatic breast cancer. Carboplatin as a single agent produces response rates of 20–35% in untreated metastatic breast cancer. Further, when combined with carboplatin and taxanes (paclitaxel, docetaxel) therapy was active and reasonably well tolerated in the first-line treatment of metastatic breast cancer, producing objective response rates of 53%–62%—substantially higher rates than those seen in other phase II trials of either drug alone. At last, phase III data suggest that adding carboplatin to a paclitaxel/trastuzumab regimen produces superior efficacy than paclitaxel/trastuzumab alone for patients with HER2+ metastatic disease. This regimen was used in preoperative systemic chemotherapy with equivalent efficacy (DFS and OS) with adriamycin/cyclophosphamide followed by paclitaxel/trastuzumab without equivalent toxicities. **Thus, incorporation of carboplatin as a standard agent in first-line treatment of primary breast cancer has support from these recent studies.**

2.10 *Biomarker Development*. No biomarkers have been established with which to identify patients who might benefit from this type of treatment which include EGFR targeted therapy. Thus, secondary objective of this study is to determine whether pCR rate correlates with EGFR expression level by immunohistochemical (IHC) staining and fluorescence in situ hybridization (FISH). Both techniques (IHC, FISH) for measuring EGFR expression level have been standardized at M. D. Anderson.

To further understand the biological effect of panitumumab as a single agent and to discover novel biomarkers, we will administer the first dose administer as a single agent. Then, perform a biopsy of the breast tumor before the second dose of panitumumab, which will be combined with chemotherapy.

We will use a new tool, layered peptide arrays, to perform multilayer IHC staining of a single section of paraffin blocks of breast tumor that has been collected. This new tool allows testing of up to 20 biomarkers. Current plans are to test the phosphorylation status of p27, EGFR, PEA15, and ERK, all of which are thought to modulate EGFR-targeting drug activities.

At last, we will collect frozen tumors for protein and mRNA profiling, and serum by registering the patient on inflammatory breast cancer registration study (2006-1072).

2.11 *Rationale.* The **hypothesis** underlying this protocol is that preoperative chemotherapy with a combination of anti-EGFR monoclonal antibody (panitumumab), carboplatin, and nab-paclitaxel with FEC will produce higher pathologic complete response rates among patients with IBC than the historical rate (about 13%). We propose here a prospective, single-arm, phase II protocol to confirm the importance of EGFR as a therapeutic target in IBC and to show that use of an anti-EGFR antibody such as panitumumab can modulate the sensitivity of IBC to chemotherapy, as indicated by an improved pathologic CR rate. Taxanes and carboplatin have known activity in breast cancer and synergistic effects with modulators of the EGF family. In particular, nab-paclitaxel is far superior to the standard formulation in metastatic breast cancer.

3.0 PRODUCT INFORMATION

3.1 Panitumumab

3.1.1 Therapeutic Classification: Antineoplastic Agent, Monoclonal Antibody

3.1.2 Mechanism of Action: Recombinant human IgG2 monoclonal antibody which binds specifically to the epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands. Binding to the EGFR blocks phosphorylation and activation of intracellular tyrosine kinases, resulting in inhibition of cell survival, growth, proliferation and transformation

3.1.3 Pharmaceutical Data:

- Half-life elimination: $<$7.5 days (range: 4-11 days)

3.1.4 Solution Preparation: Panitumumab is a protein and should be handled gently to avoid foaming, which may lead to denaturation of the protein product. This precaution applies not only to panitumumab stored in the vial, but also for diluted panitumumab prepared in the IV bag. It is, therefore, essential to avoid medication delivery methods, particularly pneumatic tube systems, which could potentially lead to excessive shaking or vibration, which would potentially lead to particulate formation in the protein product. Panitumumab must be prepared as an intravenous (IV) infusion using aseptic techniques. The dose of panitumumab will be 2.5 mg/kg and will be based upon the subject's baseline weight. The dose of panitumumab is required to be recalculated only when the subject's body weight increases or decreases by $\geq$ 10% from the original screening/baseline weight. This weight will be considered the new baseline weight from which a $\pm$ 10% variance is allowed before another recalculation is necessary. The calculated amount of panitumumab (may be rounded to the nearest ten milligrams [e.g., 456 mg rounded to 460 mg or 312 mg rounded to 310 mg]) will be removed from the vials and added to a minimum volume of 100 mL of pyrogen-free 0.9% sodium chloride solution USP. Doses higher than 1000 mg should be diluted to 150 mL with 0.9% sodium chloride injection, USP. The maximum concentration of the diluted solution to be infused should not exceed 10 mg/mL. In the event a subject's actual body weight requires greater than a 150-mL volume infusion, panitumumab will be administered over 60 to 90 $\pm$ 15 minutes, as tolerated. The panitumumab will be infused within 6 hours of dilution and will be labeled per site pharmacy standard operating procedures. The bag should be labeled per site pharmacy standard operating procedures and promptly forwarded to the clinic center for infusion.

3.1.5 Stability and Storage Requirements:

- Each vial of panitumumab will contain 10 mL of a sterile protein solution containing a 20-mg/mL solution of panitumumab. The vial will contain approximately 200 mg of panitumumab and is for single dose use only. Each vial of panitumumab will be labeled in accordance with current ICH GCP, FDA and specific national requirements.
- The supplied investigational drug must be stored at 2-8° C in a secured area upon receipt. As panitumumab contains no preservatives, vials are designed for single use only. Exposure of the material to excessive temperature above or below this range should be avoided. Do not allow panitumumab to freeze and do not use if contents freeze in transit or in storage. If vials fall out of specified temperature requirement, please contact Amgen for instructions. Records of the actual storage condition during the period of the study must be maintained (i.e., records of the date and time and initials of person checking, and the "working day" temperature of the refrigerator used for storage of trial supplies, continuous temperature recordings, or regularly maintained temperature alarm systems used in conjunction with temperature recording).
- Supply and Return: At study initiation and as needed thereafter, panitumumab will be shipped to a responsible person (e.g., a pharmacist) at the Investigator's institution, who will check the amount and condition of the drug and enter these data into the Proof of Receipt Form and Investigational Product Accountability record. The Proof of Receipt Form should then be returned to Amgen, and the original retained at the site. At the end of the study, or as directed, all panitumumab supplies, including unused, partially used, or empty containers, will be destroyed at the site.
- Panitumumab Accountability: An Investigational Product Accountability Record for panitumumab must be kept current and should contain:
- The dates and quantities of panitumumab received from Amgen
- Manufacturing batch or lot numbers for product for product received
- Subject's identification (subject number)
- Dose preparation records
- Date and quantity of drug dispensed and returned to the investigator/pharmacy, if appropriate
Authorized sponsor representative(s) and regulatory agency inspector(s) must make these inventories available for inspection. The investigator is responsible for the accountability of all used and unused trial supplies

3.1.6 Route of Administration: IV infusion only.

3.1.7 Usual Dosage Range:

3.1.7.1 Adults: Adults: Colorectal cancer: 6 mg/kg every 2 weeks

3.1.7.2 Dosing adjustment for toxicity:

- Infusion reactions, mild-to-moderate (grade 1 or 2): Reduce the infusion rate by 50% for the duration of infusion
- Infusion reactions, severe (grade 3 or 4): Immediately and permanently discontinue treatment
- Skin toxicity (grade 3 or 4): Withhold treatment; if skin toxicity does not improve to ≤ grade 2 within 1 month, permanently discontinue. If skin toxicity improves to ≤ grade 2 within 1 month (with patient missing ≤2 doses), resume treatment at 50% of the original dose. Dose may be increased in increments of 25% of the original dose (up to 6 mg/kg) if skin toxicities do not recur. For recurrent skin toxicity, permanently discontinue.

3.1.7.3 Dosage adjustment in renal impairment: Has not been studied

3.1.7.4 Dosage adjustment in hepatic impairment: Has not been studied

3.1.8 Side Effects:

3.1.8.1 The below referenced studies reflect the reported adverse events at the time of the last Panitumumab Investigator's Brochure (Version 7.0, 10June2008). Please refer to the current version of the Panitumumab Investigator's Brochure as well as the updated safety information contained in the Investigational New Drug safety letters for further updates.

3.1.8.2 Safety analyses from 16 clinical studies in subjects with a variety of solid tumors (n = 1599 receiving panitumumab) indicated that panitumumab is generally well tolerated. Among these studies, 11 enrolled subjects with mCRC (n = 1052 receiving panitumumab as a single agent). In these subjects, dermatologic-related toxicities were the most frequently reported adverse events (91% of subjects), with most events being mild to moderate. Relatively few subjects (2%) permanently discontinued panitumumab due to dermatologic adverse events. Infusion reactions to panitumumab (defined as any reported allergic reaction, anaphylactoid reaction, chills, fever, or dyspnea, occurring within 24 hours of the first dose that were not otherwise designated as either anaphylactoid or allergic reaction) were infrequent (3% of subjects; < 1% severe); particularly considering that premedication was not mandated in study protocols. Panitumumab antigenicity, as measured by enzyme-linked immunosorbent assay (ELISA) and Biacore assay, was very low and was not associated with clinical sequelae.

3.1.8.3 Panitumumab Monotherapy Studies

An integrated analysis of the safety of panitumumab has been conducted for 1052 subjects with mCRC receiving panitumumab monotherapy (mCRC Monotherapy Set). Subjects primarily received panitumumab doses of 2.5 mg/kg once weekly (15%) or 6.0 mg/kg every 2 weeks (82%).
Consistent with the published data on subjects treated with EGFr inhibitors (ie, class/target effect) (Perez-Soler and Saltz, 2005), the most commonly reported treatment-related adverse events in subjects treated with panitumumab were associated with the skin, including pruritus (52%), acneiform dermatitis (51%), erythema (50%), and rash (38%). Most subjects (833 of 1052 subjects, 79%) with any dermatologic toxicity had events that were considered to be mild or moderate. Only 3% of subjects permanently discontinued panitumumab administration for dermatologic toxicities. Dermatologic toxicities typically were observed after initiation of panitumumab, with a median time to first integument toxicity (of any severity) of 10 days (95% CI: 8, 11).
Other common treatment-related adverse events (ie, subject incidence □ 10%) included fatigue (15%) and diarrhea (13%).
Subjects in the wild-type KRAS subset received a higher number of panitumumab infusions compared with subjects in the mutant subset (mean [median] 10.0 [8.0] and 4.9 [4.0], respectively). More treatment-related adverse events occurred in the wild-type KRAS subset compared with the mutant KRAS subset, presumably due to the greater number of panitumumab infusions received. These adverse events were mainly skin toxicities (erythema, pruritus, dermatitis acneiform) likely reflecting the increased duration of exposure to panitumumab. No qualitative differences in overall adverse events were observed between the wild-type KRAS subset, the mutant KRAS subset and the overall population, however, treatment related grade 3 adverse events were reported for 25% of subjects in the wild-type KRAS subset compared with 12% of subjects in the mutant KRAS subset. Two percent of wild-type KRAS subjects and 1% of mutant KRAS subjects withdrew for panitumumab-related events.
Infusion reactions to panitumumab were infrequent even though premedication was not mandated in the panitumumab clinical program. Overall, 1% of subjects had an infusion reaction reported by the investigator as an adverse event. Using a definition consistent with the Vectibix USPI (2007), 3% of panitumumab-treated subjects had a potential infusion reaction; < 1% of subjects had a potential infusion reaction by this definition ≥ grade 3.

3.1.8.4 Panitumumab Combination Chemotherapy Studies

To date, panitumumab has been evaluated in combination with chemotherapy in subjects with CRC, NSCLC, and SCCHN.
In the mCRC setting in combination with IFL (Study 20025409), the incidence of grade 3 or 4 diarrhea (58%) was notably higher than that historically expected for this already highly GI-toxic chemotherapy regimen, and 1 subject had an episode of grade 4 diarrhea that was also considered serious. Of note, panitumumab in combination with the FOLFIRI regimen using the same agents but different doses/infusion times was better tolerated with an incidence of grade 3 or 4 diarrhea similar to that expected from the literature for this chemotherapy regimen alone (25%) (Andre et al, 1999; Saltz et al, 2000). These data suggest that the potential for additive toxicities in the gastrointestinal tract exists when panitumumab is administered in combination with GI toxic chemotherapy. However, these toxicities could be managed by appropriate selection of the concomitant chemotherapy regimen.
No clear additive effects were observed in the NSCLC setting where panitumumab was combined with carboplatin/paclitaxel (Study 20025404). One case of pulmonary fibrosis was reported in a subject treated with this combination. Although subjects with evidence of interstitial pneumonitis or pulmonary fibrosis were excluded from clinical studies (from 2004 onward), this subject, who had a previous history of underlying idiopathic pulmonary fibrosis, was enrolled before the protocol exclusions were implemented.
Amgen study 20040249 (PACCE) is an open-label, controlled study of bevacizumab and chemotherapy administered with and without panitumumab as first-line treatment of subjects with mCRC. Chemotherapy included oxaliplatin-or irinotecan-based regimens. Based on the results of a planned interim analysis (conducted after 257 progression or death events had occurred), adding panitumumab to bevacizumab and oxaliplatin-based chemotherapy did not prolong progression-free survival and contributed increased toxicity to the multi-agent regimens. Panitumumab treatment was discontinued from the study at that time (22 March 2007).
A final analysis of on-treatment efficacy and safety was performed based on available data as of 31 May 2007. The addition of panitumumab to bevacizumab and oxaliplatin-based chemotherapy showed an unfavorable benefit-to-risk profile with shorter progression-free survival time and increased toxicity. Although panitumumab treatment in the irinotecan-based chemotherapy stratum was also prematurely discontinued, there was no evidence of significant benefit with the addition of panitumumab to bevacizumab and irinotecan-based chemotherapy in first-line treatment of mCRC. Given the unfavorable benefit-to-risk outcome, the PACCE study as designed did not support the use of panitumumab with bevacizumab and oxaliplatin- or irinotecan-based chemotherapy as first-line treatment of metastatic

colorectal cancer.

3.1.8.5 Please refer to the current Panitumumab Investigator's Brochure for further details.

3.1.8.6 Panitumumab Combination Radiotherapy with or without Chemoradiotherapy Studies
An open-label, dose-finding study (Study 20040235) of AMG 706 or panitumumab when administered with induction chemotherapy (IC) and/or chemo-radiotherapy (CRT) in the treatment of subjects with loco-regionally advanced squamous cell carcinoma of the head and neck is ongoing. Five dose cohorts are currently planned for this study. As of the data cut-off date (18 May 2007), 5 subjects were enrolled in cohort A [TPF (T – docetaxel 75 mg/m2; P cisplatin 75 mg/m2; F – 5-fluorouracil 750 mg/m2 days 1 to 5) induction chemotherapy followed by chemoradiotherapy + panitumumab 1.5 mg/kg QW (n = 7) and 2.5 mg/kg (n = 3), and 4 subjects were enrolled in cohort B (TPF induction chemotherapy followed by chemoradiotherapy + AMG 706). Of the 9 subjects enrolled in cohorts A and B, 8 had completed study and 1 had treatment ongoing (data on file at Amgen Inc). Safety data was available for all 9 subjects. At least 1 treatment-emergent adverse event was reported for all 9 subjects (100%) in cohorts A and B. Two subjects in cohort A1 experienced a DLT (one each grade 3 and 4 mucositis). Subsequently, the protocol was amended to modify the DLT definition for mucositis to limit it to grade ≥ 3 toxicity that occurred in the first 5 weeks of radiotherapy or led to a 5-day radiotherapy delay. There were no further DLTs. The most common grade ≥ 3 AE during the panitumumab + chemoradiotherapy phase was mucositis (n = 6). There was 1 event each of grade 3 esophagitis, dysphagia, and odynophagia, all reported as unrelated to panitumumab. One subject also experienced grade 3 radiation dermatitis that was considered related but did not meet the criteria of a DLT. The most common grade ≥ 3 adverse events during induction chemotherapy were febrile neutropenia (n = 5) and mucositis (N = 4). No subjects in cohort A have died within 30 days of last dose of investigational product (data on file at Amgen Inc)

3.2 Nab-paclitaxel (Abraxane)

3.2.1 Therapeutic Classification: Antimicrotubular; Antineoplastic Agent, Natural Source (Plant) Derivative

3.2.2 Mechanism of Action: Paclitaxel promotes microtubule assembly by enhancing the action of tubulin dimers, stabilizing existing microtubules, and inhibiting their disassembly, interfering with the late G2 mitotic phase, and inhibiting cell replication. In addition, the drug can distort mitotic spindles, resulting in the breakage of chromosomes. Paclitaxel may also suppress cell proliferation and modulate immune response.

3.2.3 Pharmaceutical Data:

- Drug Distribution
  Abraxane® will be distributed by Celgene. No supplies will be shipped to any site until regulatory approval has been obtained. Investigational sites will be supplied with Abraxane® upon identification and screening of a potential trial subject.
  Upon identification of a potential subject, sites must fax a completed Drug Request Form to Celgene. Allow at least 5 working days for drug shipment. There are no shipments on Fridays or holidays. For re-supply of drug, please complete and fax the Drug Request Form to Celgene at 908-393-8304.
- Drug Return and Destruction
  If the investigational site does not have a policy, procedure or SOP detailing the process to follow for study drug destruction, the study drug must then be returned to Celgene using the Drug Return Form provided in the package containing the study drug. The following information must be recorded on the site's pharmacy drug accountability log: quantity of vials to be returned, expiration date and lot number. A copy of the Drug Return Form and the study drug should be returned to Celgene using the mailing address on the packaging slip that came with the original study drug order. A copy of the Drug Return Form should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records (drug dispensing log, drug accountability log and any destruction memos) must be mailed Celgene.
  If the investigational site has a policy, procedure or SOP detailing the process to follow for study drug destruction, the pharmacist or designee can choose to destroy the study drug on site. The following information must be recorded on the site's pharmacy drug accountability log: quantity of vials destroyed, expiration date and lot number. The pharmacist must document that the study drug was destroyed in accordance with their institution's drug destruction policy or SOP. A drug destruction memo and the site's drug destruction SOP/policy should be sent to Celgene. A copy of the drug destruction memo should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records (drug dispensing log, drug accountability log and any destruction memos) must be mailed to Celgene.

- Distribution: Vd: 632 L/m2

- Protein binding: 89-98%
- Metabolism: Hepatic via CYP3A4 (to minor metabolites) and 2C8 (primarily to 6-alpha-hydroxypaclitaxel)
- Half-life elimination: 27 hours
- Excretion: Urine (4% as unchanged drug, 1% as metabolites); feces (20%)
- Clearance 15 L/hour/m2

3.2.4 Storage and Stability: Unreconstituted Abraxane should be stored at controlled room temperature (20 – 25 °C or 68 – 77 °F) in its carton. Retain in the original package to protect from bright light. Unopened vials of albumin-bound paclitaxel are stable until the date indicated on the package when stored at the above temperatures in the original package. Reconstituted albumin-bound paclitaxel should be used immediately, but may be refrigerated at 2 – 8 °C (38 – 46 °F) for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

3.2.5 Solution Preparation: Each 50-mL single-use vial contains 100 mg of paclitaxel, and approximately 900 mg of human albumin. Nab-paclitaxel is supplied as a white to off-white sterile lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection USP Injection, powder for reconstitution: 100 mg contains human albumin 900 mg.

Reconstitution and use of Abraxane

1. Calculate the patient's body surface area at the beginning of the study and if the weight changes by > 10% by using the formula provided in the study manual.

2. Calculate the total dose (in mg) to be administered by:
Total Dose (mg) = BSA x (study dose mg/m^2)

3. Calculate the total number of vials required by:
Total Number of Vials = Total Dose (mg) / 100 (mg/vial)
Round up the number of vials to be reconstituted to the next higher whole number when a fractional number of vials is obtained by the above formula (eg, if the total number of vials = 4.05 or 4.5, then 5 vials would be reconstituted).

4. Using sterile technique, prepare the vials for reconstitution.

5. Swab the rubber stoppers with alcohol.

6. Reconstitute each Abraxane vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP or equivalent into each vial over a period of not less than 1 minute.

• Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe directing the solution flow onto the inside wall of the vial.

• DO NOT INJECT the 0.9% Sodium Chloride Injection, USP solution directly onto the lyophilized cake as this will result in foaming.

• Once the injection is complete, allow the vial to sit for a minimum of 5 (five) minutes to ensure proper wetting of the lyophilized cake/powder.

• Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Rapid agitation or shaking will result in foaming.

• If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

• Each ml of reconstituted product will contain 5 mg of paclitaxel.

7. Calculate the exact total dosing volume of 5 mg/ml suspension required for the patient:
Dosing volume (ml) = Total dose (mg) / 5 (mg/ml)

8. The reconstituted sample should be milky and homogeneous without visible particulates. If unsuspended powder is visible, the vial should be gently inverted again to ensure complete resuspension, prior to use.

9. Once the exact volume of reconstituted Abraxane has been withdrawn from the vials, discard any excess solution left over in accordance with standard operating procedures.

10. Further dilution is not necessary. Inject the calculated dosing volume of reconstituted Abraxane suspension into an empty sterile, standard PVC IV bag using an injection port. Inject perpendicularly into the center of the injection port to avoid dislodging plastic material into the IV bag.

11. Administer the calculated dosing volume of reconstituted Abraxane suspension by IV infusion over 30 minutes. The use of in-line filters is not necessary. If used, in-line filters with pore sizes of < 15µ should not be used.

12. Use within 8 hours of reconstitution. If not used immediately, store reconstituted Abraxane in a refrigerator for no longer than 8 hours.

3.2.6 Route of Administration: IV infusion only. IV: Administer over 30 minutes; use of DEHP-free containers or administration sets is not necessary; do not use an in-line filter

3.2.7 Usual Dosage Range:

3.2.7.1 Adults: Adults: Breast cancer: 260 mg/m2 every 3 weeks

3.2.7.2 Dosage adjustment for toxicity:

- Severe neutropenia (<500 cells/mm3) ≥1 week: Reduce dose to 220 mg/m2 for subsequent courses
- Recurrent severe neutropenia: Reduce dose to 180 mg/m2
- Severe sensory neuropathy: Reduce dose to 180 mg/m2
- Sensory neuropathy grade 3 or 4: Hold treatment until resolved to grade 1 or 2, then resume with reduced dose

3.2.7.3 Dosage adjustment in renal impairment: Safety not established for serum creatinine >2 mg/dL; use with caution

3.2.7.4 Dosage adjustment in hepatic impairment: Effects of hepatic dysfunction (serum bilirubin >1.5 mg/dL) unknown; dosage adjustment recommendations are not available. Study drug should only be administered if hepatic function is within the parameters established in the eligibility criteria. Hepatic toxicity from taxanes may occur but it is uncommon. Therefore, hepatic dysfunction that occurs while the patient is on study should prompt an evaluation to determine the cause, including the possibility of progressive metastatic disease and hepatotoxicity from concurrent medications.

3.2.7.5 Administration of Study Drug to Patients with Abnormal Hematologic Function. Abraxane dosing should not be administered at the start of each cycle until the absolute neutrophil count returns to ≥1.5 x 10^9 cells/L and the platelet count returns to >100 x 10^9 cells/L.

3.2.7.6 Hypersensitivity Reactions. Hypersensitivity reactions rarely occur. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, lower back pain, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy. Patients who experience severe hypersensitivity reactions to Abraxane should not be re-challenged.

3.2.7.7 Other Toxicities. If toxicities are ≥ grade 3, except for anemia, treatment should be withheld until resolution to ≤ grade 1 or baseline if baseline was greater than grade 1, then reinstituted, if medically appropriate, at the next lower dose level (see Table 2).

3.2.8 Drug Interactions Substrate (major) of CYP2C8, 2C9, 3A4; Induces CYP3A4 (weak)
Anthracyclines (e.g. doxorubicin, epirubicin): Paclitaxel may increase anthracycline levels/toxicity; administration of anthracycline at least 24 hours prior to paclitaxel may reduce interaction.
Carboplatin, cisplatin, oxaliplatin (platinum derivatives): When administered as sequential infusions, taxane derivatives should be administered before platinum derivatives to limit myelosuppression and to enhance efficacy.
Cardiac glycosides: Paclitaxel may decrease the absorption of cardiac glycosides (may only affect digoxin tablets); monitor.
CYP2C8 inducers: May decrease the levels/effects of paclitaxel. Example inducers include carbamazepine, phenobarbital, phenytoin, rifampin, rifapentine, and secobarbital.
CYP2C8 inhibitors may increase the levels/effects of paclitaxel. Example inhibitors include gemfibrozil, ketoconazole, montelukast, and ritonavir.
CYP3A4 inducers: CYP3A4 inducers may decrease the levels/effects of paclitaxel. Example inducers include aminoglutethimide, carbamazepine, nafcillin, nevirapine, phenobarbital, phenytoin, and rifamycin.
CYP3A4 inhibitors: May increase the levels/effects of paclitaxel. Example inhibitors include azole antifungals, clarithromycin, diclofenac, doxycycline, erythromycin, imatinib, isoniazid, nefazodone, nicardipine, propofol, protease inhibitors, quinidine, telithromycin, and verapamil.

3.2.9 Side Effects:

3.2.9.1 >10%

- Cardiovascular: EKG abnormal (60%)
- Dermatologic: Alopecia (90%)
- Gastrointestinal: Nausea (30%; grades 3/4: 3%), diarrhea (27%; grades 3/4: <1%), vomiting (18%; grades 3/4: 4%)
- Hematologic: Neutropenia (80%; grade 4: 9%), anemia (33%; grades 3/4: 1%)
- Hepatic: AST increased (39%), alkaline phosphatase increased (36%), GGT increased (grades 3/4: 14%)
- Neuromuscular & skeletal: Sensory neuropathy (71%; grades 3/4: 10%; dose dependent; may be cumulative), weakness (47%), myalgia/arthralgia (44%)
- Ocular: Vision disturbance (13%; severe [keratitis, blurred vision]: 1%)
- Respiratory: Dyspnea (12%)
  Miscellaneous: Infection (24%; primarily included oral candidiasis, respiratory tract infection, and pneumonia

3.2.9.2 1% to 10%:

- Cardiovascular: Edema (10%), hypotension (5%), cardiovascular events (grades 3/4: 3%; included chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension)
- Gastrointestinal: Mucositis (7%; grades 3/4: <1%)
- Hematologic: Bleeding (2%), neutropenic fever (2%), thrombocytopenia (2%; grades 3/4: 1%)
- Hepatic: Bilirubin increased (7%)
- Neuromuscular and skeletal: Peripheral neuropathy (grade 3: 10%)
- Renal: Creatinine increased (11%; severe 1%)
- Respiratory: Cough (7%)
- Miscellaneous: Hypersensitivity reaction (4%)

3.2.9.3 <1% (Limited to important or life-threatening): <1%: Bradycardia, cardiac ischemia, cerebrovascular attack, cranial nerve palsies, embolism, erythema, hand-foot syndrome (in patients previously exposed to capecitabine), injection site reaction, maculopapular rash, MI, motor neuropathy, nail discoloration, nail pigmentation changes, photosensitivity reaction, pneumothorax, pruritus, radiation recall, stroke, thrombosis, transient ischemic attack

3.2.9.4 It is contraindicated with hypersensitivity to paclitaxel or any component of the formulation; baseline neutrophils <1500/mm3

3.2.9.5 Adverse reactions reported with paclitaxel, which may occur with paclitaxel (protein bound): Autonomic neuropathy, cellulitis, conjunctivitis, extravasation recall, fibrosis, hepatic necrosis, hepatic encephalopathy, induration, intestinal obstruction, intestinal perforation, interstitial pneumonia, ischemic colitis, lacrimation increased, lung fibrosis, necrosis, neutropenic enterocolitis (typhlitis), optic nerve damage (persistent), pancreatitis, paralytic ileus, phlebitis, radiation pneumonitis with concurrent radiation therapy, skin exfoliation, Stevens-Johnson syndrome, toxic epidermal necrolysis

3.3 Carboplatin

3.3.1 Therapeutic Classification: Alkylating Agent; Platinum

3.3.2 Mechanism of Action: Carboplatin is an alkylating agent, which covalently binds to DNA; possible cross-linking and interference with the function of DNA

3.3.3 Pharmaceutical Data:

- Injection: 50 mg, 150 mg, 450 mg
- Distribution: Vd: 16 L/kg
- Protein binding: 0%; platinum is 30% irreversibly bound.
- Metabolism: Minimally hepatic to aquated and hydroxylated compounds.
- Half-life elimination: Terminal: 22-40 hours; CrCl >60 mL/minute: 2.5-5.9 hours
- Excretion: Urine (60-90%) within 24 hours

3.3.4 Solution Preparation: Maximum concentration: 10 mg/mL. Standard IVPB Fluid: 250 mL D5W.

3.3.5 Stability and Storage Requirements:

- Room temperature stability: 36 hours; extrapolated stability policy considering % drug lost over time
- Refrigeration stability after dilution: 5 days

3.3.6 Route of Administration: IV infusion only.

3.3.7 Usual Dosage Range:

3.3.7.1 Adults: Single agent: 360 mg/m2 once every 4 weeks; dose is then adjusted on platelet count and neutrophil count values; Carboplatin may also be prescribed by formula-based dosing using the AUC method as per the Calvert-based equations. Carboplatin, as a single agent, has been shown to be

effective in patients with recurrent ovarian carcinoma at a dosage of 360 mg/m2 IV on day 1 every 4 weeks. In general, however, single intermittent courses of carboplatin should not be repeated until the neutrophil count is at least 2,000 and the platelet count is at least 100 K. The dose adjustments in the table below were recommendations from LexiComp and are modified from a controlled trial in previously treated patients with ovarian carcinoma. Blood counts were done weekly, and the recommendations are based on the lowest post-treatment platelet or neutrophil value.

Carboplatin Dosage Adjustment Based on Pretreatment Platelet Counts

Platelets (cells/L)	Neutrophils (cells/L)	Adjusted Dose (From Prior Course)
> 100 x 10^9	> 2 x 10^9	125%
50-100 x 10^9	0.5-2 x 10^9	No adjustment
< 50 x 10^9	< 0.5 x 10^9	75%

3.3.7.2 Dosing in renal impairment: Creatinine clearance (CrCl) < 60 mL/minute are at increased risk of severe bone marrow suppression. In renally impaired patients who received single agent carboplatin therapy, the incidence of severe leukopenia, neutropenia, or thrombocytopenia has been about 25% when the following dosage modifications have been used: CrCl 41-59 mL/minute: Recommended dose on day 1 is 250 mg/m2, CrCl 16-40 mL/minute: Recommended dose on day 1 is 200 mg/m2, The data available for patients with severely impaired kidney function (CrCl <15 mL/minute) are too limited to permit a recommendation for treatment. These dosing recommendations apply to the initial course of treatment. Subsequent dosages should be adjusted according to the patient's tolerance based on the degree of bone marrow suppression.

3.3.8 Side Effects:

3.3.8.1 >10%

- Dermatologic: Alopecia
- Endocrine & metabolic: Hypomagnesemia, hypokalemia, hyponatremia, hypocalcemia; less severe than those seen after cisplatin (usually asymptomatic).
- Gastrointestinal: Nausea, vomiting, stomatitis.
- Hematologic: Myelosuppression (dose related and dose-limiting); thrombocytopenia (37-80%); leukopenia (27-38%). Nadir: <21 days following a single dose.
- Hepatic: Alkaline phosphatase increased, AST increased (usually mild and reversible).
- Otic: Hearing loss at high tones (above speech ranges, up to 19%); clinically important ototoxicity is not usually seen.
- Renal: Increases in creatinine and BUN have been reported.

3.3.8.2 1% to 10%:

- Gastrointestinal: Diarrhea, anorexia
- Hematologic: Hemorrhagic complications
- Local: Pain at injection site
- Neuromuscular & skeletal: Peripheral neuropathy (4-6%; up to 10% in older and/or previously-treated patients)
- Otic: Ototoxicity

3.3.8.3 <1% (Limited to important or life-threatening): Neurotoxicity, urticaria, rash, nephrotoxicity, secondary malignancies, anaphylaxis, malaise, and hypertension

3.3.8.4 Special Precautions: Increased toxicity can be observed with: Nephrotoxic drugs; aminoglycosides increase risk of ototoxicity, and Docetaxel, paclitaxel (taxane derivatives): When administered as sequential infusions, taxane derivatives should be administered before platinum derivatives to limit myelosuppression and to enhance efficacy.

3.3.8.5 Carboplatin is a vascular irritant.

3.3.8.6 It is contraindicated with history of severe allergic reaction to cisplatin, carboplatin, other platinum-containing formulations, mannitol, or any component of the formulation; pregnancy

3.4 Epirubicin

3.4.1 Therapeutic Classification: Anthracycline; Antineoplastic Agent

3.4.2 Mechanism of Action: Epirubicin is an anthracycline antibiotic; known to inhibit DNA and RNA synthesis by steric obstruction after intercalating between DNA base pairs; active throughout entire cell cycle. Intercalation triggers DNA cleavage by topoisomerase II, resulting in cytocidal activity. Also inhibits DNA helicase, and generates cytotoxic free radicals.

3.4.3 Pharmaceutical Data:

- Injection: 2 mg/mL (50 mg/25 mL; 200 mg/100 mL)

- Distribution: Vss 21-27 L/kg
- Protein binding: 77% to albumin
- Metabolism: Extensively via hepatic and extrahepatic (including RBCs) routes
- Half-life elimination: Triphasic; Mean terminal: 33 hours
- Excretion: Feces; urine (lesser extent)

3.4.4 Solution Preparation: Stability and Storage Requirements:

- Room temperature stability:
- Refrigeration stability:

3.4.5 Route of Administration: IV infusion only.

3.4.6 Usual Dosage Range:

3.4.6.1 Adults: Single agent:

- Recommended starting dose: 100-120 mg/m2. Epirubicin is given in repeated 3- to 4-week cycles with the total dose given on day 1 of each cycle or divided equally and given on days 1 and 8 of each cycle. Patients receiving the 120 mg/m2 regimen should also receive prophylactic antibiotics with TMP-SMX or a fluoroquinolone.
- As a component of adjuvant therapy in patients with axillary-node positive breast cancer:
- CEF-120: 60 mg/m2 on days 1 and 8 of cycle (in combination with cyclophosphamide and 5-fluorouracil); cycle is repeated every 28 days for 6 cycles
- FEC-100: 100 mg/m2 on day 1 of cycle (in combination with 5-fluorouracil and cyclophosphamide); cycle is repeated every 21 days for 6 cycles

3.4.6.2 Dosing in hepatic impairment:

- Bilirubin 1.2-3 mg/dL or AST 2-4 times the upper limit of normal: 50% of recommended starting dose
- Bilirubin >3 mg/dL or AST >4 times the upper limit of normal: 25% of recommended starting dose

3.4.6.3 Dosage adjustment in bone marrow dysfunction:

- Patients with heavy pretreatment, pre-existing bone marrow depression, or the presence of neoplastic bone marrow infiltration: Consider lower starting doses of 75-90 mg/m2
- Dosage modifications after the first treatment cycle: Nadir platelet counts
- <50,000/mm3, ANC <250/mm3, neutropenic fever, or grades 3/4 non hematologic
- Toxicity: Reduce day 1 dose in subsequent cycles to 75% of the current cycle. Day 1 chemotherapy in subsequent courses of treatment should be delayed until platelet counts are ≥100,000/mm3, ANC ≥1500/mm3, and non hematologic
- Toxicities have recovered to ≤grade 1.
- In addition, for patients receiving divided dose (day 1 and day 8) regimen:
- Day 8 platelet counts 75,000-100,000/mm3 and ANC 1000-1499/mm3: Day 8
- Dose should be 75% of the day 1 dose
- Day 8 platelet counts <75,000/mm3, ANC <1000/mm3, or grade 3 or 4
- Non hematologic toxicity: Omit day 8 dose
- Dosage adjustment in renal impairment: Severe renal impairment (serum creatinine >5 mg/dL): Lower doses should be considered

3.4.7 Side Effects:

3.4.7.1 >10%

- Central nervous system: Lethargy (1-46%)
- Dermatologic: Alopecia (69-96%)
- Endocrine & metabolic: Amenorrhea (69-72%), hot flashes (5-39%)
- Gastrointestinal: Nausea/vomiting (83-92%), mucositis (9-59%), diarrhea (7-25%)
- Hematologic: Leukopenia (50-80%; grades 3/4: 2-59%), neutropenia (54-80%; grades 3/4: 11-67%; nadir: 10-14 days; recovery: 21 days), anemia (13-72%; grades 3/4: 6%), thrombocytopenia (5-49%; grades 3/4: 5%)
- Local: Injection site reactions (3-20%)
- Ocular: Conjunctivitis (1-15%)
- Miscellaneous: Infection (15-21%)

3.4.7.2 1% to 10%:

- Cardiovascular: CHF (0.4-1.5%), decreased LVEF (asymptomatic) (1-2%); recommended maximum cumulative dose: 900 mg/m2
- Central nervous system: Fever (1-5%)

- Dermatologic: Rash (1-9%), skin changes (1-5%)
- Gastrointestinal: Anorexia (2-3%)
- Hematologic: Neutropenic fever (grades 3/4: 6%)

3.4.7.3 <1% (Limited to important or life-threatening):

- Post-marketing, case reports, and/or frequency not defined: Acute lymphoid leukemia; acute myelogenous leukemia (0.3% at 3 years, 0.5% at 5 years, 0.6% at 8 years); anaphylaxis, atrioventricular block, bradycardia, bundle-branch block, cardiomyopathy, ECG abnormalities, hypersensitivity, myelodysplastic syndrome, photosensitivity, premature menopause, premature ventricular contractions, pulmonary embolism, radiation recall, sinus tachycardia, skin and nail hyperpigmentation, ST-T wave changes (nonspecific), tachyarrhythmias, thromboembolism, thrombophlebitis, transaminases increased, urticaria, ventricular tachycardia

3.4.7.4 Drug interaction:

- Bevacizumab: May enhance the cardiotoxic effect of anthracycline antineoplastic agents.
- Cimetidine: May increase the levels/effects of epirubicin.
- Trastuzumab: May enhance the cardiotoxic effect of anthracycline antineoplastic agents.

3.4.7.5 U.S. Boxed Warning

- Potential cardiotoxicity, particularly in patients who have received prior anthracyclines, prior or concomitant radiotherapy to the mediastinal/pericardial area, or who have pre-existing cardiac disease, may occur. Acute toxicity (primarily arrhythmias) and delayed toxicity (CHF) have been described. Delayed toxicity usually develops late in the course of therapy or within 2-3 months after completion, however, events with an onset of several months to years after termination of treatment have been described. The risk of delayed cardiotoxicity increases more steeply with cumulative doses >900 mg/m2, and this dose should be exceeded only with extreme caution. (The risk of CHF is ~0.9% at a cumulative dose of 550 mg/m2, ~1.6% at a cumulative dose of 700 mg/m2, and ~3.3% at a cumulative dose of 900 mg/m2.) Toxicity may be additive with other anthracyclines or anthracenediones, and may be increased in pediatric patients. Regular monitoring of LVEF and discontinuation at the first sign of impairment is recommended especially in patients with cardiac risk factors or impaired cardiac function.
- Myelosuppression (severe) may occur; neutropenia is the dose-limiting toxicity; severe thrombocytopenia or anemia may occur. Thrombophlebitis and thromboembolic phenomena (including pulmonary embolism) have occurred.
- Reduce dosage and use with caution in mild-to-moderate hepatic impairment or in severe renal dysfunction (serum creatinine >5 mg/dL). May cause tumor lysis syndrome or radiation recall.
- Treatment with anthracyclines may increase the risk of secondary leukemias.
- For IV administration only, severe local tissue necrosis will result if extravasation occurs.
- Women ≥70 years of age should be especially monitored for toxicity; women of childbearing age should be advised to avoid becoming pregnant.
- Should be administered under the supervision of an experienced cancer chemotherapy physician. Safety and efficacy in children have not been established.

3.4.8 Contraindication: Hypersensitivity to epirubicin or any component of the formulation, other anthracyclines, or anthracenediones; previous anthracycline treatment up to maximum cumulative dose; severe myocardial insufficiency, severe arrhythmias; recent myocardial infarction; severe hepatic dysfunction; baseline

3.5 Cyclophosphamide

3.5.1 Therapeutic Classification: Antineoplastic Agent, Alkylating Agent

3.5.2 Mechanism of Action: Mechanism of Action Cyclophosphamide is an alkylating agent that prevents cell division by cross-linking DNA strands and decreasing DNA synthesis. It is a cell cycle phase nonspecific agent. Cyclophosphamide also possesses potent immunosuppressive activity. Cyclophosphamide is a prodrug that must be metabolized to active metabolites in the liver.

3.5.3 Pharmaceutical Data:

- Injection: Vd: 0.48-0.71 L/kg; crosses placenta; crosses into CSF (not in high enough concentrations to treat meningeal leukemia)
- Protein binding: 10-60% Metabolism: Hepatic to active metabolites acrolein, 4-aldophosphamide, 4-hydroperoxycyclophosphamide, and nor-nitrogen mustard Bioavailability: >75%
- Elimination: 3-12 hours Time to peak, serum.
- Excretion: (<30% as unchanged drug, 85-90% as metabolites)

3.5.4 Solution Preparation: Stability and Storage Requirements:

- Room temperature stability: Store intact vials of powder at room temperature of 15°C to 30°C (59°F to

86°F).

- Refrigeration stability: Reconstituted solutions are stable for 24 hours at room temperature and 6 days under refrigeration 2°C to 8°C (36°F to 46°F). Further dilutions in D5W or NS are stable for 24 hours at room temperature (25°C) and 6 days at refrigeration.

3.5.5 Route of Administration: IV infusion only.

3.5.6 Usual Dosage Range:

3.5.6.1 Adults: Single agent:

- 400-1000 mg/m2 in divided doses over 4-5 days as intermittent therapy IV:
- Single doses: 400-1800 mg/m2 (30-50 mg/kg) per treatment course (1-5 days) which can be repeated at 2-4 week intervals Continuous daily doses: 60-120 mg/m2 (1-2.5 mg/kg) per day
- Autologous BMT: IVPB: 50 mg/kg/dose x 4 days or 60 mg/kg/dose for 2 days; total dose is usually divided over 2-4 days

3.5.6.2 Dosing in renal impairment:

- Some authors recommend no dose adjustment unless severe renal insufficiency (CrCl <20 mL/minute) CrCl >10 mL/minute: Administer 100% of normal dose CrCl <10 mL/minute: Administer 75% of normal dose
- Hemodialysis: Moderately dialyzable (20-50%); administer dose post hemodialysis CAPD effects: Unknown CAVH effects: Unknown Dosing adjustment in hepatic impairment: The pharmacokinetics of cyclophosphamide are not significantly altered in the presence of hepatic insufficiency. No dosage adjustments are recommended.

3.5.7 Drug Interaction

Substrate of CYP2A6 (minor), 2B6 (major), 2C9 (minor), 2C19 (minor), 3A4 (major); Inhibits CYP3A4 (weak); Induces CYP2B6 (weak), 2C8 (weak),
2C9 (weak)
Allopurinol may cause increase in bone marrow depression and may result in significant elevations of cyclophosphamide cytotoxic metabolites.
Anesthetic agents: Cyclophosphamide reduces serum pseudocholinesterase concentrations and may prolong the neuromuscular blocking activity of succinylcholine; use with caution with halothane, nitrous oxide, and succinylcholine.
Cardiac glycosides: Cyclophosphamide may decrease the absorption of digoxin tablets.
CYP2B6 inducers: May increase the levels/effects of acrolein (the active metabolite of cyclophosphamide). Example inducers include carbamazepine, nevirapine, phenobarbital, phenytoin, and rifampin.
CYP2B6 inhibitors: May decrease the levels/effects of acrolein (the active metabolite of cyclophosphamide). Example inhibitors include desipramine, paroxetine, and sertraline.
CYP3A4 inducers: CYP3A4 inducers may increase the levels/effects of acrolein (the active metabolite of cyclophosphamide). Example inducers include aminoglutethimide, carbamazepine, nafcillin, nevirapine, phenobarbital, phenytoin, and rifamycin.
CYP3A4 inhibitors: May decrease the levels/effects of acrolein (the active metabolite of cyclophosphamide). Example inhibitors include azole antifungals, ciprofloxacin, clarithromycin, diclofenac, doxycycline, erythromycin, imatinib, isoniazid, nefazodone, nicardipine, propofol, protease inhibitors, quinidine, and verapamil.
Etanercept: May enhance the adverse/toxic effects of cyclophosphamide.
Mivacurium: Cyclophosphamide may increase the levels/effects of mivacurium.
Phenytoin: May decrease the levels/effects of cyclophosphamide; may increase the levels/effects of 4-hydroxycyclophosphamide.
Succinylcholine: Cyclophosphamide may increase the levels/effects of succinylcholine.

3.5.8 Side Effects:

3.5.8.1 >10%

- Dermatologic: Alopecia (40-60%) but hair will usually regrow although it may be a different color and/or texture. Hair loss usually begins 3-6 weeks after the start of therapy.
- Endocrine & metabolic: Fertility: May cause sterility; interferes with oogenesis and spermatogenesis; may be irreversible in some patients; gonadal suppression (amenorrhea)
- Gastrointestinal: Nausea and vomiting (usually beginning 6-10 hours after administration); anorexia, diarrhea, mucositis, and stomatitis are also seen
- Genitourinary: Severe, potentially fatal, acute hemorrhagic cystitis or urinary fibrosis (7-40%)
- Hematologic: Thrombocytopenia and anemia are less common than leukopenia. Onset: 7 days. Nadir: 10-14 days. Recovery: 21 days

3.5.8.2 1% to 10%:

- Cardiovascular: Facial flushing
- Central nervous system: Headache
- Dermatologic: Skin rash
- Renal: SIADH may occur, usually with doses >50 mg/kg (or 1 g/m2); renal tubular necrosis, which usually resolves with discontinuation of the drug, is also reported
- Respiratory: Nasal congestion occurs when IV doses are administered too rapidly; patients experience runny eyes, rhinorrhea, sinus congestion, and sneezing during or immediately after the infusion.

3.5.8.3 <1% (Limited to important or life-threatening):
Post-marketing, and/or case reports: High-dose therapy may cause cardiac dysfunction manifested as CHF; cardiac necrosis or hemorrhagic myocarditis has occurred rarely, but may be fatal. Interstitial pneumonitis and pulmonary fibrosis are occasionally seen with high doses. Cyclophosphamide may also potentiate the cardiac toxicity of anthracyclines. Other adverse reactions include anaphylactic reactions, darkening of skin/fingernails, dizziness, hemorrhagic colitis, hemorrhagic ureteritis, hepatotoxicity, hyperuricemia, hypokalemia, jaundice, malaise, neutrophilic eccrine hidradenitis, radiation recall, renal tubular necrosis, secondary malignancy (eg, bladder carcinoma), SAIDH, Stevens-Johnson syndrome, toxic epidermal necrolysis, weakness.

3.5.8.4 Special Precautions:

- Cardiotoxicity: May cause cardiotoxicity (CHF, usually with higher doses).
- Fertility effects: May impair fertility; interferes with oogenesis and spermatogenesis. Hemorrhagic cystitis: May occur; increased hydration and frequent voiding is recommended.
- Immunosuppression: Monitor for infections; immunosuppression may occur.
- Secondary malignancies: With use secondary malignancies (usually delayed) have been reported.
- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment may be needed.
- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment may be needed.
- May potentiate the cardiotoxicity of anthracyclines.

3.6 Fluorouracil

3.6.1 Therapeutic Classification: Antineoplastic Agent, Antimetabolite (Pyrimidine Antagonist)

3.6.2 Mechanism of Action: Action A pyrimidine antimetabolite that interferes with DNA synthesis by blocking the methylation of deoxyuridylic acid; fluorouracil inhibits thymidylate synthetase (TS), or is incorporated into RNA. The reduced folate cofactor is required for tight binding to occur between the 5-FdUMP and TS.

3.6.3 Pharmaceutical Data:

- Injection: IV Irritant. Direct IV push injection (50 mg/mL solution needs no further dilution) or by IV infusion. Doses >1000 mg/m2 are usually administered as a
- 24-hour infusion. Giving the drug as a constant infusion may reduce toxicity. Bolus doses may be administered by slow IVP or IVPB.
- Distribution: Vd: ~22% of total body water; penetrates extracellular fluid, CSF, and third space fluids (eg, pleural effusions and ascitic fluid).
- Metabolism: Hepatic (90%); via a dehydrogenase enzyme; FU must be metabolized to be active
- Half-life elimination: Biphasic: Initial: 6-20 minutes; two metabolites, FdUMP and FUTP, have prolonged half-lives depending on the type of tissue
- Excretion: Lung (large amounts as CO2); urine (5% as unchanged drug) in 6 hours

3.6.4 Solution Preparation: Stability and Storage Requirements:

- Room temperature stability:
- Refrigeration stability:

3.6.5 Route of Administration: IV infusion only.

3.6.6 Usual Dosage Range:

3.6.6.1 Adults:
IV bolus: 500-600 mg/m2 every 3-4 weeks or 425 mg/m2 on days 1-5 every 4 weeks Continuous IV infusion: 1000 mg/m2/day for 4-5 days every 3-4 weeks or 2300-2600 mg/m2 on day 1 every week or 300-400 mg/m2/day or 225 mg/m2/day for 5-8 weeks (with radiation therapy)

3.6.6.2 Dosing in renal impairment:
Hemodialysis: Administer dose following hemodialysis. Dosage adjustment for hepatic impairment: Bilirubin >5 mg/dL: Omit use.

3.6.7 Side Effects:

3.6.7.1 Common

- Cardiovascular: Angina, myocardial ischemia, nail changes
- Central nervous system: Acute cerebellar syndrome, confusion, disorientation, euphoria, headache, nystagmus
- Dermatologic: Alopecia, dermatitis, dry skin, fissuring, palmar-plantar erythrodysesthesia syndrome, pruritic maculopapular rash, photosensitivity, vein pigmentations
- Gastrointestinal: Anorexia, bleeding, diarrhea, esophagopharyngitis, nausea, sloughing, stomatitis, ulceration, vomiting
- Hematologic: Agranulocytosis, anemia, leukopenia, pancytopenia, thrombocytopenia
- Myelosuppression: Onset: 7-10 days Nadir: 9-14 days Recovery: 21-28 days
- Local: Thrombophlebitis Ocular: Lacrimation, lacrimal duct stenosis, photophobia, visual changes Respiratory: Epistaxis Miscellaneous: Anaphylaxis, generalized allergic reactions, nail loss.

3.6.7.2 Special Precautions:

- Hand-foot syndrome: Palmar-plantar erythrodysesthesia (hand-foot) syndrome has been associated with use.
- Toxicity: Discontinue if intractable vomiting, diarrhea, precipitous fall in leukocyte or platelet counts, myocardial ischemia, hemorrhage, or stomatitis occur.
- Dihydropyrimidine dehydrogenase deficiency (DPD): Administration to patients with genetic DPD has been associated with increased toxicity following administration (diarrhea, neutropenia, and neurotoxicity). Systemic toxicity normally associated with parenteral administration has also been associated with topical use, particularly in patients with DPD; discontinue if symptoms of DPD occur.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.
- Alkylating agents: Use with caution in patients who have had previous use of alkylating agents.

4.0 PATIENT ELIGIBILITY

4.1 Inclusion Criteria

4.1.1 Histological confirmation of breast carcinoma. Pathologic evidence of dermal lymphatic invasion should be noted but not required.

4.1.2 Clinical diagnosis of IBC (presence of inflammatory changes in the involved breast, including diffuse erythema, heat, ridging, and peau d'orange).

4.1.3 ≥ Age 18

4.1.4 ECOG performance status ≤ 1

4.1.5 Adequate hematologic function

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
- Platelet count ≥ 100 x 10^9/L
- Hemoglobin ≥ 9.0 g/dL

4.1.6 Adequate cardiac function (LVEF ≥ 45%)

4.1.7 Adequate Renal function

- Creatinine (Cr) ≤ 1.5 mg/dL x ULN
- Creatinine clearance (CrCl) ≥ 50 mL/min calculated by the Cockroft-Gault method as follows: Male creatinine clearance = (140 - age) x (weight in Kg) / (serum Cr x 72) Female CrCl = (140 - age) x (weight in Kg) x 0.85 / (serum Cr x 72)

4.1.8 Adequate Hepatic function

- Aspartate aminotransferase (AST) ≤ 2.5 x ULN
- Alanine aminotransferase (ALT) ≤ 2.5 x ULN
- Alkaline phosphatase (Alp) ≤ 2.5 x ULN
- Total bilirubin ≤ 1.5 x ULN

4.1.9 Ability and willingness to sign an informed consent form for this protocol

4.1.10 If female of childbearing potential (women who are post-menopausal < 1 year, not surgically sterilized, or not abstinent), urine pregnancy test is negative, and agrees to be consistent and correct use of one of the following acceptable methods of birth control: male partner who is sterile prior to the female subject's entry into the study and is the sole sexual partner for that female subject; any intrauterine device (IUD) with a documented failure rate of less than 1% per year; oral contraception, or barrier methods, including diaphragm or condom with a spermicide.

4.1.11 Patients who have metastatic disease, if the metastatic sites are amendable for local therapy (i.e. radiation and/or surgery), and are candidates for breast surgery will be eligible.

4.2 Exclusion Criteria

4.2.1 History of radiation or chemotherapy
4.2.2 HER2-positive breast carcinoma (IHC staining more than 3+ or HER2 gene amplification by FISH)
4.2.3 Recurrent breast cancer
4.2.4 History of other malignancies (except for cured non-melanomatous skin cancer or cured cervical carcinoma in situ, or malignancies with no evidence of disease and no treatment for >5 years)
4.2.5 Known positive test(s) for human immunodeficiency virus infection, hepatitis C virus, acute or chronic active hepatitis B infection
4.2.6 History of extensive interstitial lung disease e.g. pneumonitis or pulmonary fibrosis or any evidence of extensive interstitial lung disease on baseline chest CT scan
4.2.7 Patient with other significant medical or psychiatric condition that would make assessment of toxicity or efficacy difficult.
4.2.8 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
4.2.9 Peripheral neuropathy ≥ Gr II

5.0 TREATMENT PLAN

5.1 ***General:*** All patients shall be registered in CORe.
5.2 ***Information*** on histological diagnosis of malignancy, nuclear grade, estrogen and progesterone receptor, HER, flow cytometry will be collected if available
5.3 Preoperative systemic chemotherapy PNC.
5.3.1 All chemotherapy will be given based on actual body weight-derived body surface area (BSA). No dose adjustment should be made based on weight gain due to fluid retention.

5.3.2 First week of treatment will be only panitumumab. Panitumumab 2.5 mg/kg IV over 60 min by pump. Please see section 2.10 for rationale. An optional core Biopsy of the breast will be done (1 week) after this first dose but before 2nd dose.

5.3.3 Starting week 2 (day 1 of cycle 1), patients will receive 4 cycles of weekly combination of panitumumab, carboplatin, and nab-paclitaxel on a 3-week on and 1-week off schedule. During Cycle 4, patients will receive 2 weekly doses of panitumumab and 3 weekly carboplatin and nab-paclitaxel. Assuming bone marrow recovery (absolute granulocyte count >/= 1,000 and platelets >/= 100,000 per mm^3 before each dosing) Panitumumab—2.5 mg/kg IV over 30 min (If no reaction to the 1st dose), Abraxane—100 mg/m2 IV over 30 min, Carboplatin—AUC 2 IV over 30 min *Table 1. If the dose of panitumumab dose is higher than 1000 mg, it will be infused over 90 min.*

Dosage of PNC (Table 1)

	Premedications;* Precautions	***Dose***	***Route***	***Schedule***
Panitumumab	*Not required for routine infusions*	*2.5 mg/kg*	*If no reaction to the first dose of Panitumumab, 30 min for subsequent dose*	*Wk 1; C1-3 wklyX3, 1 wk off; C4 wklyX2*
Nab-paclitaxel	*Not required for routine infusions*	*100 mg/m2*	*IV over 30 min after completion of Agent Panitumumab through separate IV line*	*C1-4 wklyX3, 1 wk off*
Carboplatin	*Not required for routine infusions*	*2 AUC[a]*	*IV over 30 min after completion of Abraxane through separate IV line*	*C1-4 wklyX3, 1 wk off*

* Only for hypersensitivity, anti-emetic should be given accordinglya. Total Dose (mg) = (target AUC) X (GFR+25)
The GFR used in the Calvert formula to calculate AUC-based dosing should not exceed 125mL/min
Maximum CARBOplatin AUC 2 should not exceed 300mg

Dose-De-escalation Schedule (Table 2a)
If toxicities are deemed to be related to Panitumumab, dose of Panitumumab will be reduced.

Dose Level	Panitumumab (mg/kg)
Starting dose	2.5
Level -1	2.0
Level -2	1.5
	DC Panitumumab*
* If Panitumumab is discontinued due to panitumumab-related toxicities, patient may continue on Nab-paclitaxel and Carboplatin.	

Dose-De-escalation Schedule (Table 2b) If toxicities are deemed to be related to chemotherapy (Nab-paclitaxel and/or Carboplatin), chemotherapy dose will be reduced.

Dose Level	**Dose***	
Starting dose	***Nab-paclitaxel (Abraxane) 100 mg/m2***	***Carboplatin AUC 2***
Level -1	80	1.6
Level -2	60	1.2
	Off study*	Off study*
* If Nab-paclitaxel and/or Carboplatin continue to cause chemotherapy related toxicities at dose level -2 , patient will be off study.		

5.3.4 Panitumumab Dosage, Administration and Schedule: The starting panitumumab dose is 2.5 mg/kg. The total dose may be rounded up or down by no greater than 10 mg. The panitumumab dose will be calculated based on the subject's actual body weight at baseline and will not be re-calculated unless the actual body weight changes by at least 10%. Panitumumab will be diluted in a minimum of 100 mL of pyrogen-free 0.9% sodium chloride solution USP/PhEur (normal saline solution, supplied by the site). The maximum concentration of the diluted solution to be infused should not exceed 10 mg/mL. The volume of normal saline should be increased as needed to ensure the maximum concentration of the diluted solution does not exceed 10 mg/mL. Panitumumab will be administered IV by an infusion pump through a peripheral line or indwelling catheter using a 0.2 or 0.22-micron in-line filter infusion set-up over 1 hour ± 15 minutes by a trained healthcare professional. If the first infusion is well tolerated (i.e. without any serious infusion-related reactions) all subsequent infusions may be administered over 30 ± 10 minutes. In the event a subject's actual weight requires greater than 150 mL volume infusion, panitumumab will be administered over 90 minutes ± 15 minutes, as tolerated. If the filter extension set is not compatible with the infusion set-up at the study center, Amgen should be contacted immediately. Strict adherence to aseptic technique should be used during panitumumab preparation and administration. The bag should be labeled per site pharmacy Standard Operating Procedures and promptly forwarded to the clinical research center for infusion. The effects of overdose of panitumumab are not known. See Section 3.0 Pharmacy Guide for information on panitumumab packing and formulation, labeling, storage, preparation, supply/return, and accountability.

5.3.5 Pre-medication for Panitumumab: Panitumumab specific pre-medication is not required for routine panitumumab infusions. If, during or after any infusion, a reaction occurs, pre-medication may be used for subsequent panitumumab infusions according to institutional guideline or investigator's discretion as listed in the standard Panitumumab order set.

5.3.6 Interruption of Panitumumab Infusion: Subjects who experience any serious infusion reaction during panitumumab administration will have the infusion stopped. Continuation of dosing will be based on the severity and resolution of the event and will be at the discretion of the investigator. Suspected infusion reactions should be reported as an adverse event. All subjects who experience such an event will be

followed for safety.

5.3.7 Toxicity Assessment: Toxicities will be recorded as AEs on the Adverse Event case report form and must be graded using The National Cancer Institute's Common Toxicity Criteria (NCI-CTC) version 3.0 (Appendix A), with the exception of skin- or nail-related toxicities, which must be graded using NCI-CTC version 3.0 with modifications (see Appendix I).

5.3.8 Panitumumab Dosage Adjustments: For subjects who experience panitumumab-related Gr III and IV toxicities (no hematologic toxicities) while on study, one or more doses of panitumumab may need to be withheld, delayed, or reduced. If Panitumumab is withheld, or delayed for up to two cycles, on resolution of toxicity, two attempts to reduce panitumumab doses will be allowed (Table 2). If Panitumumab is withheld for more than 2 cycles or after 2nd dose reduction and patients remain to have panitumumab-related Gr III and IV non-hematological toxicities, panitumumab will be discontinued. Patient may continue Nab-paclitaxel and carboplatin as clinically indicated.

Panitumumab Dose Reductions (Table 3)

	Starting Dose	1st Dose Reduction	2nd Dose Reduction
Percentage (%)	100	80	60
mg/kg	2.5	2.0	1.5

5.3.9 Criteria for Withholding a Dose of Panitumumab

5.3.9.1 Skin- or nail-related toxicities:

- Symptomatic skin- or nail-related toxicity requiring narcotics, systemic steroids, or felt to be intolerable by the subject.
- Skin or nail infection requiring IV antibiotic or IV antifungal treatment.
- Need for surgical debridement.
- Any skin- or nail-related serious adverse event

5.3.9.2 Non-skin- or nail-related toxicities: Any Gr III or IV toxicity with the following exceptions:

- Panitumumab will only be withheld for symptomatic hypomagnesemia and/or hypocalcemia that persists despite aggressive magnesium and/or calcium replacement
- Panitumumab will only be withheld for Gr III or IV nausea, diarrhea, or vomiting that persists despite maximum supportive care (see Section 5.4.1 for diarrhea management guidelines)
- Panitumumab will only be withheld for Gr ≥ III anemia or Gr IV thrombocytopenia that cannot be managed by transfusion(s) or cytokine therapy

5.3.10 Criteria for re-treatment with panitumumab:

5.3.10.1 Skin- or nail-related toxicities: Panitumumab administration may recommence once: The adverse event has improved to ≤ Grade 2 or returned to baseline, or; The subject has recovered to the point where symptomatic skin- or nail-related toxicity is felt to be tolerable; or, Systemic steroids are no longer required, or IV antibiotic or IV antifungal treatment is no longer required

5.3.10.2 Non-skin- or nail-related toxicities: Panitumumab administration may recommence once the adverse event has improved to ≤ Grade 1 or returned to baseline.

5.3.11 Infusion-related reaction: Reduce infusion rate by 50% in patients experiencing a mild or moderate (grade 1 or 2) infusion reaction for the duration of that infusion. Immediately and permanently discontinue Vectibix infusion in patients experiencing severe (grade 3 or 4) infusion reactions.

5.3.12 Dose Modification Schedule: Subjects should be assessed for toxicity before each dose. Dose modification should be performed according to the schedule described below and outlined in Figure 1. Subjects who develop a toxicity that does not meet the criteria for withholding a dose of panitumumab (Section 5.3.9) should continue to receive panitumumab and their symptoms should be treated. Re-treatment with panitumumab will be allowed if panitumumab-related toxicity should return to</=1 or complete resolution.

5.3.13 For subjects who experience a toxicity that meets the criteria for withholding a dose of panitumumab:

5.3.13.1 Subjects receiving either 100% of the starting dose of panitumumab are allowed to have up to 2 subsequent doses withheld for toxicity. However a second dose should only be withheld if the toxicity has not resolved by the time that the subsequent dose is due.

5.3.13.2 Subjects treated at the 100% dose level whose toxicity resolves after 1 dose of panitumumab is withheld should be re-started at the 100% dose level (recommended but not required, reduction to the 80% dose is allowed as an alternative to re-challenge with the 100% dose).

5.3.13.3 If toxicity recurs, subjects treated at the 100% dose or 80% dose should be re-started at the 80% dose or 60% dose, respectively, when the toxicity resolves after withholding 1 or 2 doses of panitumumab.

5.3.13.4 Subjects treated at the 100% dose level whose toxicity resolves only after 2 subsequent doses of panitumumab are withheld should be re-started at the 80% dose level.

5.3.13.5 Subjects treated at the 80% dose level whose toxicity resolves after withholding 1 or 2 doses of panitumumab should be re-started at the 60% dose level.

5.3.13.6 Subjects who experience toxicity at the 60% dose level will not be re-treated with panitumumab.

5.3.13.7 It is recommended that panitumumab doses will be escalated in subjects whose toxicity resolves to the degree that meets the criteria for re-starting a dose of panitumumab (Section 5.3.9). Dose escalations are recommended but not required. Dose escalations should occur in the following manner:

5.3.13.8 Subjects treated at the 80% dose level whose toxicity does not recur should receive the 100% dose level at the next dose unless a previous attempt to re-escalate to the 100% dose level was not tolerated (re-initiation of the 80% dose is allowed as an alternative to dose escalation).

5.3.13.9 Subjects treated at the 60% dose level whose toxicity does not recur should receive the 80% dose at the next dose unless a previous attempt to re-escalate to the 80% dose level was not tolerated (re-initiation of the 60% dose is allowed as an alternative to dose escalation).

5.3.13.10 Subjects who miss more than 5 consecutive (6 weeks) scheduled doses due to toxicity or are unable to receive a dose of panitumumab within 6 weeks of having received their previous dose of panitumumab due to toxicity will be considered unable to tolerate panitumumab and will not be retreated with panitumumab.

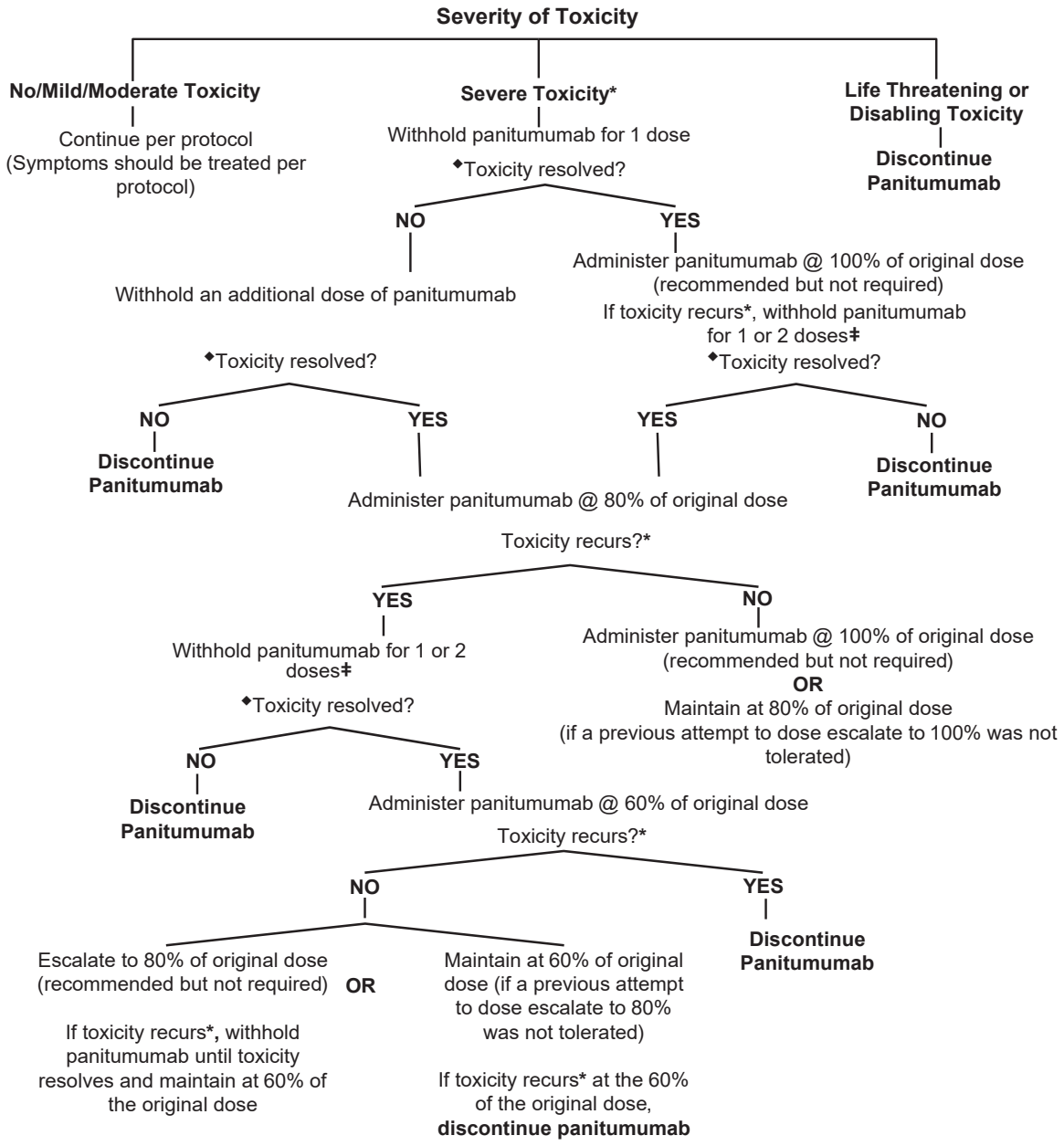
5.3.13.11 If a subject demonstrates a clinical benefit with a documented response of stable disease, partial response or complete response and there are reasons that the dose modification rules above cannot be implemented, the investigator should contact and discuss these reasons with Amgen. The investigator must obtain written agreement from Amgen before any changes in the dose modification rules can be implemented, Sponsor Approval (ORERM) will also be obtained.

5.3.13.12 Panitumumab Delayed- or Missed-Doses

5.3.13.12.1 Panitumumab should be given on the first day of each treatment period. Delays of panitumumab administration beyond 3 weeks from the previous dose of panitumumab are not allowed.

5.3.13.12.2 Reasons to withhold a dose of panitumumab are described in Section 5.3.9. More than 5 total missed doses are not allowed. Missed panitumumab doses will not be made up.

Figure 1. Panitumumab Dose Modification Algorithm for Toxicity



* Assess toxicity before each cycle. Toxicity recurs = meets the criteria for withholding a dose of panitumumab at any time during the study (See Section 4.1.6).

◆ Assess toxicity before each cycle. Toxicity resolved = meets the criteria for restarting panitumumab (see section 4.1.7). Subjects from whom > 2 subsequent cycles of panitumumab are required to be withheld should not be re-treated with panitumumab.

ą Up to 2 subsequent doses of panitumumab may be withheld but panitumumab may not be withheld longer than 6 weeks from the previous dose. The second dose should only be withheld if the toxicity has not resolved by the time that the subsequent cycle of chemotherapy is due.

5.3.14 Discontinuation of Panitumumab**:** Panitumumab will be continued as scheduled (week 1 to week 12). Subjects will be taken off study if they are unable to tolerate panitumumab, disease progression, death, or study withdrawal by the subject, investigator, or sponsor.

5.3.15 Nab-paclitaxel and Carboplatin will be continued as scheduled if clinically indicated. The dose adjustment is based on the following.

5.4 Nab-paclitaxel and Carboplatin Dose Adjustments:

5.4.1 Every effort will be made to administer the full dose regimen. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using the NCI-

CTC in **Appendix A**. If toxicity occurs, the appropriate treatment will be used to ameliorate signs and symptoms including antiemetics for nausea and vomiting, antidiarrheals for diarrhea, and antipyretics and antihistamines for drug fever, before toxicity grade is determined.

5.4.2 Dose adjustments for toxicity should be made according to guidelines, which follow.

5.4.2.1 Doses, which have been reduced for toxicity, must not be re-escalated back to starting level.

5.4.2.2 Treatment may be delayed no more than 3 weeks to allow recovery from acute toxicity, and no more than 4 weeks to allow recovery from chronic toxicity (except for alopecia, skin changes and anemia).

5.4.2.3 If toxicities are related to Nab-Paclitaxel and Carboplatin, a maximum of two dose reductions will be allowed per patient. If NC is discontinued due to toxicity before 6th cycles can be administered, the patient will be removed from the study. The investigator should attempt to obtain follow-up information on such patients.

5.4.2.4 Depending upon the toxicity, dose reduction may occur for only one drug or for both drugs [Nab-paclitaxel or Carboplatin] together. If the investigator is unsure of the cause, both drugs should be reduced. One dose reduction will consist of decreasing the dose to the next lower dose level in which the dose of the specified drug(s) actually is (are) reduced (see Table 2). If the toxicity indicates that only one drug should be reduced, the other drug should remain at the original dose level. If potentially dangerous toxicities are observed, the investigator and sponsor will discuss the need for dose reductions.

5.4.3 Myelosuppression

5.4.3.1 In the event of severe myelosuppression (platelet count < 25,000 for any length of time) the dose of Nab-paclitaxel and Carboplatin will be reduced by 1 level for both drugs.

5.4.3.2 Grade I-III myelosuppression (anemia, neutropenia, thrombocytopenia) and Gr IV neutropenia except as defined above, with recovery within 7 days, does not require dose modification.

5.4.3.3 Patients with Gr III-IV neutropenia associated with fever (one reading of oral temperature >38.5 C, or 3 readings of oral temperature > 38.0 C in a 24-hour period) or documented infection requiring hospitalization and/or oral or intravenous antibiotics will be retreated after recovery at the same dose of PNC (in order to maximize dose density/intensity); including prophylactic G–CSF during subsequent cycles. However, levofloxacin 500 mg PO qd x 7 days starting on day 5 will be added. In addition, patients may have 1 level dose reduction if they experience severe neutropenic complications requiring prolonged hospitalization and/or ICU care. If Gr IV neutropenia of > 7 days duration, or Gr III-IV neutropenia associated with fever (as defined above) or infection occur again despite the use of G–CSF and levofloxacin, the patient should be retreated at 1 lower dose level for both drug in all subsequent cycles. Therapy with G-CSF will be allowed if clinically indicated in the management of complicated symptomatic neutropenia.

5.4.4 Neurotoxicity: If Gr IV, the patient will not receive additional nab-paclitaxel and will be off study. If Gr III, patient should be retreated upon recovery (not to exceed 4 weeks) to a < Gr I toxicity with a dose reduction of 1 dose level of Nab-paclitaxel.

5.5 Preoperative Chemotherapy FEC

5.5.1 Standard of care FEC chemotherapy will be administered after completion of 13 weeks of PNC regimen. Dose modification of the FEC is based on standard of care.

5.5.2 Then, it will consist of 4 cycles of FEC (5-FU, epirubicin, cyclophosphamide), to be repeated at three-week intervals, assuming bone marrow recovery (absolute granulocyte count **>/=** 1,000 and platelets **>/=** 100,000 per mm3 before the next cycle is begun).

5.5.3 Dose modification of FEC chemotherapy will be based on standard of care practice.

Dosage of FEC (Table 4)

	Premedications; Precautions	***Dose***	***Route***	***Schedule***
Fluorouracil	*Use institutional guideline*	*500 mg/m2*	*IV*	*Every 3 weeks*
Epirubicin	*Use institutional guideline*	*100 mg/m2*	*IV over 30 min*	*Every 3 weeks*
Cyclophosphamide	*Use institutional guideline*	*500 mg/m2*	*IV*	*Every 3 weeks*

5.6 ***Definition of Toxicity:*** Toxicities will be graded according to the National Cancer Institute's NCI-CTC v3.0 (http://ctep.cancer.gov/forms/CTCAEv3.pdf)

5.7 ***Duration of Therapy:*** In the absence of treatment delays due to AEs, treatment continues until one of the following criteria applies or completion of scheduled PNC and FEC:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unexpected serious adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.8 Other Agent(s), Other Modality(ies) and/or Procedures

5.8.1 Surgery will be based on standard of the care at the time of patient treatment.

5.8.2 Patients with tumors expressing the estrogen or progesterone receptor will be given hormonal therapy after the completion of surgery and radiation therapy. Hormonal therapy drug choice and duration will be based on standard of the care at the time of patient treatment.

5.8.3 Adjuvant radiation therapy will be started after the completion surgery based on current standards and is not part of the protocol therapy.

5.8.4 Adjuvant chemotherapy is at the discretion of the investigator if clinically indicated.

6.0 PRETREATMENT EVALUATION

6.1 Complete history and physical examination including breast examination, vital signs, height, weight, demographics, and adverse events.

6.2 Documentation of Performance status [PS] (See Appendix D), menopausal status, date of last menstrual period, duration of mass or symptoms.

6.3 Careful clinical measurement of the breast and description of the breast finding of the involved area. Location and size of tumor, axillary and supraclavicular node status, clinical TNM stage. Measurements should be bi-dimensional and expressed in cm.

6.4 Digital Photography of both breasts

6.5 Complete blood count (CBC), differential count, and platelet count;

6.6 Comprehensive metabolic profiles-SMA (Na, K, Cl, HCO3, BUN, creatinine, Mg, calcium, SGOT [AST], SGPT [ALT], glucose, LDH, total billirubin)

6.7 ECG, Cardiac ejection fraction [EF] (by echocardiography or MUGA)

6.8 Urine pregnancy test if female patient is of childbearing potential.

6.9 Tumor staging (Imaging Studies)

6.9.1 Chest x-ray

6.9.2 PET/CT or Chest and Abdominal CT scan (as clinically indicated).

6.9.3 Bone scan

6.9.4 Bilateral mammography

6.9.5 Breast MRI for involved breast

6.9.6 Breast sonography with axillary assessment

6.9.7 Breast Core biopsy for frozen section and paraffin block. This is mandatory for baseline evaluation. However, if a patient is consented for both 2006-1072 (IBC registry) and 2008-0372, core needle biopsy will be performed in one setting and tissues will be collected separately for both studies. If core biopsy is already performed for protocol 2006-1072, and patient is subsequently consented for 2008-0372, we will follow the procedures below:

- If optimal samples from the core biopsy were collected for 2006-1072, a portion of the samples will be used for biomarker testing as described in protocol 2008-0372. Core biopsy will not be repeated for the purpose of protocol 2008-0372.
- If optimal samples are not available from protocol 2006-1072, patient will be subject to repeat core biopsy.

6.10 Data management: The data from diagnostic tests, physical exam, vital signs, weight, concomitant medication, history of biopsy, radiation at screening/baseline will be documented as standard of care, but not for protocol purpose, so these data will not be entered into PDMS/CORe for this study.

7.0 **EVALUATION DURING STUDY** (See Section 11.0) The window for all assessments and therapies can be within +/- 3 days.

7.1 Evaluation during PNC treatment (Cycles 1 to 4):

7.1.1 Within 2 days before day 1 of cycle 1, an optional core biopsy will be performed for frozen sections and paraffin block.

7.1.2 Patients will have CBC, differential and platelet counts before each dosing.
Patients may repeat CBC, differential and platelet counts until recovery of these measures before next cycle (absolute granulocyte counts >/= 1,000 and platelets >/= 100,000 per mm^3).

7.1.3 Medical history and physical examination with vital signs, weight, PS before each cycle ,

7.1.4 Digital photography at weeks before cycles 1, 3,

7.1.5 Toxicities will be assessed before each cycle

7.1.6 SMA (Na, K, Cl, HCO3, BUN, creatinine, Mg, calcium, SGOT [AST], SGPT [ALT], glucose, LDH, total bilirubin,) will be performed before each cycle ,

7.1.7 ECG and ECHO or MUGA will be repeated when clinically indicated.

7.2 Evaluation during preoperative chemotherapy (FEC):

7.2.1 Prior to FEC, minimum 1 week after cycle 4 of PNC:

7.2.1.1 Mammography of involved breast

7.2.1.2 Breast MRI if clinically indicated

7.2.1.3 Ultrasound of the involved breast/regional lymphatic chains

7.2.1.4 SMA (as above), CBC,

7.2.1.5 Digital photography of the breast

7.2.1.6 Careful clinical breast measurement (if measurable, ruler should be measure the size of the tumor) of the breast and description of the breast finding of the involved area.

7.2.1.7 Medical history and physical examination, with vital signs, weight, PS performance

7.2.1.8 Toxicity Evaluation

7.2.2 ***During EFC***

7.2.2.1 Assessments during EFC are standard of care, including physical examination, vital signs, weight, PS, CBC with diff, platelet counts, SMA and toxicity prior to each cycle.

7.2.2.2 Careful clinical breast measurement (if measurable, ruler should be measure the size of the tumor) of the breast and description of the breast finding of the involved area before each cycle.

7.2.2.3 ECG, ECHO/MUGA will be repeated as clinically indicated.

7.3 Evaluation before surgery

After 4th cycles of FEC [minimum of 3 week after 4th cycle of FEC and prior to surgery]

7.3.1 Mammography of involved breast

7.3.2 Breast MRI if clinically indicated.

7.3.3 Ultrasound of the involved breast/regional lymphatic chains

7.3.4 SMA(as above),CBC,

7.3.5 Digital photography of the breast

7.3.6 Careful clinical measurement (if measurable, ruler should be measure the size of the tumor) of the breast and description of the breast finding of the involved area.

7.3.7 Medical history and physical examination, with vital signs, weight, PS performance

7.3.8 PET/CT or Chest and Abdominal CT scan before surgery (as clinically indicated).

7.3.9 Toxicity evaluation

7.3.10 ECG, ECHO/MUGA will be repeated as clinically indicated.

7.4 Evaluation during surgery.

7.4.1 Breast pathologist will be notified before the surgery and they will handle resected specimen. Every attempt will be made to identify any residual tumor. If tumor is not identified grossly the area previously identified by mammogram will be extensively sampled.

7.5 Post-Surgery Follow-up:

Post-surgery follow-up and evaluation will be a part of standard of care, only survival data will be recorded for study purpose.

7.6 Data management

The data from diagnostic tests, physical exam, vital signs, weight, concomitant medication, biopsy during study, before FEC and before surgery, will be documented as standard of care, but not for protocol purpose, so these data will not be entered into PDMS/CORe. Only the chemotherapy, toxicity and treatment response will be entered into PDMS/CORe for this study.

8.0 CRITERIA FOR RESPONSE

8.1 All tumor measurements (clinical breast exam) must be recorded in centimeters and must have the longest diameter, and its perpendicular applied at the widest portion of the tumor, as well as the depth recorded, if clinically possible. Clinical breast exam will be performed before weeks 2, 5, 8 and 11, of PNC, and before each cycle of FEC. Response Criteria:

8.1.1 Complete Response [CR]

8.1.1.1 CLINICAL CR: Disappearance of all clinical evidence of active tumor by clinical evaluation, mammogram and ultrasound. The patient must be free of all symptoms.

8.1.1.2 PATHOLOGICAL CR: No evidence of residual invasive tumor, including no residual tumor in the axillary lymph nodes.

8.1.2 **Partial Response[PR]:** 50% or greater decrease for a minimum of 4 weeks in the measurable lesion as determined by the product of the perpendicular diameters of the lesion. Every lesion need not regress to qualify as a partial response. However, if any lesion progresses or if new lesions appear, the response cannot be classified as a partial response.

8.1.3 **Minor Response [MR]:** Decreases in tumor masses insufficient to qualify as a partial remission, i.e. <50%.

8.1.4 **Stable Disease [SD]**: Between MR and PD

8.1.5 **Progressive Disease [PD]**: Increase in the size by 25% of any measured lesion. Appearance of new lesions will also constitute increasing disease. Mixed responses will be considered PD.

8.2 The following patient categories will be considered inevaluable for response:

8.2.1 Early Deaths: Those patients who die within the 1st two weeks from the initiation of drug therapy due to intercurrent disease, but will be considered as failures in the intent to treat analysis.

8.2.2 Lost to Follow-up: Those patients in whom there is inadequate information to judge tumor response because of loss of contact with our institution (>2 months after missed appointment) and with referring physician in spite of repeated attempts to try to locate them. These patients will be considered failure in the intent to treat analysis.

8.2.3 Major Protocol Violation: Patients in whom there is a significant deviation from the treatment program by either adding or deleting another agent or another therapeutic maneuver or by modifying substantially the dosage and schedule of the drug under evaluation. Patients who do not fulfill the requirements outlined under Patient Eligibility (item 4.0) are also included in this category.

8.2.4 Downstaging is defined as change in tumor extent that results in reclassification of the primary tumor and/or regional lymph node metastases into a different (lower) T, N, or M subgroup.

8.3 All subjective toxicities encountered during the study will be evaluated according to the NCI-CTC grading system (0-4) in Appendix A. Objective toxicities will be considered as the maximum numerical deviation from the normal range.

8.4 The survival of patients will be measured from the date of registration. Disease-free survival will be measured from the date of surgery.

8.5 Patients will be followed minimally for 1 year after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable AEs will be followed until resolution or stabilization of the adverse event.

9.0 CRITERIA FOR REMOVAL FROM THE STUDY

9.1 Any patient showing distant metastatic disease or progressive disease will be removed from the study.

9.2 The development of unacceptable toxicity (irreversible Gr III or IV)

9.3 Death.

9.4 Patients' refusal to continue participation in the study.

10.0 **CORRELATIVE STUDIES**

10.1.1 EGFR FISH

10.1.1.1 Collection of Specimen(s): Breast Core Biopsy
10.1.1.2 Handling of Specimens(s): Savitri Krishnamurthy, MD
10.1.1.3 Shipping of Specimen(s): 1515 Holcombe Blvd. Unit 448, Houston, TX
10.1.1.4 Site(s) Performing Correlative Study: M. D. Anderson Cancer Center

10.1.2 EGFR Immunohistochemical staining

10.1.2.1 Collection of Specimen(s): Breast Core Biopsy
10.1.2.2 Handling of Specimens(s): Savitri Krishnamurthy, MD
10.1.2.3 Shipping of Specimen(s); 1515 Holcombe Blvd. Unit 448, Houston, TX
10.1.2.4 Site(s) Performing Correlative Study: M. D. Anderson Cancer Center

10.1.3 Multiplex immunohistochemical staining

10.1.3.1 Collection of Specimen(s): Breast Core Biopsy
10.1.3.2 Handling of Specimens(s): Naoto T. Ueno, MD, PhD
10.1.3.3 Shipping of Specimen(s): 1515 Holcombe Blvd. Unit 448, Houston, TX
10.1.3.4 Site(s) Performing Correlative Study: M. D. Anderson Cancer Center

10.1.4 Compare Normal Cell Interactions and EGFR signaling in the normal tissue adjacent to breast tumor.

10.1.4.1. Normal tissue will be requested from the patient paraffin embedded mastectomy samples, and unstained slides will be prepared.
10.1.4.2. Dr. Wendy Woodward's lab will perform the analysis.

*** Please refer to Section 2.10 for more details on the biomarker testing**

11.0 STUDY CALENDAR

Baseline evaluations are to be conducted within **4** weeks prior to start of protocol therapy. Core biopsy tissue can be collected any time before therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

During PNC

			Cycle 1				Cycle 2				Cycle 3				Cycle 4				
	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16	Wk 17	**Before FEC**
Panitumumab		X	X	X	X		X	X	X		X	X	X		X	X			
Carboplatin, nab-paclitaxel			X	X	X		X	X	X		X	X	X		X	X	X		
Informed consent	X																		
Demographics	X																		
History	X [g]		X				X				X				X				
Physical exam, vital signs, height, weight,	X		X				X				X				X				X
AEs	X		X				X				X				X				X
Clinical breast exam, lymph nodes status	X		X				X				X				X				X
Digital Photography of bilateral breasts	X		X								X								X
PS	X		X				X				X				X				X
CBC w/diff, Plt[b],	X		X	X	X		X	X	X		X	X	X		X	X	X		X
SMA (Serum chemistry) [a]	X		X				X				X				X				X
ECG, ECHO or MUGA [c]	X																		
Urine pregnancy test	X																		
Imaging Studies	X[d]																		X[e]
Breast Core Bx[h]	X		X[f]																

a: Na, K, Cl, HCO3, BUN, creatinine, Mg, calcium, SGOT [AST], SGPT [ALT], glucose, LDH, total bilirubin, .
b: Before each cycle, may repeat until recovery (ANC>/=1.0, Platelets >/=100,000 per mm^3
c. EKG, ECHO/MUGA will be repeated as clinically indicated
d. CXR, bone scan, Bilateral mammography, Breast MRI, Breast US with axillary, PET/CT or Chest and Abdominal CT scan (as clinically indicated).
e. Mammography of involved breast, breast MRI, US of involved breast with regional lymphatic chains,
f. Optional. 1-2 passes will be obtained.
g. including menopausal status, date of last menstruation, Duration of mass or symptoms at baseline only
h. At baseline, if a patient is consented for both 2006-1072 (IBC registry) and 2008-0372, core needle biopsy will be performed in one setting and tissues will be collected separately for both studies. If core biopsy is already performed for protocol 2006-1072, and patient is subsequently consented for 2008-0372, we will follow the procedures below:

- If optimal samples from the core biopsy were collected for 2006-1072, a portion of the samples will be used for biomarker testing as described in protocol 2008-0372. Core biopsy will not be repeated.
- If optimal samples are not available from protocol 2006-1072, patient will be subject to repeat core biopsy.

During and after FEC

	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Before surgery
FEC	X			X			X			X			
Physical exam, Vital signs, weight,				X			X			X			X
PS				X			X			X			X
CBC w/diff, plts				X			X			X			X
SMA (as above)				X			X			X			X
EKG, ECHO, MUGA (as indicated)													
Digital photography of bilateral breasts													X
Clinical breast exam,				x			X			X			X
Imaging Study													X*
AEs				X			X			X			X
Surgical sample collection													X during surgery

* Mammography, breast MRI, and Ultrasound of the involved breast/regional lymphatic chains. PET/CT or Chest and Abdominal CT scan (as clinically indicated) can be any time after last dose of FEC and before surgery.

12.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS. The ongoing review of safety data will include review of clinical AEs and SAEs including skin-related and neurological toxicity assessment and laboratory studies. The NCI-CTC version 3.0 will be used to grade all AEs, except panitumumab-related skin toxicity, which will be graded by modified NCI-CTC version 3.0 Dermatology Skin Assessment. **Appendix I**. An AE is an undesirable medical occurrence (sign, symptom, or diagnosis) or worsening of a pre-existing medical condition (diabetes, congestive heart failure, rheumatoid arthritis) that occurs after initiation of investigational product whether or not considered to be investigational product related. A worsening of an existing medical condition is one that was present at baseline (e.g., cancer, diabetes, migraine headaches,gout) and became more severe, more frequent, or increased in duration during investigational product treatment.

12.1 REPORTING PROCEDURES FOR ALL AES. All AEs (>/=2 non-hematological and >/=3 hematological AEs) occurring after informed consent signing observed by the investigator or reported by the subject (whether or not attributed to investigational product), will be documented to the medical record then entered into the case report form. Abnormal laboratory values should not be reported as AEs; however, any clinical consequences of the abnormality should be reported as AEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE. The Investigator is responsible for verifying and providing source documentation for all adverse events and assigning attribution for each event for all subjects enrolled on the trial

12.2 Serious Adverse Event Reporting (SAE)

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

• Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

• All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

• **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

• Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

• Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
• Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

• Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Investigator Communication with Supporting Companies:

All SAEs (Death, A life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect. must be reported to Amgen and Celgene Drug Safety within 1 working day of discovery or notification of the event. Initial SAE information and all amendments or additions must be recorded on an SAE Report form and faxed to Amgen at:
Amgen Global Safety
Fax: 888-814-8653

Safety Reporting Requirements and Timelines

The Sponsor-Investigator will utilize the Celgene Drug Safety SAE Completion Form for the reporting of adverse events and follow up information to those events.

All serious adverse events regardless of severity or relationship must be reported to Celgene Drug Safety

within 24 hours of the investigational staff's knowledge.

To report adverse events on all Celgene (or legacy Abraxis) products, please use the email address provided below. Please email the completed SAE Forms to:

U.S. Sites: drugsafety@celgene.com

12.2.1 **Pregnancy:** Should a pregnancy occur, it must be reported in accordance with the following procedures: If your study has a patient that experiences a pregnancy while on a Celgene product a separate pregnancy SAE Initial and follow-up must be completed. Pregnancy itself is not regarded as an AE unless there is a suspicion that the trial treatment under investigation may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented, even if the patient was discontinued from the trial. All reports of congenital abnormalities or birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

IDENTIFICATION, RECORDING AND HANDLING AEs

All staff involved in the study will have adequate procedural training regarding the identification, documentation, and reporting AEs as described in this protocol. The principal investigator will be responsible for ensuring that adequate training is performed and documented for study staff members.

Definitions and Types of Adverse Events

Adverse Event (AE)
An adverse event is defined as the development of an untoward medical occurrence, undesirable medical condition, recurrence or deterioration of a pre-existing medical condition subsequent to exposure of a pharmaceutical product or treatment. An AE is additionally defined as occurring at any dose, independent of perceived causal relationship to the product. Adverse events may or may not be formal medical diagnoses, and can also include signs, symptoms or abnormal laboratory findings. Common examples include nausea, chest pain, tachycardia, enlarged liver, or electrocardiogram abnormalities.

Causality
The definition of an AE is independent to a perceived causal relationship to the drug. Causality is a separate assessment that is performed for AEs. Causality assessment to a study drug or regimen will be a medical judgment based made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions.

Special Considerations for Laboratory Results
Any NCI-CTC Gr III or IV hematology or biochemistry laboratory values not solely considered a result of disease progression will be considered an AE.

Treatment Non-Response as an AE
"Lack of efficacy" or treatment non-response for an unproven therapy will not generally considered an AE. If there is deterioration in the underlying condition for which the study regimen is designed to treat, there may be uncertainty as to whether this is an AE. In such a case, the investigating physician must judge the treatment as a possible contributor to the deterioration. Unless local governing regulations require otherwise, such deterioration will be considered to be an issue of treatment efficacy and not an AE. This situation constitutes an exception to the general rule that AEs are initially identified regardless of perceived causality attribution. Adverse events that are unequivocally due to progression of disease should be recorded as "progressive disease" rather than as AEs. However, the development of an additional (even if similar) disease will be regarded as an AE. For example, if a patient taking an experimental drug to treat underlying breast cancer develops a second primary cancer of non-metastatic origin, this would be considered a unique AE.

Types of AEs
In the clinical study setting, AEs are most often subcategorized as either SERIOUS or NON-SERIOUS.

This distinction is critical, as SERIOUS AEs require additional documentation that is both time-sensitive and detailed.

13.0 STATISTICAL CONSIDERATIONS

13.1 The primary objective of the trial is to determine the pathological complete response rate (pCR), which will be assessed after patients have received PNC and FEC preoperative chemotherapy treatment. We plan to enroll up to 40 patients, with accrual estimated to be completed in 20 months.

13.2 Efficacy: We will enroll and evaluate a minimum of 10 patients and a maximum of 40 patients at a rate of 2 patients per month. Our primary outcome is pathologic complete response (pCR), which is assessed at 25 weeks following initiation of therapy. Our target pCR rate is at least 13% [Dawood et al., 2008]. Previous studies have shown that these IBC patients achieve a 13% pCR rate on the standard of care. Therefore, we assume a beta (0.26, 1.74) prior distribution for the pCR rate. This prior distribution has a mean of 13% and a standard deviation of 19%.

13.3 We will consider stopping the trial early if P (pCR rate ≥ 13% | data from the trial) < 0.01. That is, given the outcomes from the patients who have already been evaluated, if we determine that there is less than a 1% chance that the pCR rate is 13% or more we will consider stopping the trial. This decision rule gives the following stopping rule. Consider stopping the trial if [# of pts with pCR / # of pts evaluated] ≤ 0/17, 1/37. If none of the first 16 patients reached pCR, the accrual will be suspended until 17th patient has been evaluated. The operating characteristics of this continuous monitoring rule are shown in Table 1 (Thall *et al.*, 1996).

13.4

Table 5. Operating Characteristics for Efficacy Monitoring Rule

pCR Rate	Probability of Stopping Early	Sample Size P 25	P 50	P 75
0.03	0.770	17	17	37
0.05	0.555	17	37	40
0.07	0.372	17	40	40
0.09	0.252	37	40	40
0.11	0.164	40	40	40
0.13	0.113	40	40	40
0.15	0.070	40	40	40

13.5 Once we have completed the study we will estimate the pCR rate with a 90% credible interval. If we have pCR in 4 of the 40 patients (10%), then our 90% credible interval for the pCR rate will be 4.0-19.6%. If we have pCR in 8 of the 40 patients (20%), then our 90% credible interval for the pCR rate will be 10.6-30.4%. We will also report the posterior probability that the pCR rate is 13% or more. For example, if we have pCR in 8 of the 40 patients (20%), then the probability that the pCR rate is 13% or more is 0.869.

13.6 Toxicity: We will enroll a minimum of 10 and a maximum of 40 patients. We will continue to enroll and evaluate these patients for toxicity (severe grade 4 organ toxicity or irreversible grade 3 toxicity during the 13 weeks of therapy) as long as we are sure that the toxicity rate is not more than 10%. We will employ the following monitoring rule for toxicity. We will consider stopping the trial if P(toxicity > 10% | data from the trial) > 0.95. That is, given the outcomes from the patients who have already been evaluated, if we determine that there is more than a 95% chance that the toxicity rate is more than 10% we will consider stopping the trial. This decision rule gives the following stopping rule. We assume a beta (0.20, 1.80) prior distribution for the toxicity rate. This prior distribution has mean 10% and standard deviation of 17%. Consider stopping the trial if [# of pts with toxicity / # of pts evaluated] > 4/10, 5/15, 6/22, 7/28, 8/35 [Table 2].

The operating characteristics of this rule are shown in Table 2

Table 6. Operating Characteristics for Toxicity Monitoring Rule

Toxicity Rate	Probability of Stopping	Sample Size P_{25}	P_{50}	P_{75}
0.050	0.008	40	40	40
0.075	0.033	40	40	40
0.100	0.098	40	40	40
0.125	0.210	40	40	40
0.150	0.347	26	40	40
0.175	0.496	18	40	40
0.200	0.646	13	26	40
0.250	0.857	11	17	27

Once we have completed the study we will estimate the toxicity rate with a 90% credible interval. If we have toxicity in 4 of the 40 patients (10%), then our 90% credible interval for the toxicity rate will be 3.7% to 18.5%. If we have toxicity in 2 of the 40 patients (5%), then our 90% credible interval for the toxicity rate will be 1.1% to 11.8%.

We will also report the posterior probability that the toxicity rate is 10% or less. For example, if we have toxicity in 1 of the 40 patients (2.5%), then the probability that the toxicity rate is 10% or less is 0.980.

13.7 Once we have completed the study we will estimate the toxicity rate with a 90% credible interval. If we have toxicity in 4 of the 40 patients (10%), then our 90% credible interval for the toxicity rate will be 3.5-18.1%. If we have toxicity in 2 of the 40 patients (5%), then our 90% credible interval for the toxicity rate will be 1.0-11.4%.

13.8 We will also report the posterior probability that the toxicity rate is 5% or less. For example, if we have toxicity in 1 of the 40 patients (2.5%), then the probability that the toxicity rate is 5% or less is 0.960.

13.9 Secondary and Explanatory Objectives: Once the trial has been completed, we will determine the clinical response rate and present the rate with its corresponding 95% confidence interval.

13.9.1 We will investigate whether the pathological response rate is associated with the EGFR expression level. EGFR expression will be categorized as 1+, 2+, or 3+. A chi-square test, or Fisher's exact test if cell sizes are small, will be used to determine if a significant association is present. Significance will be assessed at the 5% level.

13.9.2 We will estimate the effects of the therapy on the micrometastatic disease in the bone marrow and peripheral blood by measuring the numbers of CTCs. The estimated levels of CTCs in the bone marrow and peripheral blood will be presented along with 95% confidence intervals.

13.9.3 We will estimate the progression-free survival and overall survival as a whole group as well as patient with triple negative breast cancer. Triple negative breast cancer will be defined as ER negative (< 10% by immunohistochemical staining), PR negative (< 10% by immunohistochemical staining), and HER-2 negative by FISH.

14.0 References

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Appendix I. Dermatology/Skin/Nail Assessment (from CTCAE version 3.0 with modifications)

AE (Short Name)	Grade 1	Grade 2	Grade 3	Grade 4
Nail changes (Nail changes)	Discoloration; ridging (koilonychias; pitting) paronychia: intervention not indicated	Partial or complete loss of nail(s); pain in nailbed(s), paronychia: intervention indicated	Interfering with activities of daily living (ADL)	___
Erythema (Erythema)	Painless erythema	Painful erythema	Erythema with desquamation*	Life-threatening; disabling
Pruritis/itching (Pruritis)	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	___
Rash: acne/acneiform (Acne)	Intervention not indicated	Intervention indicated	Associated with pain requiring narcotic analgesics, ulceration, or desquamation*	___
Rash/desquamation* (Rash) [Use for non-acneiform rash or non-folliculitis rash]	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritis or other associated symptoms; localized desquamation* or other lesions covering < 50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation* covering ≥ 50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis
Ulceration (Ulceration)	___	Superficial ulceration < 2 cm size; local wound care; medical intervention indicated	Ulceration ≥ 2 cm size; operative debridement, primary closure or other invasive intervention indicated (eg, hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (eg complete resection, tissue reconstruction, flap, or grafting)

***Desquamation is defined as sloughing of skin and does not apply to dry flaking skin.**

Appendix II. Panitumumab Pharmacy Guide

Packaging, Formulation, Labeling and Storage

Panitumumab will be manufactured and packaged by Amgen and distributed using Amgen's clinical trial drug distribution procedures. Each vial of panitumumab will contain 10 mL of a sterile protein solution containing a 20-mg/mL solution of panitumumab. The vial will contain approximately 200 mg of panitumumab and is for single dose use only. Each vial of panitumumab will be labeled in accordance with current ICH GCP, FDA and specific national requirements.

The supplied investigational drug must be stored at 2-8° C in a secured area upon receipt. As panitumumab contains no preservatives, vials are designed for single use only. Exposure of the material to excessive temperature above or below this range should be avoided. Do not allow panitumumab to freeze and do not use if contents freeze in transit or in storage. If vials fall out of specified temperature requirement, please contact Amgen for instructions.

Records of the actual storage condition during the period of the study must be maintained (ie, records of the date and time and initials of person checking, and the "working day" temperature of the refrigerator used for storage of trial supplies, continuous temperature recordings, or regularly maintained temperature alarm systems used in conjunction with temperature recording).

Preparation

NOTE: Panitumumab is a protein and should be handled gently to avoid foaming, which may lead to denaturation of the protein product. This precaution applies not only to panitumumab stored in the vial, but also for diluted panitumumab prepared in the IV bag. It is, therefore, essential to avoid medication delivery methods, particularly pneumatic tube systems, that could potentially lead to excessive shaking or vibration that would lead to particulate formation in the protein product.

Panitumumab must be prepared as an intravenous infusion using aseptic techniques. The dose of panitumumab will be 6 mg/kg (or 9mg/kg, depending on the study) and will be based upon the subject's baseline weight. The dose of panitumumab is required to be recalculated only when the subject's body weight increases or decreases by $\geq$ 10% from the original screening/baseline weight. This weight will be considered the new baseline weight from which a $\pm$ 10% variance is allowed before another recalculation is necessary. The calculated amount of panitumumab (may be rounded to the nearest ten milligrams [eg, 456 mg rounded to 460 mg or 312 mg rounded to 310 mg]) will be removed from the vials and added to a minimum volume of 100 mL of pyrogen-free 0.9% sodium chloride solution USP. The maximum concentration of the diluted solution to be infused should not exceed 10 mg/mL. In the event a subject's actual body weight requires greater than a 150-mL volume infusion, panitumumab will be administered over 60 to 90 $\pm$ 15 minutes, as tolerated. The panitumumab will be infused within 19 hours of dilution

and will be labeled per site pharmacy standard operating procedures. The bag should be labeled per site pharmacy standard operating procedures and promptly forwarded to the clinic center for infusion.

Supply and Return

At study initiation and as needed thereafter, panitumumab will be shipped to a responsible person (eg, a pharmacist) at the Investigator's institution, who will check the amount and condition of the drug and enter these data into the Proof of Receipt Form and Investigational Product Accountability record. The Proof of Receipt Form should then be returned to Amgen Inc., and the original retained at the site. At the end of the study, or as directed, all panitumumab supplies, including unused, partially used, or empty containers, will be destroyed at the site.

Panitumumab Accountability

An Investigational Product Accountability Record for the panitumumab must be kept current and should contain:

- The dates and quantities of panitumumab received from Amgen Inc.
- Manufacturing batch or lot numbers for product received
- Subject's identification (subject number)
- Date and quantity of panitumumab dispensed (and remaining, if from individual subject drug units)
- The initials of the dispenser
- Dose preparation records
- Date and quantity of drug returned to the investigator/pharmacy, if appropriate

Any discrepancies must be documented and subsequently reported to Amgen Inc. immediately.

These inventories must be made available for inspection by authorized sponsor representative(s) and regulatory agency inspector(s). The investigator is responsible for the accountability of all used and unused trial supplies.