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Combined Targeted Therapies for Triple Negative Advanced Breast Cancer - A Phase II Trial of Weekly Nab-Paclitaxel and Bevacizumab Followed by Maintenance Targeted Therapy with Bevacizumab and Erlotinib

NCT00733408

Current Version: April 14, 2014
Previous Version: October 14, 2013

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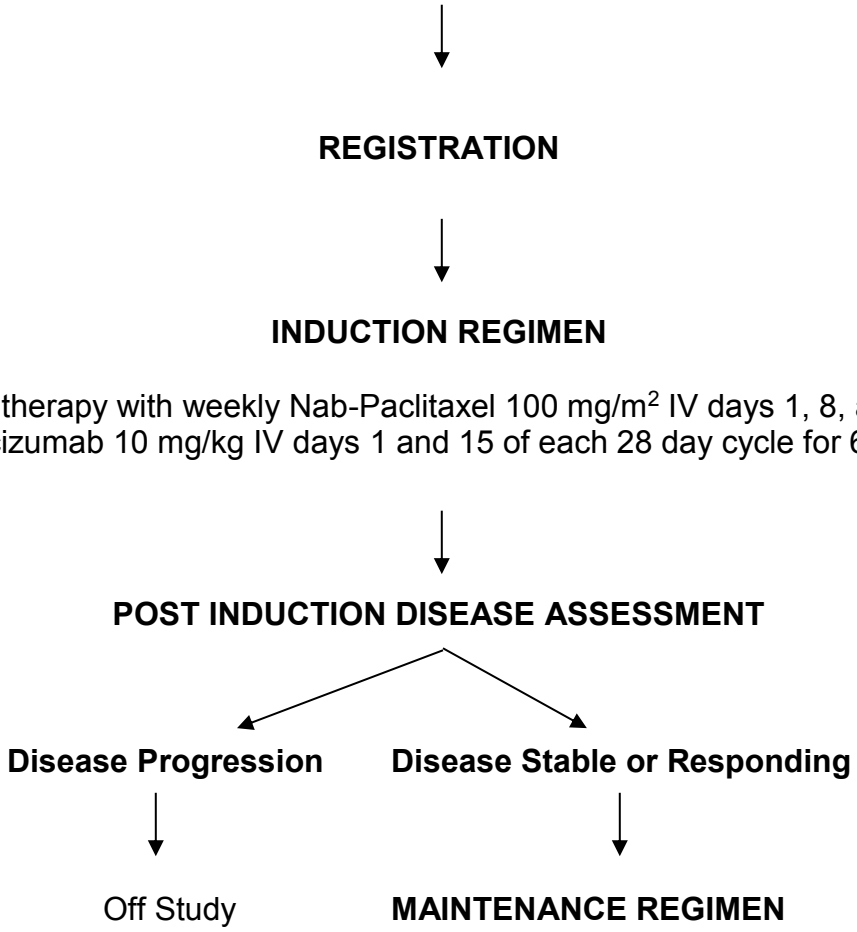
SCHEMA


REGISTRATION
INDUCTION REGIMEN
Induction therapy with weekly Nab-Paclitaxel 100 mg/m2 IV days 1, 8, and 15 and Bevacizumab 10 mg/kg IV days 1 and 15 of each 28 day cycle for 6 cycles
POST INDUCTION DISEASE ASSESSMENT
Disease Progression
Disease Stable or Responding
Off Study
MAINTENANCE REGIMEN
Bevacizumab 10 mg/kg IV Q 14 days or 15 mg/kg IV Q 21 days and Erlotinib 150 mg PO daily until disease progression

1.0 OBJECTIVES

1.1 Primary Objective

The primary objective is progression free survival.

1.2 Secondary Objectives

The secondary objectives are:

- Response rate,
- Overall survival,
- Safety and toxicity,
- Exploratory biomarkers will be assessed as potential predictors of response to treatment including:
  - Expression of EGFR and SPARC in the primary tumor and
  - Changes in levels of circulating tumor cells (CTCs) and circulating endothelial cells (CECs).

2.0 BACKGROUND

It is now recognized that patients with breast cancer which expresses the basaloid or "triple negative" phenotype (ER negative, PR negative, HER2 non-overexpressing) have a particularly aggressive and virulent form of the disease. In the adjuvant setting, their prognosis is worse than that of other subgroups (luminal A, luminal B) defined by DNA genotyping [1], and with recent improvements in the outcome of adjuvant therapy for HER2 over-expressing patients, it appears they will also have a much worse outcome in that setting than the HER2 over-expressing patients. There is little as yet reported about the prognosis or response to chemotherapy of these patients in the setting of advanced disease; however, our institutional experience with combination chemotherapy, in pilot studies involving antitubulin combinations, indicates a response rate over 50% (comparable to other phenotypes) but a relatively short median time to progression of 4.4 months in the first line setting [2].

The biology of triple negative disease is under intensive study. It is known that familial cancers with BRCA 1 mutations which involve loss of function, usually express this phenotype [3-7]. Further, work from the group at the University of Chicago suggests that, even among "sporadic" tumors with the triple negative phenotype, there is often down-regulation of expression of the BRCA 1 protein, apparently due to epigenetic mechanisms involving suppression of promoter function [8]. There are data from preclinical systems which suggest that loss or down-regulation of the function of BRCA 1, a gene known to be involved in the repair of DNA damage, may predispose to alteration in the pattern of chemosensitivity for standard agents, with an increase in sensitivity to the platinators [9, 10] and to vinorelbine, but not docetaxel [11]. It is not yet known whether these preclinical observations will be borne out in the setting of human cancer.

Epidermal Growth Factor Receptor Expression and Significance in Cancer

The control of cell growth is mediated by a complex network of signaling pathways responsive to external influences, such as growth factors, as well as to internal controls and checks. Epidermal growth factor (EGF) was one of the first growth factors to be described. It was shown to be mitogenic, an effect mediated by the binding of EGF (or other ligands) to the cell surface EGF receptor (EGFR), stimulating autophosphorylation of the intracellular tyrosine kinase domain of the receptor. Subsequent investigations revealed EGFR to be one of a family of closely related receptors that includes EGFR (HER1), HER2, HER3, and HER4. Over-expression, at the protein level, of EGFR (erbB1), demonstrated by radioligand binding assay [12] and by immunohistochemistry [13,14] is another alteration common to the triple negative breast cancer phenotype. However, unlike the situation with HER2, where gene amplification occurs in 20% or more of human breast cancers, gene amplification by the same criteria appears to be very rare in human breast cancer, even among specimens selected for expression of the triple negative phenotype [15, 16].

EGFR and other HER family members are considered to be important in the development, progression, and aggressive behavior of human epithelial malignancies and to be relevant therapeutic targets. A number of human malignancies are associated with aberrant or over-expression of EGFR [17]. Stimulation of tumor cells via the EGFR is important for both tumor growth and tumor survival in vivo. Over-expression of EGFR in certain human tumors, including non–small cell lung carcinoma (NSCLC), has been correlated with both chemo-resistance and poor prognosis [18-30]. Inhibitors of EGFR tyrosine kinase activity have been in development for a number of years, and although earlier compounds lacked specificity and potency, newer compounds have proven active in nonclinical and clinical studies.

Erlotinib (Tarceva, previously known as OSI-774) is an orally active, potent, selective inhibitor of the EGFR tyrosine kinase. Early clinical data with erlotinib indicate that the compound is generally safe and well tolerated at doses that provide the targeted effective concentration based on nonclinical experiments. In non-small cell lung cancer, for example, there is significant benefit to the administration of small-molecule inhibitors of EGFR, such as erlotinib, among patients with disease progression after chemotherapy, independent of evidence for gene amplification by the usual criteria, but with some relationship to expression of the protein [31-33]. In colorectal cancer, administration of cetuximab, a monoclonal antibody directed against EGFR, appears to be effective, regardless of the level of expression of EGFR [34].

It is now clear, from randomized trials in metastatic breast cancer [35], non-small cell lung cancer [36] and colorectal cancer [37] that the addition of bevacizumab, a monoclonal antibody which targets VEGF, improves response rate and time to progression, compared to chemotherapy alone. However, it has so far been impossible to demonstrate consistent correlates of VEGF status with clinical outcome in these diseases. In ECOG 2100, first line therapy for metastatic breast cancer in HER2 non-amplified patients with paclitaxel and bevacizumab was compared to paclitaxel alone in a randomized phase III trial and reported at SABC 2005. The combination of paclitaxel and bevacizumab was associated with a significant improvement in progression free survival for patients with ER positive and ER negative disease (11.4 months for paclitaxel and bevacizumab versus 6.11 months for paclitaxel alone; HR 0.51, $p<0.0001$). This outcome in E2100 will serve as a historical control for this trial of

combined targeted therapies with continued bevacizumab and erlotinib after induction therapy with nab-paclitaxel and bevacizumab.

Unlike the situation with bevacizumab, where concurrent administration with chemotherapy appears beneficial, the concurrent administration of erlotinib with chemotherapy appeared deleterious in patients with non-small cell lung cancer [38]. The reasons for this are not clear, but a sequential approach (chemotherapy, then small molecule targeted inhibitor) seems, at present, to be the preferred approach for erlotinib.

Scientific Rationale for Dosing Schema

The dosing for nab-paclitaxel (Abraxane) proposed for this study is 100 mg/m^2 intravenously days 1, 8 and 15 every 28 days until best response. The rationale for this dose is based upon the following: 1) -nab-paclitaxel was superior to paclitaxel in a phase III, randomized trial, both for response rate and for time to progression [39]; 2) weekly nab-paclitaxel appears to be anti-angiogenic [40, 41], and there are now data which establish the optimal tolerated weekly dose for this compound [41]. Bevacizumab will be dosed at 10 mg/kg intravenously every 14 days during induction and at either 10 mg/kg intravenously every 14 days or 15 mg/kg intravenously every 21 days during maintenance. Bevacizumab 10 mg/kg intravenously every 14 days has been previously evaluated for toxicity and efficacy in metastatic breast cancer [35]. Erlotinib is being administered at its FDA-approved dose and schedule.

Hypothesis/Objectives:

We propose to explore the combination of nab-paclitaxel and bevacizumab in first-line therapy for metastatic disease among patients with the triple negative phenotype, based on evidence that: 1) nab-Paclitaxel was superior to paclitaxel in a phase III, randomized trial, both for response rate and for progression free survival [39]; and 2) the combination of paclitaxel on a weekly schedule and bevacizumab was superior to paclitaxel alone, in a population of patients with advanced breast cancer whose tumors did not over-express HER2 [35]. The schedule proposed for nab-paclitaxel is weekly, since this appears to be anti-angiogenic [40, 41], and there are now data which establish the optimal tolerated weekly dose for this compound [41]. At the completion of 24 weeks of induction chemotherapy, nab-paclitaxel will be discontinued, and patients who remain on study without evidence of disease progression will receive combined, targeted “maintenance” therapy with bevacizumab and erlotinib, a combination which has been studied with acceptable toxicity and promising preliminary results [42]. We hypothesize that the combination of targeted, biologic therapies aimed at the critical pathways of angiogenesis (VEGF) and signaling via EGFR may result in prolonged progression free survival after chemotherapy.

The primary endpoint will be progression free survival with secondary endpoints to include response rate, overall survival, safety and toxicity, and correlation of response with EGFR and SPARC expression in the primary tumor, changes in levels of circulating tumor cells (CTCs), and circulating endothelial cells (CECs) as potential predictors of treatment response.

Correlative Studies:

We propose to study, in patients entered on this trial, the expression of EGFR and SPARC (secreted protein acidic and rich in cysteine, also known as BM40 or osteonectin) in their primary tumors by immunohistochemistry. EGFR is the target of erlotinib and is often overexpressed at the protein level in triple negative breast cancers. SPARC is an albumin-binding protein secreted by tumor cells into the interstitium [43]. Nab-paclitaxel achieves a high intracellular tumor concentration, and its intracellular concentration is at least, in part, achieved by an albumin-mediated transendothelial transport via the gp60 pathway [50]. SPARC is a matricellular protein that is upregulated in several aggressive tumors, and its presence is associated with poor outcomes. Expressed in 40-50% of breast cancers, SPARC also shares sequence homology with the C terminus of the gp60 pathway (an important pathway in nab-paclitaxel intracellular transport) and binds albumin. By exploiting both caveolin-1 and the SPARC protein, nab-paclitaxel may preferentially enhance drug delivery to tumors. Expression of EGFR and SPARC protein by IHC methodology in primary tumors will be correlated in an exploratory fashion to treatment response.

In addition, levels of circulating tumor cells (CTC) and circulating endothelial cells (CEC) will be quantitated over time including pre-therapy, prior to weeks 5 and 17 of induction, prior to weeks 1 and 9 of maintenance and at disease progression if the patient is removed from study treatment due to disease progression. The number of CTCs detectable in patients with metastatic breast cancer prior to initiation of therapy has been shown to be an independent predictor of progression-free and overall survival [44] [45], however, the predictive value of CTCs in regimens containing targeted, biologic therapies has not been well-established. Flow cytometry studies have indicated that circulating endothelial cells (CECs) are significantly increased in number and percentage viability in untreated cancer patients compared with healthy subjects [46], and animal models and studies in cancer patients suggest that CECs and their putative progenitor cells (CEPs) may be used as quantitative surrogate pharmacodynamic markers of antiangiogenic therapies [47,48]. In advanced breast cancer patients receiving metronomic chemotherapy, an increase in apoptotic CECs after 2 months of therapy was associated with prolonged progression-free and overall survival with follow up of greater than 2 years [49].

Measurement of circulating endothelial cells (CECs) isolated from peripheral blood will be performed in a serial fashion and will be correlated in an exploratory fashion with angiogenic factors and with patient clinical response to treatment. We hypothesize that decreases in level of CTC may predict longer time to disease progression, and increases in apoptotic CEC may also be predictive of response to chemotherapy and bevacizumab.

Based upon the prolongation in PFS observed in E2100 where patients with ER and PR negative, HER2 non-overexpressing metastatic breast cancer were treated with the combination of bevacizumab and paclitaxel, we would consider a prolongation in the median progression free survival (PFS) for these patients from 8 to 13 months to be of sufficient interest to warrant further exploration of this combination in the setting of a randomized trial. It will be necessary to enter 63 patients on the trial in order to be able to detect this degree of improvement. Secondary objectives will be the assessment of response rate, survival and the proportion of patients with grade 3 or 4 toxicity.

3.0 DRUG INFORMATION

3.1 Nab-Paclitaxel: (ABI-007, Abraxane, albumin-bound paclitaxel)

Nab-paclitaxel for Injectable Suspension (paclitaxel albumin-bound particles for injectable suspension) is indicated for the treatment of

- Metastatic breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.
- Locally advanced or metastatic non-small cell lung cancer (NSCLC), as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.
- Metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine.

Nab-paclitaxel is a Cremophor EL-free, albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. 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.

3.1.1 Introduction

Nab-paclitaxel (Abraxane) 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 [50]. A protein specifically secreted by the tumor (SPARC) binds and entraps the albumin, allowing release of the hydrophobic drug to the tumor cell membrane [50]. 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.

3.1.2 Preclinical Studies with Nab-Paclitaxel

Preclinical studies comparing nab-paclitaxel to Taxol demonstrated lower toxicities, with a MTD approximately 50% higher for nab-paclitaxel compared to Taxol. At equal doses there was less myelosuppression and improved efficacy in a xenograft tumor model of human mammary adenocarcinoma. At equitoxic doses of nab-paclitaxel was found to be markedly more efficacious than Taxol [51]

3.1.3 Clinical Studies with Nab-Paclitaxel

Every 3 Week Schedule

In a phase I study, the maximum tolerated dose (MTD) of nab-paclitaxel was determined to be 300 mg/m^2 by 30 minute infusion every 3 weeks, without premedication or G-CSF support [52] No severe hypersensitivity reactions occurred with nab-paclitaxel despite the absence of premedication. Dose-limiting toxicities included sensory neuropathy, stomatitis, and superficial keratopathy, which occurred at a dose of 375 mg/m^2.

Two multicenter phase II studies have evaluated 2 dose levels of nab-paclitaxel (300 mg/m^2, n=63, and 175 mg/m^2, n=43) in patients with metastatic breast cancer [53] The overall response rates in these 2 phase II trials were 40% (95% CI 25-54%) for the 175 mg/m^2 dose, and 48% (95% CI 35-60%) for the 300 mg/m^2 dose. Of 39 patients receiving 300 mg/m^2 as first-line therapy for metastatic breast cancer, 64% (95% CI 49-79%) responded. This was contrasted with a 45% response rate in similar patients at the lower dose level. Grade 4 neutropenia was noted in 24% of patients at the higher dose level, occurred primarily during the first cycle and resolved rapidly.

A Phase III trial in patients with metastatic breast cancer compared nab-paclitaxel 260 mg/m^2 to Taxol 175 mg/m^2 given every 3 weeks [39] Efficacy analyses were based on the ITT population. The ORR was significantly greater for nab-paclitaxel than for Taxol 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 Taxol 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 ≥ 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 [48] = 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 Taxol 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 grade) was low for both arms (1% for nab-paclitaxel and 2% for Taxol). No severe (grade 3 or 4) treatment-related hypersensitivity reactions occurred in any of the patients in the nab-paclitaxel group despite the absence of premedication. In contrast, grade 3 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 grade 4 neutropenia was significantly lower in the nab-paclitaxel group than in the Taxol group (9% v 22%, respectively; *P* < 0.001), with a higher mean neutrophil nadir (1.67 *v* 1.31x10^9/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 grade 3 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 grade 2 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 grade 3 sensory neuropathy was the same (n = 4) in both study arms. No episodes of motor neuropathy or grade 4 sensory neuropathy were reported in either group.

The only clinical chemistry value that was notably different between the two treatment arms was higher serum glucose levels in the paclitaxel–treated patients, who also had a higher incidence of hyperglycemia reported as an AE compared with nab-paclitaxel–treated patients (7% *v* 1% respectively; *P* =0.003).

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 for 3 Weeks, Every 4 Weeks Schedule

Thirty-nine patients were enrolled into A Phase I study of nab-paclitaxel administered weekly for 3 weeks followed by a 1 week rest in patients with advanced solid tumors [54]. The MTDs for heavily and lightly pre-treated patients were 100 and 150 mg/m^2 respectively. Dose limiting toxicities included grade 4 neutropenia and grade 3 sensory neuropathy. Premedication was not required, and unexpected, non-taxane associated toxicities were not observed.

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 nab-paclitaxel100 mg/m^2 on this schedule [55] Nab-paclitaxel weekly regimen was well tolerated. 91% of patients were treated at the full dose of 100 mg/m^2 of nab-paclitaxel without dose reductions. Based on the activity and low toxicity documented with the nab-paclitaxel 100 mg/m^2 weekly regimen, this study was expanded to evaluate the efficacy and safety/tolerability of a higher dose of nab-paclitaxel 125 mg/m^2 weekly regimen in 75 additional patients. Results of this dose-finding study confirm the dose of nab-paclitaxel 100 mg/m^2 as the appropriate dose for further study in this patient population [56]

3.1.4 Potential Risks of Nab-Paclitaxel

Please refer to the FDA approved prescribing information for risk and safety information for Nab-Paclitaxel.

Advantages of Nab-Paclitaxel

Nab-Paclitaxel is a novel Cremophor EL-free, non-crystalline, amorphous, albumin-bound particle form of paclitaxel suspended in normal saline with several advantages over Taxol:

- Preclinical models consistently demonstrated improved tolerability, increased antitumor activity and higher intratumor paclitaxel levels for nab-paclitaxel compared to paclitaxel. Recent mechanistic studies indicate that this increased antitumor activity may be due to increased

tumor uptake of paclitaxel that is mediated through albumin-receptors on tumor neovasculature (Desai et al, 2006).

- Nab-Paclitaxel does not require steroid co-medication and can be administered weekly or every 3 weeks.

- Nab-Paclitaxel is better tolerated than paclitaxel. In a Phase I trial using an every 3 week schedule of administration, the maximum tolerated dose of nab-paclitaxel (300 mg/m^2) was substantially higher than the labeled dose for paclitaxel (175 mg/m^2) (Investigator's Brochure 8th Ed). Improved tolerability compared to Taxol was also demonstrated using a schedule of weekly administration for 3 weeks with a week of rest in which a recently completed Phase I study found the MTDs and recommended Phase II doses to be 100 and 150 mg/m^2 in heavily and minimally pretreated patients respectively [54].

- The antitumor activity of nab-paclitaxel is greater than that of paclitaxel. In Phase II trials, antitumor activity was documented in metastatic breast cancer (Ibrahim et al 2005 and Investigator's Brochure 7th Ed) and a Phase III study utilizing nab-paclitaxel at a dose of 260 mg/m^2 every 3 weeks demonstrated increased objective response rates and time to tumor progression compared to standard doses of Taxol in women with metastatic breast cancer [39]. Antitumor activity with very little toxicity has also been seen in a Phase II trial of 100 mg/m^2 weekly in heavily pretreated patients with paclitaxel-refractory metastatic breast cancer [55].

- The major components of nab-paclitaxel are unmodified paclitaxel and human serum albumin. The absence of Cremophor EL in the formulation allows the infusion of nab-paclitaxel in approximately 30 minutes.

- Nab-Paclitaxel is Cremophor EL-free and therefore associated with a reduced risk of hypersensitivity and no requirements for premedication as compared to Taxol.

- The Cremophor EL constituent in Taxol requires special non-DEHP tubing and in-line filters for intravenous administration, since Cremophor EL causes leaching of the tubing plasticizers. Nab-Paclitaxel requires no special tubing or in-line filters.

3.1.5 Packaging, Labeling, and Storage of Study Drug

Nab-Paclitaxel is commercially available in single-use vials, but will be supplied free of charge by Celgene for patients who are enrolled after the IRB approves modification to the study design.

3.1.6 Study Medication Administration

Nab-Paclitaxel will be stored, reconstituted and administered per FDA approved package insert instructions and administered to the patient at the study site.

3.2 Bevacizumab (Avastin®)

Bevacizumab is a monoclonal antibody that has been studied in a multitude of Phase I, II, and III clinical trials in more than 5000 patients and in multiple tumor types. The following discussion summarizes bevacizumab's safety profile and presents some of the efficacy results pertinent to this particular trial. Please refer to the Bevacizumab Investigator Brochure for descriptions of all completed Phase I, II, and III trials reported to date.

3.2.1 Description

Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile liquid concentrate for solution for intravenous (IV) infusion. Bevacizumab may be supplied in 20-cc (400-mg), and 50-cc (1000-mg) glass vials containing 4 mL or 16 mL of bevacizumab, respectively (all at 25 mg/mL). Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection (SWFI), USP. Vials contain no preservative and are suitable for single use only.

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

3.2.2 Clinical Data

In a large phase III study (AVF2107g) in patients with metastatic colorectal cancer, the addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), to irinotecan/5-fluorouracil/leucovorin (IFL) chemotherapy resulted in a clinically and statistically significant increase in duration of survival, with a hazard ratio of death of 0.67 (median survival 15.6 vs. 20.3 months; $p < 0.001$). Similar increases were seen in progression-free survival (6.2 vs. 10.6 months; $p < 0.001$), overall response rate (35% vs. 45%; $p < 0.01$) and duration of response (7.1 vs. 10.4 months; $p < 0.01$) for the combination arm versus the chemotherapy only arm [57]

Based on the survival advantage demonstrated in Study AVF2107g, bevacizumab was designated for priority review and was approved on 26 February 2004 in the United States for first-line treatment in combination with IV 5-FU–based chemotherapy for subjects with metastatic colorectal cancer.

3.2.3 Safety Profile

In the initial Phase I and II clinical trials, four potential bevacizumab-associated safety signals were identified: hypertension, proteinuria, thromboembolic events, and hemorrhage. Additional completed Phase II

and Phase III studies of bevacizumab as well as spontaneous reports have further defined the safety profile of this agent. Bevacizumab-associated adverse events identified in phase III trials include congestive heart failure (CHF), gastrointestinal perforations, wound healing complications, and arterial thromboembolic events (ATE). These and other safety signals are described in further detail as follows and in the Bevacizumab Investigator Brochure.

Hypertension: Hypertension has been commonly seen in bevacizumab clinical trials to date and oral medications have been used to manage the hypertension when indicated. Grade 4 and 5 hypertensive events are rare. Clinical sequelae of hypertension are rare but have included hypertensive crisis, hypertensive encephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS) [58], Glusker, 2006 #78]. RPLS may include signs and symptoms of headache, altered mental function, seizures, and visual disturbances / cortical blindness and requires treatment, which should include control of hypertension, management of specific symptoms, and discontinuation of bevacizumab.

Proteinuria: Proteinuria has been commonly seen in bevacizumab clinical trials to date. The severity of proteinuria has ranged from asymptomatic and transient events detected on routine dipstick urinalysis to nephrotic syndrome; the majority of proteinuria events have been grade 1 or 2. In study AVF2107g, none of the 118 patients receiving bolus-IFL plus placebo, three of 158 patients (2%) receiving bolus-IFL plus bevacizumab, and two of 50 (4%) patients receiving 5-FU/LV plus bevacizumab who had a 24-hour collection experienced grade 3 proteinuria (> 3.5 g protein/24 hr). Rare events of nephrotic syndrome have occurred, and bevacizumab should be discontinued in patients with nephrotic syndrome.

Thromboembolic Events: Both venous and arterial thromboembolic (TE) events, ranging in severity from catheter-associated phlebitis to fatal, have been reported in patients treated with bevacizumab in the colorectal cancer trials and, to a lesser extent, in patients treated with bevacizumab in NSCLC and breast cancer trials. In the phase III pivotal trial in metastatic CRC, there was a slightly higher rate of **venous TE** events that was not statistically significant in patients treated with bevacizumab plus chemotherapy compared with chemotherapy alone (19% vs. 16%). There was also a higher rate of **arterial TE** events (3% vs. 1%) such as myocardial infarction, transient ischemia attack, cerebrovascular accident/stroke and angina/unstable angina**.** A pooled analysis of the rate of arterial TE events from 5 randomized studies (1745 patients) showed that treatment with chemotherapy plus bevacizumab increased the risk of having an arterial TE event compared with chemotherapy alone (3.8% vs. 1.7%, respectively) [59] Furthermore, subjects with certain baseline characteristics (age ≥ 65 years and/or a history of a prior arterial TE event) may be at higher risk of experiencing such an event. See the Bevacizumab Investigator Brochure for additional information on risk factors.

Aspirin is a standard therapy for primary and secondary prophylaxis of arterial thromboembolic events in patients at high risk of such events, and the use of aspirin ≤ 325 mg daily was allowed in the five randomized studies discussed above. Use of aspirin was assessed routinely as a baseline or concomitant medication in these trials, though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and arterial thromboembolic events, retrospective analyses of the ability of aspirin to affect the risk of such events were inconclusive. However, similarly retrospective analyses suggested that the use of up to 325 mg of aspirin daily does not increase the risk of grade 1-2 or grade 3-4 bleeding events, and similar data with respect to metastatic colorectal cancer patients were presented at ASCO [60]. Further analyses of the effects of concomitant use of bevacizumab and aspirin in colorectal and other tumor types are ongoing.

Gastrointestinal perforation Patients with metastatic carcinoma may be at increased risk for the development of gastrointestinal perforation when treated with bevacizumab and chemotherapy. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation. A causal association of intra-abdominal inflammatory process and gastrointestinal perforation to bevacizumab has not been established. Nevertheless, caution should be exercised when treating patients with intra-abdominal inflammatory processes with bevacizumab. Gastrointestinal perforation has been reported in other trials in non-colorectal cancer populations (e.g., ovarian, renal cell, pancreas, and breast) and may be higher in incidence in some tumor types.

Wound healing complications: Wound healing complications such as wound dehiscence have been reported in patients receiving bevacizumab. In an analysis of pooled data from two trials in metastatic colorectal cancer, patients undergoing surgery 28-60 days before study treatment with 5-FU/LV plus bevacizumab did not appear to have an increased risk of wound healing complications compared to those treated with chemotherapy alone [61] Surgery in patients currently receiving bevacizumab is not recommended. No definitive data are available to define a safe interval after bevacizumab exposure with respect to wound healing risk in patients receiving elective surgery; however, the estimated half-life of bevacizumab is 20 days. Bevacizumab should be discontinued in patients with severe wound healing complications.

Hemorrhage: Overall, grade 3 and 4 bleeding events were observed in 4.0% of 1132 patients treated with bevacizumab in a pooled database from eight phase I, II, and III clinical trials in multiple tumor types [57]. The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage (see below) and minor mucocutaneous hemorrhage.

Tumor-associated hemorrhage – was observed in phase I and phase II bevacizumab studies. Six serious events, of which 4 had fatal outcome, were observed in a phase II trial of patients with non-small cell lung cancer receiving bevacizumab. These events occurred suddenly and

presented as major or massive hemoptysis in patients with either squamous cell histology and/or tumors located in the center of the chest in close proximity to major blood vessels. In five of these cases, these hemorrhages were preceded by cavitation and/or necrosis of the tumor. Tumor-associated hemorrhage was also seen rarely in other tumor types and locations, including central nervous system (CNS) bleeding in a patient with hepatoma with occult CNS metastases and continuous oozing of blood from a thigh sarcoma with necrosis.

Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated with bevacizumab. These were most commonly grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen. There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

Congestive heart failure: In clinical trials CHF was observed in all cancer indications studied to date, but predominantly in patients with metastatic breast cancer. In the Phase III clinical trial of metastatic breast cancer (AVF2119g), 7 (3%) bevacizumab-treated patients experienced CHF, compared with two (1%) control arm patients. These events varied in severity from asymptomatic declines in left ventricular ejection fraction (LVEF) to symptomatic CHF requiring hospitalization and treatment. All the patients treated with bevacizumab were previously treated with anthracyclines (doxorubicin cumulative dose of 240−360 mg/m2). Many of these patients also had prior radiotherapy to the left chest wall. Most of these patients showed improved symptoms and/or left ventricular function following appropriate medical therapy (Miller et al. 2005).

In a randomized, Phase III trial of patients with previously untreated metastatic breast cancer (E2100), the incidence of LVEF decrease (defined as NCI-CTC Grade 3 or 4) in the paclitaxel + bevacizumab arm was 0.3% versus 0% for the paclitaxel alone arm.

No information is available on patients with preexisting CHF of New York Heart Association (NYHA) Class II−IV at the time of initiating bevacizumab therapy, as these patients were excluded from clinical trials.

Prior anthracyclines exposure and/or prior radiotherapy to the chest wall may be possible risk factors for the development of CHF. Caution should be exercised before initiating bevacizumab therapy in patients with these risk factors.

A Phase II trial in patients with refractory acute myelogenous leukemia reported 5 cases of cardiac dysfunction (CHF or LVEF decrease to < 40%) among 48 patients treated with sequential cytarabine, mitoxantrone, and bevacizumab. All but 1 of these patients had significant prior exposure to anthracyclines as well (Karp et al. 2004).

Patients receiving anthracyclines or with prior exposure to anthracyclines should have a baseline MUGA or ECHO with a normal ejection fraction.

Additional Adverse Events: See the Bevacizumab Investigator Brochure for additional details regarding the safety experience with bevacizumab.

3.2.4 Bevacizumab Administration

Bevacizumab will be diluted in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP. Administration will be as a continuous IV infusion. Anaphylaxis precautions should be observed during study drug administration.

The initial dose will be delivered over 90 ± 15 minutes. If the first infusion is tolerated without infusion-associated adverse events (fever and/or chills), the second infusion may be delivered over 60 ± 10 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 ±10 minutes.

If a subject experiences an infusion–associated adverse event, he or she may be premedicated for the next study drug infusion; however, the infusion time may not be decreased for the subsequent infusion. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30 ±10 minutes as long as the subject continues to be premedicated. If a subject experiences an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90 ±15 minutes. Similarly, if a subject experiences an infusion-associated adverse event with the 30-minute infusion, all subsequent doses should be given over 60 ±10 minutes.

3.2.5 Bevacizumab Storage

Upon receipt of the study drug, vials are to be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE. Vials should be protected from light. Opened vials must be used within 8 hours. VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 subject may not be used for any other subject. Once study drug has been added to a bag of sterile saline, the solution must be administered within 8 hours.

3.2.6 Supplier and Drug Accountability

Bevacizumab is commercially available but will be supplied by Genentech free of charge for the study.

The investigator, or an approved representative, e.g. pharmacist, will ensure that all study drugs are stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. All study drug supplies must be kept in a locked

limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the investigator or other site personnel supply study drug to other investigators, patients, or clinics, or allow supplies to be used other than directed by this protocol.

The investigator must maintain adequate records documenting the receipt, use, loss or other deposition of the investigational product, including batch or code numbers, and account for its disposition on patient-by-patient basis, including specific dates and quantity per institutional guidelines. The prescribed dose should also be recorded in the patient's medical records.

Destruction must be adequately documented.

3.3 Erlotinib (Tarceva®)

Erlotinib is an EGFR tyrosine kinase inhibitor that has been investigated in several Phase III studies. An overview of relevant nonclinical and clinical information is presented below; complete details are available in the Erlotinib (Tarceva®) Investigator Brochure.

3.3.1 Non-clinical Data

3.3.1.1 Pharmacology

Erlotinib, a quinazoline, directly and reversibly inhibits the human EGFR tyrosine kinase with an IC_{50} of 2 nM (0.79 ng/mL) in an in vitro enzyme assay and reduces EGFR autophosphorylation in intact tumor cells with an IC_{50} of 20 nM (7.9 ng/mL). This potent inhibition is selective for the EGFR tyrosine kinase both in assays assessing the effects of erlotinib on a variety of other isolated tyrosine kinases and in cellular bioassays designed to isolate this functional pathway. Erlotinib is designed to inhibit EGF-dependent proliferation of cells at submicromolar concentrations and blocks cell cycle progression in the G1 phase.

Data on drug exposure and anti-tumor responses in human tumor xenograft models (HN5 and A431) were analyzed in order to estimate the plasma concentration of erlotinib associated with anti-tumor activity. Based on these efficacy models, the minimum steady-state plasma concentration targeted for clinical activity in humans is projected to be 500 ng/mL.

3.3.1.2 Toxicology

Toxicology studies have been performed in mice, rats (up to 6 months), dogs (up to 1 year), and monkeys (1 week). Treatment-related effects observed in at least one species or study included effects on the cornea (atrophy, ulceration), skin (follicular degeneration and inflammation, redness, and alopecia), ovary (atrophy), liver (necrosis), kidney (papillary necrosis and tubular

dilatation), lacrimal glands (atrophy), salivary glands (atrophy), mandibular lymph nodes (inflammation), spleen (hematopoiesis), gastrointestinal tract (delayed gastric emptying and diarrhea), and embryo-fetal toxicity. Red blood cell parameters were decreased, and white blood cells (primarily neutrophils) were increased. There were treatment-related increases in ALT, AST, triglyceride and bilirubin; and decreases in albumin. Increases in bilirubin were likely caused by a treatment-related impairment of bilirubin metabolism.

3.3.2 Clinical Trial Experience

As of April 2004, erlotinib has been studied clinically in more than 4000 healthy subjects and patients (excluding patients exposed to placebo) in a number of Phase I, II, and III studies.

3.3.2.1 Dose Selection for Single Agent Trials of erlotinib

Phase I trials of erlotinib explored both schedule and dose to evaluate the safety, tolerability, and pharmacokinetic profile of the compound given as a single agent. A number of pharmacokinetic trials in healthy subjects have been conducted, along with three classic Phase I trials in patients with advanced cancer. The single-agent maximum tolerated dose (MTD) was estimated to be 150 mg administered once daily.

The primary toxicities of single-agent erlotinib consisted of rash (dermatosis), diarrhea, nausea, fatigue, stomatitis, vomiting, and headache. When given daily, dose-limiting toxicity (diarrhea) was observed at 200 mg/day. At 150 mg/day, diarrhea was manageable with the addition of loperamide therapy; this dose was considered the maximal tolerated dose.

Rash (variously referred to as dermatitis, acneiform rash, or maculopapular rash) has been variable in onset, duration, and severity, but typically appears on the face, neck, scalp, chest, and back starting after ~1 week of treatment. The mechanistic basis of the rash remains uncertain; histopathologic examination of biopsies of the rash demonstrated inflammatory cell infiltrate and mild epidermal hyperproliferation. In some cases, the rash gradually improved despite continued dosing and, in general, resolved without sequelae following erlotinib discontinuation. The rash did not result in study discontinuation in patients with cancer in the Phase I trials.

Laboratory abnormalities observed infrequently with single-agent erlotinib involved primarily liver function tests, including elevation of ALT, AST, and/or bilirubin.

Selection of the 150 mg/day dose of erlotinib for subsequent single-agent studies was based on pharmacokinetic parameters,

as well as the safety and tolerability profile of this dose in Phase I trials in heavily pretreated patients with advanced cancer. Drug levels seen in patients with cancer receiving the 150 mg/day dose were consistently above the average plasma concentration of 500 ng/mL targeted for clinical efficacy.

3.3.2.2 Pharmacokinetics

Oral erlotinib is well absorbed and has an extended absorption phase, with mean peak plasma levels occurring at 3 hours after oral dosing of 150 mg/dL at steady state. A study in healthy subjects provided an estimate of bioavailability of 59% (95% CI: 55%, 63%). The time to reach steady-state plasma concentration was ~5 days. The accumulation ratio with daily dosing of erlotinib was estimated to be 2.0. From a population pharmacokinetic analysis of 708 patients, the median trough concentration (C_{min}) 24 hours following the previous dose was 1041 ($\pm$697) ng/mL. Median AUC achieved during the dosing interval at steady state was 19,801 ng • hr/mL. Exposure after an oral dose is increased by food.

There is extensive binding of erlotinib and metabolites to both serum albumin and AAG (alpha-1-acid glycoprotein), with total plasma protein binding for erlotinib and OSI-420 of ~95% and 91%, respectively. Erlotinib is extensively metabolized in the liver by the hepatic cytochromes in humans–primarily by CYP3A4 and to a lesser extent by CYP1A2. The primary metabolite of erlotinib, OSI-420, has potency comparable to that of erlotinib, but is present at levels that are $<$ 10% of erlotinib levels. Erlotinib is excreted predominantly via the feces ($>$ 90%). The elimination half-life after a 150-mg oral dose is ~30 hours. In population-based data analyses, no relationships were identified between predicted steady-state trough concentration and patient age, body weight, sex, ethnicity, or creatinine clearance.

3.3.2.3 Phase II and III Trials in Patients with Advanced Breast Cancer

Multiple Phase II trials evaluating the safety, tolerability, and antitumor activity of erlotinib have been conducted in patients with advanced, refractory malignancies including cancer of the head and neck, lung, aerodigestive tract, ovary, breast, central nervous system (glioma), and others. Erlotinib has been evaluated both as a single agent and administered concurrently with conventional chemotherapy agents using various doses and schedules.

Evidence of activity has been observed in squamous cell carcinoma of the head and neck, ovarian, breast and pancreatic carcinoma, non–small cell lung cancer (NSCLC), and glioblastoma multiforme (GBM). Patients received 150 mg/day of erlotinib in all of these studies except the GBM study where dose escalation was

allowed until limited by rash and where a higher starting dose was tested in subjects receiving concomitant enzyme inducing anti-epileptic drugs. Dose reduction was allowed in all studies in the case of intolerance. Diarrhea was treated with loperamide therapy and/or dose reduction. Rash was treated with a variety of agents, including oral and topical antibiotics, corticosteroids, and other agents.

Patients receiving erlotinib in combination with various chemotherapy agents have generally experienced the same type of adverse events (AEs) as with either agent alone.

The first randomized placebo controlled trial to demonstrate a survival advantage for an EGFR inhibitor was the Phase III study, BR21. This international trial, conducted by the National Cancer Institute of Canada Clinical Trial Group (NCIC CTG), included 731 patients with incurable Stage IIIb/IV NSCLC who have failed standard therapy for advanced or metastatic disease. Patients randomized in a 2:1 ratio to single-agent erlotinib 150 mg/day obtained a 42.5% improvement in median survival over placebo, from 4.7 to 6.7 months. The one-year survival increased significantly (from 22% to 31%) as did the median and 6 month PFS, response rate, and the time to deterioration of tumor related symptoms of pain, cough, and dyspnea [63].

In BR-21, of the 727 patients evaluable for safety (485 erlotinib, 242 placebo), the most common AEs in the erlotinib arm were rash (75% erlotinib, 17% placebo), diarrhea (54% erlotinib, 18% placebo) and stomatitis (17% erlotinib, 18% placebo) events. The majority of these events were mild to moderate in severity. The incidence of interstitial lung disease (ILD) reported was the same in the placebo and erlotinib groups at 0.8% in each arm.

Two large, Phase III, randomized studies in first-line NSCLC patients evaluated erlotinib in combination with platinum-based two-drug combination chemotherapy. A total of 1079 previously untreated patients received carboplatin/paclitaxel with either erlotinib or placebo in the TRIBUTE trial (OSI2298g) conducted in the United States. An additional 1172 patients received cisplatin/gemcitabine plus either erlotinib or placebo in the TALENT trial (BO16411) conducted in 27 countries in Europe and other ex-U.S. locations. Neither study met its primary endpoint of improved overall survival or a secondary endpoint of improved time to disease progression or overall response rate. Overall, the number of adverse events and serious adverse events were well balanced between the two arms of each study, with two exceptions. As expected, rash and diarrhea occurred more frequently in the erlotinib arms. In the TRIBUTE study, more serious adverse events resulting in death were seen in the erlotinib arm compared with the placebo arm (53 vs. 27). Most of

the apparent imbalance was due to events reported as pneumonia or progression of underlying cancer [36].

3.3.2.4 Patients with Hepatic or Renal Impairment

The influence of hepatic metastases and/or hepatic dysfunction on the pharmacokinetics of erlotinib is not yet known. However, erlotinib is cleared predominately by the liver, and caution should be used when administering erlotinib to patients with hepatic dysfunction. Erlotinib is also a strong inhibitor of the UDP-glucuronosyltransferase UGT1A1 enzyme responsible for the glucuronidation of bilirubin. Hyperbilirubinemia appears most often to be a side effect related to genetic polymorphisms of UGT1A1. Rare cases of hepatic failure (including fatalities) have been reported during the postmarketing use of erlotinib. Confounding factors for severe hepatic dysfunction have included pre-existing liver disease such as cirrhosis, viral hepatitis, hepatocellular carcinoma, hepatic metastases or concomitant treatment with potentially hepatotoxic drugs.

Rare cases of myocardial infarction (including fatalities) have been reported during the postmarketing use of erlotinib.

No clinical studies have been conducted in patients with compromised renal function since erlotinib and its metabolites are not significantly excreted by the kidneys.

3.3.3 Adverse Event Using Erlotinib

Common adverse events associated with erlotinib administration include rash and diarrhea. Other common adverse events include nausea/vomiting, mucositis/stomatitis, headache, and fatigue.

A rash occurred in 75% of erlotinib-treated NSCLC patients enrolled in BR.21. Similar incidences of rash have occurred when erlotinib was administered concurrently with chemotherapy including gemcitabine, paclitaxel/carboplatin and gemcitabine/cisplatin. Other dermatologic manifestations reported in clinical studies or postmarketing use of erlotinib include nail changes, paronychia, painful fissures or cracking of the skin on the hands and feet and hair growth abnormalities (alopecia, thinning hair, eyelash/eyebrow changes, hirsutism). A pustular rash manifesting most often on the face and upper trunk was common across all studies, but rash was rarely the cause of study drug discontinuation. Wearing of contact lenses while receiving erlotinib therapy is not recommended. The incidence of diarrhea in BR.21 was 54% of erlotinib-treated NSCLC patients. The median time to onset of skin rash was 8 days and median time to occurrence of first diarrheal symptom was 9 days.

There have been infrequent reports of serious (including fatal) interstitial lung disease (ILD) in patients receiving erlotinib for treatment of NSCLC

or other advanced solid tumors. In Study BR.21, the incidence of ILD (0.8%) was the same in the placebo and erlotinib groups. The overall incidence in erlotinib-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) is approximately 0.6%. Included in this rate of ILD are reported diagnoses of pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, acute respiratory distress syndrome, alveolitis, and lung infiltration, irrespective of investigator assessed causality. Most of the cases were associated with confounding or contributing factors such as concomitant/prior chemotherapy, prior radiotherapy, preexisting parenchymal lung disease, metastatic lung disease, or pulmonary infections.

Rare cases of acute renal failure or renal insufficiency have been reported (including fatalities). Many of these cases have been associated with dehydration associated with nausea, vomiting, diarrhea and/or anorexia. There have been rare reports of renal failure in patients receiving erlotinib in combination with platinum-containing chemotherapy regimens. Febrile neutropenia has been reported in patients receiving concomitant chemotherapy.

Co-administration of erlotinib with omeprazole, a proton pump inhibitor, decreased the exposure of erlotinib (AUC) by 46% and the maximum concentration (C_{max}) by 61%. There was no change to Tmax or half-life. Therefore, drugs that alter the pH of the GI tract may alter the solubility of erlotinib and hence its bioavailability.

The exposure to erlotinib (AUC) increased to a moderate extent, by 39%, and the maximum concentration (C_{max}) by 17%, when erlotinib was co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2.

Co-administration of erlotinib with an inhibitor of CYP3A4 metabolism (ketoconazole, 200 mg po BID for 5 days) resulted in increased exposure to erlotinib as measured by an 86% increase in median erlotinib AUC and a 69% increase C_{max}, compared with administration of erlotinib alone.

Induction of CYP3A4 metabolism by a known enzyme inducer (rifampin, 600 mg po QD for 7 days) resulted in a 69% decrease in the median erlotinib AUC, compared with administration of erlotinib alone. However, the effect of rifampin on C_{max} was negligible. In another study, rifampicin pretreatment followed by co-administration of rifampicin with a single 450 mg dose of erlotinib resulted in a mean erlotinib exposure (AUC) that was 57.6% of that observed following a single 150 mg erlotinib dose in the absence of rifampicin treatment. Therefore, a potential for drug-drug interaction exists when erlotinib is co-administered with drugs that are highly protein bound or that are potent CYP3A4 inhibitors or inducers.

International normalized ratio (INR) elevations and/or bleeding events have been reported in some cancer patients while on erlotinib alone and

in combination with other chemotherapeutic agents, and concomitant NSAIDS or anticoagulants including warfarin.

3.3.4 General Plan to Manage Safety Concerns

Skin toxicities will be monitored by routine physical examination and managed symptomatically. The following agents may be used to treat rash: diphenhydramine, topical or oral corticosteroids and topical (clindamycin) or oral antibiotics (tetracycline, minocycline, doxycycline). Topical drying agents are not recommended.

Liver function abnormalities, including elevated serum ALT, AST and/or bilirubin, have been observed infrequently with single agent erlotinib and occasionally with erlotinib in combination with concomitant chemotherapy. Periodic monitoring of liver function is recommended. Erlotinib dosing should be interrupted if changes in liver function are severe.

Women of childbearing potential should have a negative pregnancy test prior to starting therapy with erlotinib and should use adequate contraceptive methods during and for at least 2 weeks after erlotinib therapy. Treatment should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the fetus. If erlotinib is used during pregnancy, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

It is not known whether erlotinib is excreted in human breast milk. Because many drugs are excreted in human milk and because the effects of erlotinib on infants have not been studied, women should be advised against breast-feeding while receiving erlotinib therapy.

3.3.5 Supplier and Drug Accountability

Erlotinib is commercially available but will be supplied by Genentech free of charge for the study.

The investigator, or an approved representative, e.g. pharmacist, will ensure that all study drugs are stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. All study drug supplies must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the investigator or other site personnel supply study drug to other investigators, patients, or clinics, or allow supplies to be used other than directed by this protocol.

The investigator must maintain adequate records documenting the receipt, use, loss or other deposition of the investigational product, including batch or code numbers, and account for its disposition on patient-by-patient basis, including specific dates and quantity per institutional guidelines. The prescribed dose should also be recorded in the patient’s medical records.

Destruction must be adequately documented.

4.0 STAGING CRITERIA

4.1 Definition of TNM

Primary Tumor (T)

Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. The *telescoping* method of classification can be applied. If the measurement is made by physical exam, the examiner will use the major headings (T1, T2). If other measurements, such as mammographic or pathologic, are used, the telescoped subsets of T1 can be used.*

T1 Tumor 2 cm of less in greatest dimension

- T1a 0.5 cm or less in greatest dimension
- T1b More than 0.5 but not more than 1 cm in greatest dimension
- T1c More than 1 cm but not more than 2 cm in greatest dimension

T2 Tumor more than 2 cm but not more than 5 cm in greatest dimension

T3 Tumor more than 5 cm in greatest dimension

T4 Tumor of any size with direct extension to the chest wall or skin

- T4a Extension to the chest wall†
- T4b Edema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
- T4c Both (T4a and T4b)
- T4d Inflammatory carcinoma

*Note: Paget's disease associated with a tumor is classified according to the size of the tumor.

†Note: Chest wall includes ribs, intercostal muscles and serratus anterior muscle but not pectoral muscle

Regional Lymph Nodes (N)

N0 No regional lymph node metastasis

N1 Metastasis to movable ipsilateral axillary lymph node(s)

N2 Metastasis in ipsilateral axillary lymph nodes(s) fixed or matted, or in clinically apparent* ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastasis.

- N2a Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures.

N2b Metastasis only in clinically apparent* ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastasis

N3 Metastasis in ipsilateral infraclavicular lymph node(s), with or without axillary node involvement, or in clinically apparent* ipsilateral internal mammary lymph nodes in the *presence* of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s), with or without axillary or internal mammary lymph node involvement.

N3a Metastasis in ipsilateral infraclavicular lymph node(s).
N3b Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s).
N3c Metastasis in ipsilateral supraclavicular lymph node(s).

Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.

Distant Metastasis (M)

Clinical history and routine imaging studies including CT chest, abdomen and bone scan will be obtained prior to protocol therapy to assess for presence of distant metastasis prior to initiation of protocol therapy.

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

4.2 Stage Groupings

Stage I	T1	N0	M0
Stage IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1, N2	M0

Stage IIIB	T4	N0, N1, N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

5.0 ELIGIBILITY CRITERIA

5.1 Patients must meet the following criteria to be included:

5.1.1 Have histologically confirmed invasive breast cancer that is ER negative (≤10%), PR negative (≤ 10%) and HER-2 normal (≤ 10% of cells) by IHC or FISH.

5.1.2 Be receiving first-line therapy for metastatic disease.

5.1.3 Patients must satisfy *either* 5.1.3.1 or 5.1.3.2:

5.1.3.1 Measurable disease by RECIST criteria (see Section 10.1.1). X-rays, scans or physical examinations used for tumor measurement must have been completed within 28 days prior to registration. X-rays, scans or other tests for assessment of non-measurable disease must have been performed within 42 days prior to registration.

5.1.3.2 Non-measurable disease only (see Section 10.1.2), with rising serum CA15-3 or CA 27.29 or CEA documented by two consecutive measurements taken at least 14 days apart with the most recent measurement being within 42 days prior to registration. The second CA 15-3 or CA 27.29 or CEA value must have at least a 20% increase over the first and for CA 15-3 or CA 27.29 be greater than or equal to 40 units/mL or for CEA be greater than or equal to 4 ng/mL.

5.1.4 Subjects with brain metastases as their first site of disease recurrence may be eligible if treated by definitive radiation (stereotactic radiosurgery or whole brain) with clinically controlled neurologic symptoms for a period of 21 days prior to study treatment.

5.1.5 Bilirubin ≤ 1.5 mg/dL

5.1.6 Patients must have adequate liver function: AST and ALT ≤ 2.5 X upper limit of normal, alkaline phosphatase ≤ 2.5 X upper limit of normal, unless bone metastasis is present in the absence of liver metastasis

5.1.7 Patients must have adequate bone marrow function: Platelets >100,000 cells/mm^3, hemoglobin > 9.0g/dL and ANC ≥ 1,500 cells/mm^3

5.1.8 Patients must have adequate renal function: creatinine ≤1.5 mg/dL is recommended; however, institutional norms are acceptable.

5.1.9 If of childbearing potential must have a negative pregnancy test and use an effective method to avoid pregnancy for the duration of the trial and for at least 6 months after completion of study therapy.

5.1.10 Pre-existing peripheral neuropathy, if present, must be < grade 2 (per CTCAE Version 3.0)

5.1.11 Patients must be informed of the investigational nature of this study and must sign and give informed consent in accordance with institutional standards and federal guidelines.

5.2 Patients who fulfill any of the following criteria will be excluded:

5.2.1 Recurrent disease within 12 months after completion of adjuvant chemotherapy containing a weekly taxane.

5.2.2 CNS metastases that are symptomatic and/or requiring steroids.

5.2.3 Pre-existing nephritic syndrome.

5.2.4 Serious intercurrent medical or psychiatric illness including serious active infection.

5.2.5 Inadequately controlled hypertension (defined as systolic blood pressure >150 and/or diastolic blood pressure > 100 mmHg on antihypertensive medications).

5.2.6 Any prior history of hypertensive crisis or hypertensive encephalopathy.

5.2.7 New York Heart Association (NYHA) rgade II or greater congestive heart failure (see Appendices).

5.2.8 History of myocardial infarction or unstable angina within 6 months prior to study enrollment.

5.2.9 History of stroke or transient ischemic attack within 6 months prior to study enrollment.

5.2.10 Significant vascular disease (e.g., aortic aneurysm, aortic dissection).

5.2.11 Symptomatic peripheral vascular disease.

5.2.12 Evidence of bleeding diathesis or coagulopathy.

5.2.13 Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to study enrollment or anticipation of need for major surgical procedure during the course of the study.

5.2.14 Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to study enrollment.

5.2.15 History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to study enrollment.

5.2.16 Serious, non-healing wound, ulcer, or bone fracture.

5.2.17 Proteinuria at screening as demonstrated by either

- Urine protein:creatinine (UPC) ratio $\geq$ 1.0 at screening OR

- Urine dipstick for proteinuria > 2+ (patients discovered to have > 2+ proteinuria on dipstick urinalysis at baseline must have a UPC ratio done that is <1.0 to be eligible. If the UPC ratio is ≥ 1.0 then the patient should undergo a 24-hour urine collection which must demonstrate ≤ 1g of protein in 24 hours for the patient to be eligible.)

5.2.18 Known hypersensitivity to any component of bevacizumab or to nab-paclitaxel.

6.0 STRATIFICATION FACTORS

There is no stratification.

7.0 TREATMENT PLAN

For protocol related questions, please contact Dr. Jennifer Specht at (206) 288-6889 (e-mail: jspecht@u.washington.edu).

A number of measures will be taken to ensure the safety of patients participating in this trial. These measures will be addressed through routine monitoring as follows.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements. Patients will be evaluated for adverse events (severity grade 2 or greater), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study. Patients discontinued from the treatment phase of the study for any reason will be evaluated ~30 days (28–42 days) after the decision to discontinue treatment.

7.1 Good Medical Practice

The following pre-study tests should be obtained prior to registration in accordance with good medical practice. Results of these tests do not determine eligibility and minor deviation are acceptable if they do not impact on patient safety in the clinical judgment of the treating physician. Dr. Specht must be contacted if there are significant deviations in the values of these tests.

a. Patients should have normal left ventricular ejection fraction by MUGA or transthoracic echocardiogram at study entry. Reassessment is required only if clinical symptoms arise.

7.2 Induction Therapy: Nab-Paclitaxel and Bevacizumab

In this single-arm, phase II trial, patients will receive induction therapy with nab-paclitaxel 100 mg/m^2 IV days 1, 8 and 15 and bevacizumab 10 mg/kg IV days 1 and 15 of each 28 day cycle for 6 cycles. All attempts should be made to maintain treatment schedule; however, deviation in weekly treatment + or – one

day is permitted. Patients who develop toxicity and require discontinuation of nab-paclitaxel prior to completing all six cycles of induction and who have evidence of disease response or stability may transition to maintenance therapy after a discussion between the treating physician and the principal investigator.

Induction Therapy:				
DRUG	***DOSE***	***FREQUENCY***	***# of DOSES***	***Route of Administration***
Nab-Paclitaxel	100 mg/m^2	Days 1, 8, and 15 of each 28 day cycle	18 doses	IV
Bevacizumab	10 mg/kg	Days 1 and 15 of each 28 day cycle	12 doses	IV

Patients do not require premedication prior to nab-paclitaxel administration, as hypersensitivity reactions are not expected. In the unlikely event of a hypersensitivity reaction, premedication may be administered using the premedication regimen the institution typically uses for paclitaxel.

If patients on treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4-8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin/restart bevacizumab until 4 weeks after that procedure (in the case of high risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 weeks and bevacizumab no earlier than 8 weeks after surgery).

Dose modifications for adverse events are allowed as described in Sections 8.1, 8.2 and 8.3. Treatment is continued until disease progression or other reason for termination of study therapy (Section 7.4).

7.3 Maintenance Therapy

At the completion of induction chemotherapy, nab-paclitaxel will be discontinued, and patients with CR, PR, SD will remain on study and receive combined, targeted “maintenance” therapy with bevacizumab 10 mg/kg IV Q 14 days or 15 mg/kg Q 21 days and erlotinib 150 mg PO daily until disease progression or unacceptable toxicity. The choice of dosing schedules for bevacizumab (Q14 days or Q21 days) during the maintenance period is at the discretion of the treating physician and allowed to accommodate flexibility for patients.

Maintenance Therapy For patients with CR, PR or stable disease following induction therapy:				
DRUG	***DOSE***	***FREQUENCY***	***# of DOSES***	***Route of Administration***
Bevacizumab	10 mg/kg or 15 mg/kg	Q 14 days or Q 21 days	Until progression	IV

Erlotinib	150 mg	daily	Until progression	PO

Patients who develop toxicity and require discontinuation of bevacizumab or erlotinib and who continue to have evidence of disease response or stability may continue maintenance therapy after a discussion between the treating physician and the principal investigator.

Erlotinib will be self-administered in an open-label, unblinded manner to all patients enrolled in the study. During the treatment period, patients will receive erlotinib 150 mg/day. Tablets should be taken at the same time each day with 200 mL of water at least 1 hour before or 2 hours after a meal. Patients who are unable to swallow tablets may dissolve the tablets in distilled water for administration.

Erlotinib tablets will be supplied in white, high-density polyethylene (HDPE) bottles with child-resistant closures and should be stored at temperatures between 15°C and 30°C (59°F and 86°F).

Dose reductions for adverse events will be permitted (see Sections 8.3 and 8.4). Treatment is continued daily until disease progression or other reason for termination of study therapy (see Section 7.4).

If patients on treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4-8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin/restart bevacizumab until 4 weeks after that procedure (in the case of high risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that bevacizumab be restarted no earlier than 8 weeks after surgery).

7.4 Criteria For Removal From Protocol Treatment

Patients have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study in the event of intercurrent illness, treatment related toxicity, treatment failure, protocol violations, administrative reasons or other reasons.

Should a patient decide to withdraw prematurely, all efforts will be made to complete and report the end of treatment observations as thoroughly as possible.

Subjects will be removed from protocol treatment for the following reasons:

- Progressive disease.
- Inability of subject to comply with study requirements.
- Pregnancy.
- Patient wishes.
- Physician discretion.
- Nephrotic syndrome.
- Gastrointestinal perforation.
- Clinically significant deterioration of the patient’s condition.

- Wound dehiscence requiring surgical intervention.
- Any grade arterial thromboembolic event.
- Grade ≥ 2 pulmonary or CNS hemorrhage; any Grade 4 hemorrhage.
- Persistent (≥ 3 weeks) NCI-CTCAE version 3.0 Grade 3 or Grade 4 adverse event or any significant adverse event that compromises the patient's ability to participate in the study.
- Symptomatic Grade 4 venous thromboembolic event.
- Grade 4 hypertension or reversible posterior leukoencephalopathy syndrome (RPLS).
- Grade 4 congestive heart failure.
- All Grade 4 events thought to be related to nab-paclitaxel, bevacizumab or erlotinib by the investigator.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 The following general principles apply in all cases.

8.1.1 This study will use the NCI CTC (Common Terminology Criteria) Version 3.0 for treatment related toxicity and adverse event reporting. A copy of the CTC Version 3.0 can be down loaded from the CTEP home page (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

8.1.2 Dose adjustments are to be made according to the system showing the greatest degree of treatment related toxicity.

8.1.3 For any event present at baseline, the dose modification will apply according to the corresponding shift in toxicity grade if the investigator feels it is appropriate (e.g. if a patient has a grade 1 asthenia at baseline which increases to grade 2 during treatment, this will be considered a shift of 1 grade and treated as a grade 1 treatment related toxicity for dose modification purposes).

8.1.4 If in the opinion of the Investigator, a specific treatment related toxicity is considered solely due to one drug, dose modification of the other drug is not required.

8.1.5 For treatment related toxicities which are considered by the Investigator unlikely to develop into serious or life-threatening events (e.g. alopecia, altered taste, etc.), treatment will be continued at the same dose without reduction or interruption. In addition, no dose reductions or interruptions will be required for anemia as it can be satisfactorily managed by transfusions or erythropoietic growth factors.

8.1.6 Patients will be evaluated for adverse events at each study visit for the duration of their participation in the study and for 30 days after the discontinuation.

8.2 Dose Modifications – Nab-Paclitaxel

Use the table below to determine a patient's dose:

Dose Modification Table

Dose Level	Nab-Paclitaxel (mg/m^2)
0	100
-1	80
-2	65

8.2.1 Abnormal Hematologic Function

Nab-paclitaxel dosing should not begin unless the absolute neutrophil count is $\geq$ 1500 cells/mm^3 and the platelet count is >100,000 cells/mm^3. For each subsequent dose of nab-paclitaxel patients must have an ANC $\geq$ 1000 cells/mm^3 and platelets $\geq$ 75,000 cells/mm^3. If the ANC or platelets are not adequate for treatment, the dose is to be omitted. If the dose is omitted for ANC < 1000 cells/mm^3 institute G-CSF as outlined in the table below.

8.2.2 Dose Reductions and Use of Growth Factors for Hematologic Toxicity

The table below provides a recommended guideline for implementing dose reductions and growth factor treatment for hematologic toxicity:

Use of G-CSF and Dose reductions for Hematologic Toxicity

Adverse Event	**Occurrence**	**Action to be Taken**
Neutropenia (ANC < 1000 cells/mm^3).	1st Occurrence	Nab-paclitaxel is held and G-CSF is started. Nab-paclitaxel dose is maintained when ANC recovers to $\geq$ 1000 cells/mm^3. Prophylactic antibiotics may be given at physician's discretion in the setting of ANC < 500 or neutropenic fever.
	Recurrence	In the event that neutropenia (ANC < 1000 cells/mm^3) re-occurs in the face of G-CSF, dose reduction to the next lower level will be required for subsequent doses once ANC is $\geq$ 1000 cells/mm^3.
Thrombocytopenia Grade 3 (platelet count at least 25,000 but less than 50,000/mm^3) or Grade 4 (platelet count <25,000)	1st Occurrence	Dose reduction to next lower level
	Recurrence	Dose reduction to next lower level

8.2.3 G-CSF Administration: should be given according to NCCN guidelines and the treating physician's clinical judgment. When G-CSF is given with

weekly nab-paclitaxel it should begin the day after the nab-paclitaxel is given.

8.2.4 Abnormal Hepatic Function

Nab-paclitaxel should not begin unless AST and ALT $\leq$ 2.5 x upper limit of normal and alkaline phosphatase $\leq$ 2.5 x upper limit of normal, unless bone metastasis is present in the absence of liver metastasis, and bilirubin $\leq$ 1.5 mg/dL. 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.

8.2.5 Sensory Neuropathy

Nab-paclitaxel should be withheld in patients who experience $\geq$ Grade 2 sensory neuropathy. Treatment may be resumed at the next lower dose level (see Dose Modification Table in Section 8.2 above) in subsequent cycles after the sensory neuropathy improves to $\leq$ Grade 1. In those patients who experience Grade 4 sensory neuropathy, study drug should be withheld, and treatment resumed at a reduction of 2 dose levels (Dose Modification Table in Section 8.2) in subsequent cycles after the sensory neuropathy improves to $\leq$ Grade 1.

8.2.6 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 a severe hypersensitivity reaction to nab-paclitaxel should not be re-challenged.

8.2.7 Other Toxicities

If toxicities are $\leq$ grade 2, manage symptomatically if possible, and retreat without dose reduction.

If toxicities are $\geq$ grade 3, except for anemia, treatment should be withheld until resolution to $\leq$ grade 1 or baseline if baseline was greater than grade 1, then reinstituted, if medically appropriate, at the next lower dose level (see Dose Modification Table in Section 8.2 above).

8.3 Dose Modifications – Bevacizumab

There are no reductions in the bevacizumab dose. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes.

Any toxicities associated or possibly associated with bevacizumab treatment should be managed according to standard medical practice. Bevacizumab has a terminal half-life of 2 to 3 weeks; therefore, its discontinuation results in slow elimination over several months. There is no available antidote for bevacizumab. Subjects should be assessed clinically for toxicity prior to, during, and after each infusion. If unmanageable toxicity occurs because of bevacizumab at any time during the study, treatment with bevacizumab should be discontinued.

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

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

Adverse events requiring delays or permanent discontinuation of bevacizumab are listed in the table below. Regardless of the reason for holding study drug treatment, the maximum allowable length of treatment interruption is 2 months.

Bevacizumab Dose Management Due to Adverse Events

Event	Action to be Taken
Hypertension	
Grade 3	At treating physician's discretion, treatment may be held for a maximum duration of two months. If not controlled to 150/100 mmHg with medication, discontinue bevacizumab.
Grade 4 (including RPLS (confirmed by MRI) or hypertensive encephalopathy)	Discontinue bevacizumab.
Hemorrhage	
Grade ≥ 2 pulmonary or CNS hemorrhage	Discontinue bevacizumab.
Grade 3 nonpulmonary and non-CNS hemorrhage	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have study treatment held until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. Subjects who experience a repeat Grade 3 hemorrhagic event will be discontinued from receiving bevacizumab.
Grade 4	Discontinue bevacizumab.
Venous Thrombosis	
Grade 3/ Asymptomatic Grade 4	Hold study drug treatment. If the planned duration of full-dose anticoagulation is <2 weeks, study drug should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is >2 weeks, study drug may be resumed during the period of full-dose anticoagulation if all of the following criteria are met: • The subject must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin (or other anticoagulant) prior to restarting study drug treatment. • The subject must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation. • The subject must not have had evidence of tumor involving major blood vessels on any prior CT scan.
Symptomatic Grade 4	Discontinue bevacizumab.

Bevacizumab Dose Management due to Adverse Events (continued)	
Arterial Thromboembolic event (Angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event)	
Any grade	Discontinue bevacizumab.
Congestive Heart Failure (Left ventricular systolic dysfunction)	
Grade 3	Hold bevacizumab until resolution to Grade ≤ 1.
Grade 4	Discontinue bevacizumab.
Proteinuria should be monitored by urine dipstick or urine protein creatinine (UPC) ratio every 8 weeks. If dip is >2+ then a UPC ratio should be performed	
Grade 3 (UPC ≥ 3.5)	Hold bevacizumab treatment until UPC recovers to < 3.5
Grade 4 (nephrotic syndrome)	Discontinue bevacizumab
GI Perforation	Discontinue bevacizumab.
Bowel Obstruction	
Grade 1	Continue patient on study for partial obstruction NOT requiring medical intervention.
Grade 2	Hold bevacizumab for partial obstruction requiring medical intervention. Patient may restart upon complete resolution.
Grade 3/4	Hold bevacizumab for complete obstruction. If surgery is necessary, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion.
Wound dehiscence requiring surgical therapy	Discontinue bevacizumab.
Other Unspecified Bevacizumab-Related Adverse Events	
Grade 3	Hold bevacizumab until recovery to ≤ Grade 1
Grade 4	Discontinue bevacizumab.

8.4 Dose Modifications – Erlotinib

Skin toxicities will be monitored by routine physical examination and managed symptomatically. Because secondary bacterial infections are common and can lead to more serious complications, topical or systemic antibiotics may be considered. Anecdotally, topical or a short course of systemic corticosteroids can be helpful. See tables below for management guidelines, including erlotinib dose reduction/interruption.

Management of a tolerable Grade 2 or 3 rash should include continuation of erlotinib at the current dose and symptomatic management. If skin rash is intolerable, dose reduction according to the table below should be considered. When skin toxicity improves by at least one grade level, the dose may be re-escalated as tolerated. In Phase II trials, this approach enabled dose re-escalation for the majority of patients requiring dose reduction for skin toxicity. Patients experiencing Grade 4 skin toxicity should be discontinued from study treatment.

Diarrhea will be monitored and managed symptomatically. Guidelines for management include administration of loperamide and erlotinib dose reduction/interruption as described in the tables below.

For Grade 1 or 2 diarrhea, early intervention should include continuation of erlotinib at the current dose and initiation of loperamide therapy as described in in the table below**.** Grade 2 diarrhea that persists over 48–72 hours, despite optimal medical management, should be managed by dose reduction as specified in the tables below**.** Patients experiencing Grade 3 diarrhea should interrupt erlotinib until resolution to Grade ≤1 and re-start at a reduced dose as described in the table below. Patients should be maintained at the reduced dose without attempt at dose re-escalation. Patients experiencing Grade 4 diarrhea should be discontinued from erlotinib.

Although quite rare, interstitial lung disease (ILD) can be life threatening. Therefore, patients should be monitored closely for symptoms consistent with ILD, such as new onset dyspnea without an obvious cause. In the event that ILD is suspected, erlotinib treatment should be discontinued and the patient should receive appropriate medical management. Although there is no proven therapy, systemic corticosteroids are often provided. Erlotinib should not be restarted in those patients suspected of having drug-related ILD. See tables below for management guidelines, including erlotinib dose interruption.

Erlotinib should not be restarted in those suspected of having drug-related ILD.

If a patient becomes pregnant despite contraceptive precautions, she should be apprised of the potential risk of fetal morbidity or loss.

Dose reduction or interruption of erlotinib for toxicity may take place at any time during the study. Dose level reductions are presented in the table below. If patients do not tolerate the second dose reduction, erlotinib is to be discontinued.

Erlotinib Dose Level Reductions		
Starting Dose	First Reduction	Second Reduction
150 mg/day	100 mg/day	50 mg/day

Dosage Modifications and Management Guidelines for Erlotinib-Related Toxicities

NCI-CTCAE (v 3.0) Grade	Erlotinib Dose Modification	Guideline for Management
Diarrhea		
Grade 1	None	Consider loperamide (4 mg at first onset, followed by 2 mg q 2–4 hours until free of diarrhea for 12 hours)
Grade 2	None (Dose reduction of erlotinib is necessary if diarrhea persists over 48–72 hours despite optimal medical management)	Loperamide (4 mg at first onset, followed by 2 mg q 2–4 hours until diarrhea free for 12 hours)
Grade 3	Interrupt then dose reduce erlotinib. Erlotinib should not be re-escalated.	Interrupt erlotinib until resolution to Grade $\leq$1, and restart at next reduced dose
Grade 4	Discontinue study treatment.	
Pulmonary Events if possibly ILD		
All Grades	Temporarily interrupt erlotinib pending the diagnostic evaluation. If the pulmonary adverse event is assessed as related to erlotinib, discontinue the patient from study treatment.	Unexplained dyspnea, either new or progressive, should be aggressively evaluated.
Rash		
Grade 1 and 2 Tolerable rash	None	Any of the following: oral antibiotics (tetracycline, minocycline, doxycycline), topical clindamycin, diphenhydramine, topical or oral corticosteroids at discretion of investigator
Grade 3 Intolerable rash	Consider interruption and or dose reduction if unresponsive to symptomatic management. Re-escalation is allowed.	Manage as described above
Grade 4	Discontinue erlotinib.	Manage as described above

8.5 Concomitant Medications

Irradiation is not allowed during the study. Administration of other chemotherapy, immunotherapy, or anti-tumor hormonal therapy during the study is not allowed. Use of concurrent investigational agents is not permitted. Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the Investigator. Concurrent treatment with bisphosphonates is allowed. All concomitant treatments, including blood and blood products, must be reported on the case report form. Erythropoietin may be administered at the discretion of the investigator, consistent with institutional guidelines. G-CSF should be administered according to the guidelines in this protocol.

Low-dose aspirin (≤ 325 mg/d) may be continued in subjects at higher risk for arterial thromboembolic disease. Subjects developing signs of arterial ischemia or bleeding on study should be evaluated for possible bevacizumab discontinuation per Table 1, Bevacizumab Dose Management Due To Adverse Events.

There are potential interactions between both nab-paclitaxel and erlotinib and CYP3A4 inhibitors and CYP3A4 promoters. Although caution and careful monitoring are recommended when use of these compounds is necessary, use of these compounds does not exclude patients from participating in this trial (see Appendices for a list of CYP3A4 inhibitors and inducers).

Grapefruit juice is a CYP3A4 inhibitor, therefore, consumption of grapefruit or grapefruit juice should be avoided during nab-paclitaxel and erlotinib treatment.

The solubility of erlotinib is pH dependent. Erlotinib solubility decreases as pH increases. Co-administration of erlotinib with omeprazole, a proton pump inhibitor, decreased the exposure of erlotinib (AUC) by 46% and the maximum concentration (C_{max}) by 61%. There was no change to Tmax or half-life. Therefore, drugs that alter the pH of the GI tract may alter the solubility of erlotinib and hence its bioavailability.

The exposure to erlotinib (AUC) increased to a moderate extent, by 39%, and the maximum concentration (C_{max}) by 17%, when erlotinib was co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2.

Erlotinib clearance can be induced by smoking via CYP1A2 induction. Potential drug-drug interaction is expected when erlotinib is taken with CYP1A2 inducers or inhibitors. In a single-dose study in healthy volunteers, the AUC was reduced by 64% in smokers when compared with nonsmokers. In BR.21, current smokers achieved erlotinib trough plasma concentrations that were approximately 2-fold lower than never smokers. Smokers should be advised to stop smoking while taking erlotinib as plasma concentrations of erlotinib are reduced due to the effect of cigarette smoking.

Pretreatment or co-administration of erlotinib did not alter the clearance of a prototypical CYP3A4 substrate, midazolam. Therefore, significant metabolic interactions with other CYP3A4 substrates are unlikely. However, the oral bioavailability of midazolam decreased by up to 24% following erlotinib treatment, which was not attributed to a metabolic interaction.

Patients taking warfarin or other warfarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR.

9.0 Study Calendar

Required Procedures	Pre-study	Induction				Maintenance				Follow up[9]
		Weeks 1, 2 & 3	Every 2 Weeks	Monthly	Every 8 Weeks	Daily	Each Bevacizumab Infusion	Monthly	Every 8 Weeks	
Vital Signs	X		X				X			X
Blood Pressure[1]			X[1]				X[1]			X[1]
Clinic Visit	X			X	X			X		X
Adverse Event Notation	X			X	X			X		X
Disease Assessment	X				X				X	
LABORATORY										
CBC/ANC/Platelets	X	X						X		X
Metabolic Panel[2]	X			X				X		X
AST/ALT	X			X				X		X
Alkaline Phosphatase	X			X				X		X
Bilirubin	X			X				X		X
CEA and CA 27.29 or CEA and CA 15-3	X				X				X	X
Pregnancy Test[3]	X									
Assessment for Proteinuria[4]	X				X				X	
IMAGING										
X-rays/scans if required for disease assessment	X				X				X	X
MUGA/Echocardiogram	X[5]									
RESEARCH SPECIMENS										
CEC	X			X[6]				X[7]		
CTC	X			X[6]				X[7]		
EGFR/SPARC	X									

TREATMENT										
Nab-Paclitaxel		X[8]								
Bevacizumab			X				X			
Erlotinib						X				

[1] Hypertension will be monitored through evaluation of blood pressure prior to each bevacizumab treatment. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on bevacizumab.

[2] Basic Metabolic Panel includes sodium, potassium, chloride, glucose, BUN, creatinine and calcium.

[3] Women of childbearing potential only.

[4] Urine should be assessed via dipstick or random urine creatinine and protein every 8 weeks. If dipstick is >2+, then a UPC ratio should be performed. See appendices for instructions for calculating the ratio. During screening if UPC $\geq$ 1.0, patient should undergo a 24-hour urine collection which must demonstrate $\leq$ 1g of protein in 24 hours for patient to be eligible. During study treatment if dipstick or UPC demonstrates proteinuria, see table on page 37 for instructions for holding or discontinuing bevacizumab due to proteinuria.

[5] Assessment of left ventricular ejection fraction by MUGA or transthoracic echocardiogram at study entry is considered good medical practice. Reassessment is only required if clinical symptoms arise.

[6] Prior to weeks 5 and 17 of nab-paclitaxel and bevacizumab and at time of disease progression. If the patient is removed from protocol treatment for reasons other than disease progression, CTC and CEC assays do not need to be done at the time of disease progression.

[7] Prior to weeks 1 and 9 of bevacizumab and erlotinib and at time of disease progression. If the patient is removed from protocol treatment for reasons other than disease progression, CTC and CEC assays do not need to be done at the time of disease progression.

[8] Days 1, 8 and 15 of each 28 day cycle

[9] Follow up per physician discretion. Patients with on-going treatment related grade 4 or serious adverse event at the time of discontinuation from study treatment will continue to be followed until resolution of the event or until event is considered irreversible.

10.0 CRITERIA FOR EVALUATION AND END POINT DEFINITIONS

10.1 Measurability of Lesions

10.1.1 **Measurable Disease:** Lesions that can be accurately measured in at least one dimension by 1) medical photograph (skin or oral lesion), palpation, plain x-ray, CT, MRI or other conventional technique with longest diameter 2 cm or greater in the axial plane (bone lesions not included) or 2) spiral CT scan with longest diameter 1 cm or greater. Ultrasound is suitable only for superficial disease (superficial palpable nodes, subcutaneous lesions, thyroid nodules).

Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

10.1.2 **Non-measurable disease**: All other lesions including lesions too small to be considered measurable, pleural or pericardial effusions, ascites, bone disease, inflammatory breast disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed and followed by imaging techniques, cystic lesions or disease documented by indirect evidence only (e.g. lab values), previously radiated lesions that have not progressed.

10.2 **Objective Status at Each Evaluation**: Objective status is to be reported at each evaluation. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. All measurable lesions not identified as target lesions are non-target lesions and are included as non-measurable disease. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable lesions.

10.2.1 **Complete Response (CR)**: Complete disappearance of all measurable and non-measurable disease. No new lesions. No disease related symptoms. Normalization of markers and other abnormal lab values. All disease must be assessed using the same technique as baseline.

10.2.2 **Partial Response (PR)**: Applies only to patients with at least one measurable lesion. Greater than or equal 30% decrease under baseline of the sum of longest diameters of all target lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

10.2.3 **Stable**: Does not qualify for CR, PR, Progression or symptomatic deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

10.2.4 **Progression**: Either of the following must occur.

10.2.4.1 **RECIST Progression:** One or more of the following must occur: 20% increase in the sum of longest diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site, although some exceptions may be allowed if the treating physician feels that the area was inadequately evaluated on baseline imaging (an explanation must be provided). Death due to disease without prior documentation of progression and without symptomatic deterioration.

10.2.4.2 **Confirmed bone disease progression:** Confirmed bone disease progression is defined as development of one or more new bone lesions from baseline (an increase in size or intensity of known lesions will not constitute progression) confirmed by a subsequent bone scan with further development of new lesions at least 6 weeks after the first. Patients will also be deemed to progress if they require therapy for a bone lesion such as surgery, radiation therapy, radiofrequency ablation or other local therapy. Date of progression will be defined as the date of the scans that first indicated new bone lesions.

10.2.5 **Symptomatic Deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

10.2.6 **Assessment Inadequate, Objective Status Unknown**: Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

10.2.7 Objective Status Notes

10.2.7.1 Non-measurable and non-target measurable disease do not affect objective status except in determination of CR (must be absent). A patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed will be classified as having a PR. Non-measurable and non-target measurable disease will also affect determination of progression if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician.

10.2.7.2 An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.

10.2.7.3 In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

10.2.7.4 Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

10.2.7.5 For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression.

10.2.7.6 Appearance or worsening of pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin.

10.2.7.7 If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.3 **Best Response**: this is calculated from the sequence of objective statuses.

10.3.1 CR: Two or more objectives statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

10.3.2 PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration but not qualifying as CR.

10.3.3 Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

10.3.4 Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

10.3.5 Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration but not qualifying as anything else above.

10.3.6 Increasing disease: Objective status of progression or asymptomatic deterioration within 12 weeks of registration not qualifying as anything else above.

10.3.7 Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 Progression-Free Survival: Time from date of registration to date of first documentation of progression or symptomatic deterioration or death due to any

cause. Patients last known to be alive and progression-free are censored at last date of contact.

10.5 **Overall Survival**: Time from date of registration to date of death due to any cause. Patients last known to be alive are censored at last date of contact.

10.6 **Tumor Marker (MUC-1 or CEA) Antigen Response:**

10.6.1 Objective status at each evaluation: Objective tumor marker response is to be recorded prestudy and every 8 weeks.

10.6.1.1 Tumor Marker Complete Response: Reduction in MUC-1 (CA 15-3 or CA 27.29) or CEA such that MUC- 1 or CEA ≤ ULN.

10.6.1.2 Tumor Marker Partial Resonse: Greater than or equal to a 50% reduction in MUC-1 or CEA from baseline, but not qualifying as CR.

10.6.1.3 Tumor Marker Progression: Greater than or equal to a 50% increase in MUC-1 or CEA from baseline.

10.6.1.4 Tumor Marker Stable Disease: MUC-1 or CEA response not qualifying as CR, PR, or Progression.

10.6.1.5 Tumor Marker Inadequate Assessment, response unknown: MUC-1 or CEA response has not been adequately assessed.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design

This is a single-arm phase II multicenter clinical trial. The treatment period is 24 weeks of induction therapy followed by maintenance therapy until disease progression.

The primary end point is progression free survival (PFS), which will be compared to historical controls of patients with metastatic basaloid breast cancer treated with chemotherapy and bevacizumab.

We consider a 60% increase in median PFS (from 8 to 13 months) to represent justification for further exploration of this combination.

11.2 Sample Size

Targeted enrollment will be 59 evaluable patients to detect this degree of improvement with one-sided alpha = .05, power = .80.

11.3 Interim Analysis and Early Stopping Guidelines

Formal interim analyses and stopping rules are not planned. As this is an open-label study, data will be reviewed and summarized in an on-going manner. In addition, the principal investigator will review serious adverse events during the course of the study as they are reported.

Excluding patients who withdraw from the study due to progression, if 7 of the first 30 patients withdraw prior to completion of induction therapy (due to toxicity or other reasons beside progression), the study may be terminated if the treatment regimen does not appear to be well-tolerated. Note that dose reductions alone are not considered as withdrawal.

11.4 Methods of Analysis

This study is being conducted to assess the efficacy and safety of a regimen of chemotherapy and combined targeted biologic therapy for patients with the triple negative phenotype of metastatic breast cancer. Efficacy data will be collected and summarized on all patients who receive at least one dose of study drug and some follow up for progression. Safety data will be collected and summarized for all patients who receive at least one dose of study drug.

11.4.1 Efficacy analysis

Assessments of progression and survival will continue for at least 24 weeks after the last accrued patient has begun study treatment. Kaplan-Meier survival curves will be used to describe PFS and overall survival. For PFS, patients without documented disease progression or death will be treated as censored on the date of the last tumor assessment. Overall survival time will be censored on the last date the patient was known to be alive. Response rate will be summarized and an exact 90% binomial confidence interval determined for evaluable subjects.

A 95% confidence interval for the median PFS will be calculated. A lower bound greater than 8 months would be strong evidence that Nab-Paclitaxel- bevacizumab induction therapy followed by bevacizumab-erlotinib maintenance therapy is superior to paclitaxel and bevacizumab. However, a median PFS of 13 months or greater (regardless of whether the 95% confidence interval for the median extends below 8 months) could also indicate promising results.

11.4.2 Safety analysis

Safety assessments will consist of monitoring and recording protocol-defined adverse events (AEs) and serious adverse events (SAEs); measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drugs.

Adverse events will be graded using the Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events version 3.0. Adverse events that meet severity grade 2 or greater will be collected and reported. The number and percent of subjects reporting adverse events (all, severe or worse, serious and related) will be summarized for all patients, and stratified by center and other subgroups of interest. Narratives of all serious adverse events and deaths on-study will be provided.

The investigator is responsible for ensuring that all reportable AEs and SAEs that are observed or reported during the study are recorded on the CRF and reported to the funding agencies in accordance with protocol instructions.

Death as a result of disease progression is only to be assessed with regard to efficacy measures and not as an AE or SAE.

Investigators will assess the occurrence of AEs and SAEs at all patient evaluation time points during the study. All reportable AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning or detected through physical examination, laboratory test or other means will be recorded in the patient's medical record and on the appropriate AE or SAE case report form page.

Each recorded AE or SAE will be described by its severity (***see Table 3***), regulatory seriousness criteria if applicable, suspected relationship to the investigational product and actions taken.

Table 3: **Adverse Event Grading (Severity) Scale**

Grade	Severity	Alternate Description [a]
1	Mild (apply event-specific NCI-CTCAE grading criteria)	Transient or mild discomfort (< 48 hours); no interference with the patient's daily activities; no medical intervention/therapy required
2	Moderate (apply event-specific NCI-CTCAE grading criteria)	Mild to moderate interference with the patient's daily activities; no or minimal medical intervention/therapy required
3	Severe (apply event-specific NCI-CTCAE grading criteria)	Considerable interference with the patient's daily activities; medical intervention/therapy required; hospitalization possible
4	Very severe, life threatening, or disabling (apply event-specific NCI-CTCAE grading criteria)	Extreme limitation in activity; significant medical intervention/therapy required, hospitalization probable
5	Death related to AE	

Note: Regardless of severity, some events may also meet regulatory serious criteria. Refer to definitions of an SAE (see Section 16.1).

[a] Use these alternative definitions for Grade 1, 2, 3, and 4 events when the observed or reported AE is not in the NCI-CTCAE listing.

11.4.3 Additional Analyses

The number of subjects who withdraw from study before the scheduled end of study will be quantified with the reason for withdrawal and timing of withdrawal.

At a minimum, the following demographic, baseline and on-study characteristics will be summarized for all patients and by center:

- Age and race
- Clinical stage of disease
- Clinical response to nab-paclitaxel and bevacizumab
- Clinical response to bevacizumab and erlotinib
- Relapse rate following nab-paclitaxel and bevacizumab
- Dose adjustments to nab-paclitaxel, bevacizumab, and erlotinib (missed, withheld, decreased)
- Median dose intensity for nab-paclitaxel and bevacizumab, and bevacizumab and erlotinib
- Cytokine use
- PFS and overall survival (OS) will be summarized with Kaplan-Meier curves; the median survival time with 95% confidence limits will be provided. Exploratory subgroup analyses will look at PFS and OS separately for groups defined by dose delivered, treatment history, and biomarker values.

11.5 Expected gender, ethnic and racial composition:

TARGETED/PLANNED ENROLLMENT: NUMBER OF SUBJECTS			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	2	0	2
Not Hispanic or Latino	61	0	61
Ethnic Category Total of All Subjects*	63	0	63
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	3	0	3
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	4	0	4
White	55	0	55
Racial Categories: Total of All Subjects *	63	0	63

12.0 DISCIPLINE REVIEW

There is no discipline review.

13.0 REGISTRATION GUIDELINES

13.1 Before a subject participates in the trial, the investigator or delegate is responsible for obtaining written informed consent after adequate explanation of the aims, methods, anticipated benefits, potential hazards, and subject responsibilities including the use of adequate methods to prevent pregnancy. Consent must be obtained before any on-study procedures or any study medications are administered.

13.2 All patients must be registered before the start of treatment. Patients seen at the Seattle Cancer Care Alliance (SCCA) are registered by contacting the Breast Program Research Coordinator assigned to the study. Patients who are seen at external performance sites are registered by calling the SCCA Network office at 206-288-7232), 8:00 AM to 5:00 PM Pacific time, Monday through Friday. Materials required to complete the registration may be faxed (206 288-1310) or scanned/e-mailed (SCCANetResearch@seattlecca.org) and include:

- Consent Form
- HIPAA Authorization
- Registration Form
- Eligibility Checklist and all supporting documentation
- Race and Ethnicity Form
- Medical records documenting eligibility

14.0 DATA SUBMISSION SCHEDULE

Data forms will be completed by research staff at the Seattle Cancer Care Alliance for all subjects registered to the study. Records may be faxed, e-mailed or mailed to:

Seattle Cancer Care Alliance Network
825 Eastlake Avenue East
Mail Stop LG-200
Seattle, WA 98109-1023
(206) 288-1310 (fax)
sccanetresearch@seattlecca.org

Medical records are due at the following time points to allow for completion of study-specific case report forms:

14.1 **At the time of registration**: all medical records from the time of diagnosis of breast cancer and the consent form, HIPAA Authorization, Race and Ethnicity Form.

14.2 **At the end of each cycle of treatment**: physical exams, laboratory test results, radiology examinations, treatment orders, treatment administration records, concomitant medication lists.

14.3 **At the end of each regimen** (e.g. nab-paclitaxel bevacizumab or bevacizumab/erlotinib): Assessment of response and disease progression

14.4 **Every three months for the first three years, every six months for the next two years, annually thereafter:** Clinic notes and disease assessments (if off study for reason other than disease progression)

15.0 SPECIAL INSTRUCTIONS

15.1 General Specimen Submission Instructions

15.1.1 All specimens must be labeled with the protocol number (6628), patient number, patient initials and date of specimen collection.

15.1.2 The federal guidelines for shipment are as follows:

15.1.2.1 The specimen must be wrapped in an absorbent material.

15.1.2.2 The specimen must be placed in an AIRTIGHT container (like a resealable bag).

15.1.2.3 Pack the resealable bag and specimen in a Styrofoam shipping container.

15.1.2.4 Pack the Styrofoam shipping container in a cardboard box.

15.1.2.5 The cardboard box must be marked as “BIOHAZARD”.

15.2 Immunohistochemistries

Tumor tissue that is available from subjects will be analyzed for expression of the SPARC (secreted protein and rich in cysteine) protein and for endothelieal growth factor receptor (EGFR). Participation in these additional analyses is optional. Subjects will indicate in the consent form whether they agree to make their tissue sample available for these analyses. Subjects may choose not to allow their tumor tissue to be used for testing of SPARC and EGFR expression. Tumor tissue that is available from biopsy will be used. Additional procedures will not be performed for the purpose of obtaining tumor tissue for SPARC or EGFR analyses.

15.2.1 EGFR

Immunohistochemistry for assessment of EGFR will be performed at the University of Washington Medical Center.

Procedures for Tumor Sample Preparation and Shipping

Tumor samples obtained in accordance with applicable regulations will be collected.

Tissue specimens will be prepared as paraffin embedded blocks. Send blocks to Dr. Jennifer Specht at the Seattle Cancer Alliance to be inventoried and submitted to the pathology department for EGFR staining. The pathology department will process the specimens according to standard procedures for EGFR assays. Tissue blocks will be returned to the sites of origin as soon as EGFR testing is complete.

An alternative, but not preferred, method is to utilize slides generated at the specimen collection sites. Ten unstained slides, cut from archival

paraffin-embedded tumor blocks, will be obtained for evaluation of tumor EGFR expression by IHC methodology. Thickness of the sections should be at 4 micron. Tumor specimens must be unstained and placed specifically on Super Frost Plus Slides and baked at 55 - 60^{o}C for 1 hour.

All blocks or slides for EGFR analysis will be shipped as follows:

Ship specimens to:

Seattle Cancer Care Alliance Network
825 Eastlake Avenue East; MS LG-200
Seattle, WA 98109-1023
Phone: (206) 288-7232

Samples will be de-identified by research staff before shipment to outside laboratory. Samples will be coded with a unique study identifier that will be assigned at study registration.

Data Analysis

Data reports from the IHC analysis will be distributed to the appropriate parties when analysis of the entire data set is complete.

15.2.2 SPARC

15.2.2.1 Background and Rationale

Nab-Paclitaxel achieves a high intracellular tumor concentration, and its intracellular concentration is at least, in part, achieved by an albumin-mediated transendothelial transport via the gp60 pathway. SPARC (secreted protein acidic and rich in cysteine) is a matricellular protein (also known as BM40 or osteonectin) that is upregulated in several aggressive tumors and its presence is associated with poor outcomes. Expressed in 40-50% of breast cancers, SPARC also shares sequence homology with the C terminus of the gp60 pathway (an important pathway in Nab-Paclitaxel intracellular transport) and binds albumin. By exploiting both caveolin-1 and the SPARC protein, nab-paclitaxel may preferentially enhance drug delivery to tumors. Correlative studies evaluating the presence of SPARC expression on tumors, disease prognosis, and response to therapy are underway.

15.2.2.2 Objective

To investigate a possible correlation between treatment response and the expression of tumor SPARC protein by IHC methodology

15.2.2.3 Eligibility

Patients must be eligible for, enrolled to and treated on the current protocol. Patients must sign an informed consent specific for the

use of their tumor tissue in investigating expression of the SPARC.

15.2.2.4 Study Treatment

Patients will receive treatment as outlined in this protocol.

15.2.2.5 Procedures for Tumor Sample Preparation and Shipping

Tumor samples obtained in accordance with applicable regulations will be collected.

Tissue specimens will be prepared as paraffin embedded blocks.

An alternative, but not preferred method will be to utilize slides generated at the specimen collection sites. Ten unstained slides**,** cut from archival paraffin-embedded tumor blocks, will be obtained at baseline for evaluation of tumor SPARC expression by IHC methodology. Thickness of the sections should be at 5 micron. Tumor specimens must be unstained and placed specifically on Super Frost Plus Slides and baked at 55^{o}C for 1 hour. If pretreatment archival tissue specimen is inadequate or technical difficulties are encountered, tissue processing from the post-induction surgery residual tumor will be attempted.

Samples will be de-identified before shipment to outside sites. Samples will be coded with a unique study identifier that will be assigned at study registration.

Data Analysis
Data reports from the IHC analysis will be distributed to the appropriate parties when analysis of the entire data set is complete.

Patient Response Assessment
Responses will be defined as outlined in protocol section 10.3 for correlation with SPARC expression.

Sample Size
Because patient participation in this tumor tissue SPARC analyses are optional, and this analysis is exploratory in nature, a sample size will not be determined.

15.3 Submission of blood for analysis of circulating tumor cells and circulating endothelial cells

15.3.1 Investigators are required to submit whole blood for analysis of circulating tumor cell (CTC) and circulating endothelial cell (CEC) analysis.

15.3.2 Directions for obtaining, handling and submitting samples for CTC and CEC testing

15.3.2.1 All participating sites should have blood collection tubes and shipping supplies onsite at the time of registration. To obtain collection tubes, call (206) 288-6355. The initial supplies you receive will include the following: CellSave® tubes, shipping containers, pre-printed airbills.

15.3.2.2 Timing of collections: Blood for testing for all study patients is to be obtained at baseline prior to initiation of study treatment, prior to weeks 5, 9 and 17 of nab-paclitaxel and bevacizumab, prior to week 1 and 9 of bevacizumab and erlotinib and at the time of disease progression. All samples should be obtained prior to infusion of chemotherapy or before taking the first dose of oral therapy for the interval.

15.3.2.3 Materials required for blood collections are: two (2) 10 mL purple/yellow top CellSave® blood collection tubes, Vacutainer® brand adapter and needles. The blood may be drawn by a physician, registered nurse or licensed phlebotomist at the clinical site. NOTE: Clinical labs for the day should be obtained prior to filling the CellSave® tube using the same needle stick. This decreases the chance of contamination of the CTC or CEC sample with skin epithelial cells which may occur when the needle enters the skin.

15.3.2.4 Complete the top portion of the CTC and CEC Blood Draw and Results CRF noting the lot number and expiration date of each of the CellSave® tubes. For each patient, obtain the blood sample via a venous puncture or from a port or other central venous catheter using appropriate access needles and techniques. Fill each of the blood collection tubes (minimum blood volume of 9 mL for each tube). Invert each tube a minimum of eight (8) times to ensure proper mixing of the additives contained in each ®tube. Write the study number, patient number and date of collection on the tubes. Complete the remainder of the CTC and CEC Blood Draw and Results CRF.

15.3.2.5 The filled CellSave® tubes must be maintained at ambient (10 – 30° C) temperature avoiding extremes of heat and cold at all times.

15.3.2.6 Place each filled collection tube into the styrofoam shipping container. One shipping container accommodates up to two collection tubes. Place the Styrofoam box into a ziplock bag and secure the lid of the outer cardboard box.

15.3.2.7 Complete Section 1 of the airbill and make sure the box under “Does this shipment contain dangerous goods?” is checked “No”. Packages may be sent Monday through Thursday for Tuesday through Friday delivery only. Specimens cannot be received or processed on the weekend.

15.3.2.8 Place the completed CTC and CEC Blood Draw and Results CRF into the express mail envelope.

15.3.2.9 Call the laboratory to alert the lab of the shipment. Ship all blood tubes overnight delivery to:

Daniel Sabath, M.D.
Seattle Cancer Care Alliance
825 Eastlake Avenue East
Mail Stop G7-800
Seattle, WA 98109-1023
(206) 288-7060

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Definitions

Adverse Events

An adverse event (AE) is any new, undesirable medical occurrence or worsening of a pre-existing condition that occurs during or after treatment, whether or not considered to be product related. Therefore, adverse events are treatment-emergent signs or symptoms.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies)
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period
- Diagnoses and/or symptoms associated with breast cancer should be reported as AEs if they worsen or change in character. Clinical progression of breast cancer should not be reported as an AE.

Adverse events that meet severity grade 2 or greater will be collected from the initiation of study treatments to 30 days subsequent to study completion or withdrawal. Follow up of these events will follow the same procedure as described in Section 16.3.1 for AEs observed during the study period.

Life-threatening Adverse Event

Any adverse drug experience that places the research subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. This does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious Adverse Events (SAE)

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has initiated study therapy and until 30 days after the patient has stopped study treatment must be reported within 24 hours of learning of the event. Any SAE experienced after the 30-day period should only be reported if the investigator suspects a causal relationship to the study drugs. Dr.

Specht and her staff will be responsible for reporting to Celgene, Genentech and the IRB.

A serious adverse event as defined by IHC is any adverse drug experience that at any dose meets any of the following conditions:

- Results in death
- Is life-threatening (The patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity or
- Is a congenital anomaly or birth defect.

The terms "serious" and "severe" are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe myocardial infarction). The event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on patient/event outcome or action criteria usually associated with adverse events, which pose a threat to a patient's life or functionality. Seriousness (not severity) is the criterion used to define reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the case report form.

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations; for example, important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Related to Study Treatment

An adverse event is related to a study product, treatment or procedure if it is certain or reasonably possible that it was caused by the product, treatment or procedure. An adverse event is not related to a study product, treatment or procedure if: (i) it is caused by the subject's medical condition or concomitant therapy that is not part of the study treatment or intervention or (ii) there is no plausible temporal, behavioral or biological relationship to the product, treatment or procedure.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Related = YES

There is a plausible temporal relationship between the onset of the AE and administration of the investigational product, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the investigational product; and/or the AE abates or resolves upon discontinuation of the investigational product or dose reduction and, if applicable, reappears upon re-challenge.

Related = NO

Evidence exists that the AE has an etiology other than the investigational product (e.g., preexisting medical condition, underlying disease, intercurrent illness or concomitant medication); or the AE has no plausible temporal relationship to administration of the investigational product (e.g., cancer diagnosed 2 days after first dose of study drug).

Unexpected Adverse Event

Any adverse drug experience, the specificity or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vaculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g. included in the investigator brochure).

16.2 SAE Reporting Period

The SAE reporting period is from the date of the first dose of study drug to 30 days after discontinuation of all study drugs. After this period, investigators should only report SAEs that are attributed to prior study treatment.

16.3 SAE Reporting Guidelines

16.3.1 All serious adverse events experienced by patients seen at performance sites other than the Seattle Cancer Care Alliance (SCCA) Lake Union site must be reported by calling (206) 288-6355. The reporting requirements for the IRB and the funding agencies (Celgene and Genentech) differ. The SCCA Network office will assist external sites with preparing the appropriate reports and will forward the completed reports to the principal investigator and Breast Cancer Research Program study staff for submission to the appropriate agencies. SAEs experienced at the SCCA or UWMC will be reported to the appropriate agencies by the Principal Investigator with assistance from Breast Cancer Research Program study staff.

All SAEs must be followed until resolved or considered stable. The following attributes must be reported:

- Description of event;
- Dates of onset and resolution;
- Severity;
- Assessment of relatedness to study drug, and
- Action taken.

The investigator may be asked to provide follow-up information and will assist in investigating any SAE and will provide any follow-up information reasonably requested by the Principal Investigator.

16.3.2 Reporting Requirements for the IRB

The IRB requires the principal investigator to ensure that adverse events that meet the expedited reporting criteria defined below are reported to the IRB not later than ten (10) calendar days after she becomes aware of them.

- All adverse events that are unexpected, related or possibly related to the research and serious or suggest that the research places research participants or others at greater risk of physical or psychological harm than was previously known or recognized.
- Death of the research participant within thirty (30) days from the start of administration of the study product, treatment, or procedure
- AEs that must be reported on an expedited basis to comply with the protocol on which a research participant is being treated.

Note: If a principal investigator submits an AE that does not meet the Expedited Reporting Criteria, the IRB office will log in the AE and then return it to the Principal Investigator (PI)/contact person. A copy of the AE report not meeting the Expedited Reporting Criteria will not be kept by the IRB. At time of Continuation Review, the PI will be responsible for submitting a summary of the AE reports.

16.3.3 Reporting Requirements for Celgene

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. This study will use the MEDWATCH 3500A form. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (AX-CL-BRST-PI-003828) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission

confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

Celgene Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr.
Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

16.3.4 Reporting Requirements for Genentech

Investigators will submit written reports of all SAEs, regardless of attribution, to Genentech within 48 hours of learning of the events. For initial SAE reports, investigators should record all case details that can be gathered within 48 hours on an SAE CRF page. For this study, the MEDWATCH 3500A form will be considered the SAE case report form page. The completed SAE CRF page and SAE Fax Cover Sheet should be faxed immediately upon completion to Genentech's Drug Safety Department at:

(650) 225-4682 or
(650) 225-5288.

and to the GNE Drug Safety Hotline at (888) 835-2555.

Relevant follow-up information should be submitted to Genentech's Drug Safety as soon as it becomes available and/or upon request.

16.4 Monitoring for Data Accuracy and Compliance

Protocol implementation will be reviewed and summarized in an on-going manner. The principal investigator will review (1) all serious adverse events and (2) data concerning disease progression.

Teleconferences or videoconferences with performance sites other than the SCCA at Southeast Lake Union will occur at regular intervals to discuss the progress of the study. The conversations will be summarized and discussed at the monthly of the study team which includes the principal investigator, Breast Cancer Research Program study coordinator and staff of the SCCA Network office. The following topics will be discussed and summarized:

- Screening activity
- Enrollment
- Status of each patient receiving study treatment (e.g. number of weeks on study treatment, toxicity experienced, response to date, etc.)
- Reports of serious, unexpected adverse events related to study treatment

- IND safety reports of serious, unexpected adverse events that are related to study drugs
- Instances of disease progression
- Vital status of study participants
- Pending protocol or consent form changes
- Other issues related to accrual or protocol implementation as necessary.

Written summaries of serious, unexpected adverse events occurring on the study that are related to the study drugs and IND safety reports received from Celgene or Genentech will be distributed by the Coordinating Center to the lead investigator at each external (e.g. non-SCCA at Southeast Lake Union) performance site. Protocol modifications and consent form changes will be distributed to each performance site as they are approved by the IRB with instructions as to whether subjects must be re-consented.
Formal trial monitoring will be conducted at least annually and in accordance with the Cancer Consortium Institutional Data and Safety Monitoring Plan, and FHCRC/UW Cancer Consortium Guidelines for Conducting Multi-Center Trials where FHCRC/UW serves as the Coordinating Center. Monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of the previous visits. The purpose of the monitoring visits is to verify the accuracy of the study data, assess compliance with the protocol and with Good Clinical Practice (GCP) regulations, and assure the timely and complete reporting of safety (adverse event) data. To assure protocol compliance and data consistency, the medical records for all patients enrolled to the study will be submitted to the Coordinating Center for review, data abstraction and protocol monitoring.

Depending on the source of the participant's registration, the monitoring activities will be carried out by:

- ❑ For registrations from the Seattle Cancer Care Alliance (SCCA), monitoring will be performed by staff of the Research Support Office (RSO) or by external contractors engaged by the RSO.
- ❑ For registrations from SCCA Network sites or other Northwest sites managed through the SCCA Network Office, monitoring will be performed by staff of the SCCA Network or by contractors engaged by the SCCA Network.

Each monitor will be qualified by experience and training to perform these services.

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18.0 APPENDICES

18.1 NEW YORK HEART ASSOCIATION (NYHA) GUIDELINES CHF Guidelines

In order to determine the best course of of therapy, physicians often assess the stage of heart failure according to the New York Heart Association (NYHA) functional classification system. This system relates symptoms to everyday activities and the patient's quality of life.

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

18.2 UPC Ratio

Procedure for Obtaining a Urine Protein / Creatinine Ratio

1) Obtain at least 4 ml of a random urine sample (does not have to be a 24-hour urine)

2) Determine protein concentration (mg/dL)

3) Determine creatinine concentration (mg/dL)

4) Divide #2 by #3 above: urine protein / creatinine ratio = protein concentration (mg /dL) / creatinine concentration (mg /dL)

The UPC directly correlates with the amount of protein excreted in the urine per 24 hrs (i.e. a UPC of 1 should be equivalent to 1g protein in a 24hr urine collection)

Protein and creatinine concentrations should be available on standard reports of urinalyses, not dipsticks. If protein and creatinine concentrations are not routinely reported at an Institution, their measurements and reports may need to be requested.

18.3 CYP3A4 Inhibitors and Inducers

The following are known inhibitors of CYP3A4:

Delaviridine	Indinavir
Nelfinavir	Ritonavir
Saquinavir	Amiodarone
Cimetidine	Ciprofloxacin
Clarithromycin	Diethyl-dithiocarbamate
Diltiazem	Erythromycin
Fluconazole	Fluvoxamine
Gestodene ++	Grapefruit juice
Itraconazole	Ketoconazole
Mifepristone	Nefazodone
Norfloxacin	Norfluoxetine
Mibefradil	Troleandomycin
Atazanavir	Indinavir
Telithromycin	Voriconazole

The following are known inducers of CYP3A4:

Rifampicin	Phenytoin
Rifabutin	Rifapentine
Carbamazepine	Phenobarbital
St. John’s Wort	