CITY OF HOPE NATIONAL MEDICAL CENTER

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DEPARTMENT OF MEDICAL ONCOLOGY AND THERAPEUTICS RESEARCH

TITLE: Efficacy and Tolerability of Nanoparticle Albumin Bound Paclitaxel (Abraxane) in patients 65 and older with Locally Advanced or Metastatic Breast Cancer

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Efficacy and Tolerability of Nanoparticle Albumin Bound Paclitaxel (Abraxane) in Patients 65 and Older with Locally Advanced or Metastatic Breast Cancer

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In Memory of Dr. Arti Hurria

SYNOPSIS

Study Objectives

The primary objective of the study is to evaluate the tolerability (grade 2-5 toxicity, need for dose reductions, or delays) of weekly *nab*- paclitaxel (abraxane) in older adults with locally advanced or metastatic breast cancer. In addition, we will capture neuropathy (grade 2 or higher). The secondary objectives are (1) to determine efficacy (response and time to progression) of weekly *nab*-paclitaxel in older adults with locally advanced metastatic breast cancer, and (2) to explore predictors of the need for dose reduction, dose delays, or grade 2-5 toxicity and neuropathy grade 2 or higher based on a cancer-specific geriatric assessment.

Eligibility:

Locally advanced or metastatic breast cancer, first or second line chemotherapy treatment for metastatic disease, age $\geq$65 years., KPS $\geq$70%, resolution of grade $\geq$ 2 toxicity from prior therapy (other than alopecia), peripheral neuropathy $\leq$ grade 1, hematologic inclusion (absolute neutrophil count $\geq$1,500/mm^3, platelets $\geq$100,000cells/mm^3, and Hb $\geq$ 9.0g/dl), hepatic and renal inclusion (AST and ALT $\leq$ 2.5 x institutional upper limit of normal, alkaline phosphatase $\leq$ 2.5 x upper limit of normal unless bone metastasis are present in the absent of liver metastases, bilirubin $\leq$ 1.5mg/dl, CrCl $\geq$ 30ml/min), ability to understand and the willingness to sign a written informed consent document.

Exclusion criteria:

KPS < 70%, patients may not be receiving any other investigational agents, untreated CNS metastases or symptomatic CNS metastases requiring escalating doses of corticosteroids, peripheral neuropathy of severity greater than grade 1, known history of allergic reactions to paclitaxel, presence of any serious or uncontrolled infection

Treatment regimen:

Nab-paclitaxel 100mg/m^2 3 weeks on +/- 1 day from indicated dates, 1 week off

Response evaluation:

Radiological studies will be conducted after every 2 cycles to assess response to therapy. Toxicity will be evaluated utilizing the NCI CTC version 4.0.

Sample size: 40 patients

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1.0. OBJECTIVES

1.1. Primary objective:

1.1.1 To evaluate the tolerability (grade 2-5 toxicity, neuropathy grade 2 or higher, need for dose reductions, or delays) of weekly *nab*-paclitaxel in older adults with locally advanced or metastatic breast cancer

1.2. Secondary objectives:

1.2.1. To evaluate the efficacy (response and time to progression) of weekly nab-paclitaxel in older adults with locally advanced or metastatic breast cancer using a stratification factor based on patient age (at least 5 patients age 75 years or older and no more than 15 patients age 65-70 years)

1.2.2. To explore predictors of the need for dose reduction, dose delays, or grade 2-5 toxicity and neuropathy grade 2 or higher based on a cancer-specific geriatric assessment

2.0. BACKGROUND

2.1. Pharmacology and Aging

Aging brings about a progressive decrease in physiologic reserve that affects each individual at a unique pace.[1, 2] The age-related physiological decline in organ systems typically begins in the 3rd decade of life and is not evident at times of rest but becomes most apparent when the body is stressed.[3] Either cancer or cancer treatment can be considered a physiological stressor, and the age-related decrease in physiologic reserve may affect tolerance to cancer treatment.

A number of age-related changes in drug absorption, distribution, metabolism, and excretion with aging may contribute to differences in treatment tolerance between older and younger patients. The absorption of drugs can be affected by decreased gastrointestinal motility, decreased splanchnic blood flow, decreased secretion of digestive enzymes, and mucosal atrophy.[4, 5] With the increased use of oral therapy, drug compliance is an important issue.[6] As a person ages, body composition changes, with an increase in body fat and decrease in lean body mass and total body water. The increase in body fat leads to a rise in the volume of distribution for lipid soluble drugs and a diminution in the volume of distribution for hydrophilic drugs. In the cancer population, malnutrition and hypoalbuminemia may result in an increased concentration of drugs that are albumin-bound.[7]

Hepatic mass and blood flow decrease with age.[1, 8] The impact of the decline in hepatic mass and blood flow on hepatic enzyme function is controversial.[9-11] In a study of 226 patients, the cytochrome P450 content in liver biopsy samples decreased by approximately 30% in patients over the age of 70.[12] Phase 1 metabolism occurs primarily via the cytochrome P450 microsomal system and exhibits genetic variability. [13, 14]

Over a lifespan, renal mass decreases by approximately 25% to 30%, and renal blood flow decreases by 1% per year after age 50.[7] The decline in glomerular filtration rate with age is estimated at 0.75 ml/minute/year after age 40; however, approximately one third of patients have no change in creatinine clearance with age.[15] This reduced renal function, however, does not usually result in increased serum creatinine levels because of the simultaneous loss of muscle mass.[16] Therefore, serum creatinine is not an adequate indicator of renal function in the older patient.

2.2. Age-Related Changes in the Pharmacokinetics of Taxane Chemotherapy

2.2.1. Paclitaxel

The pharmacokinetics of paclitaxel given at 175 mg/m^2 over 3 hours every 3 weeks was studied by Lichtman and colleagues on behalf of the Cancer and Leukemia Group B. The 153 patients who entered the study were divided into 3 cohorts based on age: cohort 1 age 55-64 (n=51), cohort 2 age 65-74 (n=56), cohort 3 age $\geq$75 (n=46), Pharmacokinetic data for the first cycle of chemotherapy were available in 122 of the 153 patients. The mean area under the curve (AUC) of paclitaxel increased (P = .01), and the mean paclitaxel clearance decreased (P = .007) across cohorts of increasing age. Older patients experienced an increased incidence of grade $\geq$3 neutropenia and lower absolute neutrophil count nadir than younger patients; however, this did not translate into an increased incidence of hospitalization, fever >38°C, or receipt of intravenous antibiotics.[17]

The results of pharmacokinetic studies of weekly paclitaxel in older patients have conflicted. Fidias and colleagues reported on the efficacy and toxicity of weekly paclitaxel (90 mg/m^2 over 1 hour) in 35 patients over the age of 70 (median age 76; range 70 to 85). Among these patients, 13 consented to pharmacokinetic sampling, and 8 patients had pharmacokinetic sampling performed with the first and 6th cycle. The authors compared the pharmacokinetic parameters from this cohort to values that had been reported in younger patients and concluded that the pharmacokinetics did not differ by age and the values did not change with repeated weekly dosing.[18] Smorenburg and colleagues reported on the pharmacokinetics of weekly paclitaxel in 8 patients age 70 and older (median age 77; range 70 to 84) and 15 patients less than age 70 (median 54 years, range 22 to 69). The younger group received paclitaxel 100 mg/m^2 over 1 hour, and the older group received 80 mg/m^2 over 1 hour. The authors found that the clearance of unbound (P = .002) and bound paclitaxel (P = .04) was significantly lower in older patients, and that clearance was inversely related to age. There was an approximate 50% decrease in the clearance of unbound paclitaxel in older versus younger patients. Despite receiving a lower dose of paclitaxel, older patients experienced similar decreases in white

blood cell and absolute neutrophil count in comparison to younger patients. Possible explanations for this finding include the increased exposure to paclitaxel or decreased bone marrow reserve in older patients.[19]

2.2.2. *Nab*-Paclitaxel

Nab-paclitaxel is a novel biologically interactive albumin-bound paclitaxel combining a protein with a chemotherapeutic agent in the particle form. This composition provides a novel approach of increasing intra-tumoral concentration of the drug by a receptor-mediated transport process allowing transcytosis across the endothelial cell wall, thereby breaching the blood/tumor interface. This albumin-specific receptor mediated process involves the binding of a specific receptor (gp60) on the endothelial cell wall, resulting in activation of a protein caveolin-1, which initiates an opening in the endothelial wall with formation of a little caves or caveolae, with transport of the albumin-bound chemotherapeutic complex via these caveolae to the underlying tumor interstitium.[25] A protein specifically secreted by the tumor (SPARC) binds and entraps the albumin, allowing release of the hydrophobic drug to the tumor cell membrane.[26] *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.

2.2.2.1 Preclinical Studies with *Nab*-paclitaxel

Preclinical studies comparing *nab*-paclitaxel to paclitaxel demonstrated lower toxicities, with a MTD approximately 50% higher for *nab*-paclitaxel compared to paclitaxel. At equal doses there was less myelosuppression and improved efficacy in a xenograft tumor model of human mammary adenocarcinoma. At equitoxic doses of paclitaxel, *nab*-paclitaxel was found to be markedly more efficacious than paclitaxel.[27]

2.2.2.2. Clinical Studies with *Nab*-paclitaxel

2.2.2.2.1. Every 3 Weeks 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.[28] 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.[29] 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 paclitaxel 175 mg/m^2 given every 3 weeks.[30] Efficacy analyses were based on the ITT population. The ORR was significantly greater for *nab*-paclitaxel than for paclitaxel for all patients (33% *v* 19%, respectively; $P = 0.001$), patients who received first-line therapy (42% *v* 27%, respectively; $P = 0.029$), patients who received second-line or greater therapy (27% *v* 13%, respectively; $P = 0.006$), and patients who had received prior anthracycline therapy in either the adjuvant/metastatic setting (34% *v* 18%, respectively; $P = 0.002$) or the metastatic setting only (27% *v* 14%, respectively; $P = 0.010$). Tumor response rate was also significantly higher for *nab*-paclitaxel than for paclitaxel in patients with visceral dominant lesions (34% *v* 19%, respectively; $P = 0.002$) and in patients aged younger than 65 years (34% *v* 19%, respectively; $P < 0.001$). ORR also was greater for *nab*-paclitaxel compared with standard paclitaxel in patients with nonvisceral dominant lesions (34% *v* 19%, respectively) and in patients ≥ 65 years old (27% *v* 19%, respectively), but the results did not reach statistical significance because of the small number of patients in these subsets.

Median TTP was significantly longer with *nab*-paclitaxel than with paclitaxel for all patients (23.0 *v* 16.9 weeks, respectively; hazard ratio [HR] = 0.75; $P = 0.006$). 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; $P = .024$).[30] The incidence of hypersensitivity reactions (any grade) was low for both arms (1% for *nab*-paclitaxel and 2% for paclitaxel). 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 paclitaxel group (9% v 22%, respectively; $P < 0.001$), with a higher mean neutrophil nadir (1.67 *v* 1.31x109/L, respectively; $P = 0.046$), suggesting that polyethylated castor oil may have contributed to this toxicity in patients who received standard paclitaxel.

As expected with a higher dose of paclitaxel, treatment-related 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. In the patients ≥ 65 years old, 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. Overall, however, the incidence of these adverse effects (neutropenia, leukopenia, nausea, hyperglycemia, flushing) were lower in the *nab*-paclitaxel vs. standard paclitaxel groups in patients over age 65.

2.2.2.2.2 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.[31] 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*-paclitaxel 100 mg/m^2 on this schedule.[32] *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.[33]

2.2.2.2.3 Weekly Schedule

The NSABP studied the administration of *nab*-paclitaxel in a neoadjuvant setting to patients with locally advanced breast cancer at a dose of 100 mg/m^2 weekly for 12 weeks, with no break.[34] Four cycles of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) were administered sequentially based on patients' HER2 status: HER2 negative patients received FEC-100 (F: 500 mg/m^2, E: 100 mg/m^2, C: 500 mg/m^2 Q3 weeks) and HER2 positive patients received weekly trastuzumab in addition to FEC-75 (F: 500 mg/m^2, E: 75 mg/m^2, C: 500 mg/m^2 Q3 weeks). Weekly trastuzumab was permitted during *nab*-paclitaxel and FEC-75 treatment at the discretion of the investigator. The primary objective of the trial was to determine the pathologic complete response rate (pCR) in the breast. At the time of initial report at SABCS 2006, 65 patients had been entered on study and were evaluable for cCR and safety. Following 12 weeks of *nab*-paclitaxel, a clinical complete response rate (cCR) of 32% was noted. The therapy was well tolerated, with 48/65 patients receiving 12 doses in 12 weeks and 13/65 receiving 12 doses in 13-14 weeks. The incidence of peripheral (sensory) neuropathy was low (11% grade 2, 5% grade 3) as was neutropenia (3% grade 3 and no grade 4). The authors concluded that the administration of *nab*-paclitaxel 100 mg/m2 weekly x 12 was both effective and tolerable.

2.2.2.2.4 Phase II Studies of *Nab*-Paclitaxel in Metastatic Breast Cancer

<u>Single Agent Therapy</u>

a. In a phase II trial performed by Ibrahim and colleagues[29], 63 patients with metastatic breast cancer received 300 mg/m^2 of *nab*-paclitaxel every three weeks. The average age of participants in the study was 48.2 years, with a range between 28-69 years. The distribution of patients ≥ age 65 is not specified. The median time to disease progression was 26.6 weeks, and median overall survival was 63.6 weeks. Overall response rate was 48%. The main toxicities included grade 3-4 neutropenia (51%), grade 3-4 leukopenia (24%), grade 3 sensory neuropathy (11%), and grade 4 febrile neutropenia (5%). The age-specific tolerability of toxicities in patients ≥ age 65 is not specified.

b. In a phase II trial performed by Blum and colleagues[68], 181 patients with metastatic breast cancer received 100 mg/m^2 or 125 mg/m^2 on days 1, 8, and 15 on a 28-day cycle. The median age of participants in the study was 53 years, range 34-76, at 100 mg/m^2 and 53 years, range 33-74, at 125 mg/m^2. The percentage of participants ≥65 years was 19% at 100 mg/m^2 and 25% at 125 mg/m^2. Median progression-free survival time was 3 months at 100 mg/m^2 and 3.5 months at 125 mg/m^2. Median survival time was 9.2 months at 100 mg/m^2 and 9.1 months at 125 mg/m^2. Overall response rate was 14% for 100 mg/m^2 and 16% for 125 mg/m^2. The main toxicities at 100 mg/m^2 were grade 3-4 neutropenia (17%), grade 3-4 leukopenia (19%), and grade 3 sensory neuropathy

(8%). The main toxicities at 125 mg/m^2 were grade 3-4 neutropenia (32%), grade 3-4 leukopenia (33%), and grade 3 sensory neuropathy (19%). In patients receiving 100 mg/m^2, there was a greater incidence of grade 3-4 neutropenia, fatigue, and diarrhea in patients ≥ age 65. In patients receiving 125 mg/m^2, there was a greater incidence of sensory neuropathy and diarrhea in patients ≥ age 65.

c. In an open-label, randomized phase II trial performed by Gradishar and colleagues[71], 302 patients with metastatic breast cancer received 300 mg/m^2 *nab*-paclitaxel every 3 weeks, 100 mg/m^2 *nab*-paclitaxel weekly, 150 mg/m^2 *nab*-paclitaxel weekly, or 100 mg/m^2 docetaxel every 3 weeks. The mean age was 54.0 years, with 17% patients ≥ 65 years. By independent radiologist review, overall response rate was 49% for 150 mg/m^2 *nab*-paclitaxel, 45% for 100 mg/m^2 *nab*-paclitaxel, 37% for 300 mg/m^2 *nab*-paclitaxel, and 35% for docetaxel. The 100 mg/m^2 and 150 mg/m^2 *nab*-paclitaxel treatments exhibited a higher overall response rate than docetaxel, but this difference did not reach statistical significance. Also by independent radiologist review, progression-free survival was 12.9 months for 150 mg/m^2 *nab*-paclitaxel, 12.8 months for 100 mg/m^2 *nab*-paclitaxel, 11.0 months for 300 mg/m^2 *nab*-paclitaxel, and 7.5 months for docetaxel. The 150 mg/m^2 *nab*-paclitaxel treatment demonstrated statistically and clinically significant longer progression-free survival over the docetaxel treatment, supported by both the independent radiologist and investigator evaluations. The 100 mg/m^2 *nab*-paclitaxel treatment also showed a significantly higher progression-free survival over the docetaxel treatment, but this was not confirmed by the investigator assessment. The main toxicities included grade 3 neutropenia (39% v. 20% v. 35% v. 19% for 300 mg/m2 *nab*-paclitaxel, 100 mg/m^2 *nab*-paclitaxel, 150 mg/m2 *nab* paclitaxel, and docetaxel, respectively), grade 4 neutropenia (5% v. 5% v. 9% v. 75% for 300 mg/m2 *nab*-paclitaxel, 100 mg/m2 *nab*-paclitaxel, 150 mg/m2 *nab* paclitaxel, and docetaxel, respectively), and grade 3 sensory neuropathy (17% v. 8% v. 14% v. 12% for 300 mg/m2 *nab*-paclitaxel, 100 mg/m2 *nab*-paclitaxel, 150 mg/m2 *nab* paclitaxel, and docetaxel, respectively). The age-specific tolerability of toxicities in patients ≥ age 65 is not specified.

<u>Combination Therapy</u>

a. In a phase II trial performed by Lobo and colleagues[66], 30 patients with metastatic breast cancer received 150 mg/m^2 *nab*-paclitaxel and 1500 mg/m^2 gemcitabine, and 10 mg/kg bevacizumab on days 1 and 15 of a 28-day cycle until disease progression. The median age of participants in the study was 53.8 years, with range 34-69 years. The distribution of patients ≥ age 65 is not specified. Median progression-free survival was 10.4 months, and the overall response rate was 75.9%. Grade 3 or 4 toxicities potentially related to the study treatment were experienced in eight patients; these included port-a-cath infections (6.9%) and abscess, fever/sepsis, breast abscess, hematuria, leukopenia, peripheral neuropathy, seizure/syncope, shortness of breath, cardiac tamponade, thrombocytopenia, and UTI (3.4% each). The age-specific tolerability of toxicities in patients ≥ age 65 is not specified.

b. In a retrospective analysis performed by Link and colleagues[67], 33 patients with metastatic breast cancer received 80-125 mg/m^2 *nab*-paclitaxel on days 1, 8, and 15 on a 28-day cycle or 170-200 mg/m^2 *nab*-paclitaxel every 14 days on a 28-day cycle. In addition, 10 mg/kg every 14 days of bevacizumab was given to all patients. The median age of participants in the study was 46 years, range 31-71 years. The distribution of patients ≥ age 65 is not specified. Median time to progression for the responders was 128 days (4.2 months). Overall response rate was 48.5%. The main toxicities included grade 3 neuropathy (1 pt, 2.5%), grade 3 anemia (2 pts, 5%), and grade 3 pain or bone pain (3 pts, 7.5%). The age-specific tolerability of toxicities in patients ≥ age 65 is not specified.

Table 1. Phase II clinical studies of *nab*-paclitaxel

Author	**Regimen**	**# of Patients**	**Median Age**	**Efficacy Profile (Overall Response Rate, %)**	**Toxicity**
Ibrahim et al[29]	*Nab*-paclitaxel 300 mg/m^2 q3w	63	48.2	48	Neutropenia g3-4 (51%) Leukopenia g3-4 (24%) Sensory Neuropathy g3 (11%) Febrile Neutropenia g4 (5%)
Lobo et al[66]	*Nab* paclitaxel 150 mg/m^2 q2w, Gemcitabine 1500 mg/m^2 q2w, and Bevacizumab 10 mg/kg q2w	30	53.8	75.9	Neutropenic fever g4 (1 pt) PortAcath infection g3 (2 pts) Leukopenia g3 (1 pt) Thrombocytopenia g3 (1 pt) Peripheral neuropathy g3 (1 pt) Abscess (1 pt)
Link et al[67]	*Nab*-paclitaxel (varied dosing) and Bevacizumab 10mg/kg q2w	33	46	48.5	Neuropathy g3 (1 pt) Anemia g3 (3 pts) Pain/Bone Pain g3 (3 pts)
Blum et al[68]	*Nab*-paclitaxel 100 mg/m^2 q3/4w *Nab*-paclitaxel 125 mg/m^2 q3/4w	181	53	14 16	Neutropenia g3-4 (17%) Leukopenia g3-4 (19%) Sensory Neuropathy g3 (9%) Neutropenia g3-4 (32%) Leukopenia g3-4 (33%) Sensory Neuropathy g3 (19%)
Gradishar et al[71]	*Nab*-paclitaxel 300 mg/m^2 q3w *Nab*-paclitaxel 100 mg/m^2 w *Nab*-paclitaxel 150 mg/m^2 w	76 76 74	51.7 55.4 53.3	46 63 74	Neutropenia g3 (39%) Neutropenia g4 (5%) Sensory Neuropathy g3 (17%) Neutropenia g3 (20%) Neutropenia g4 (5%) Sensory Neuropathy g3 (8%) Neutropenia g3 (35%) Neutropenia g4 (9%) Sensory Neuropathy g3 (14%)

	Docetaxel 100 mg/m^2 q3w	74	55.4	39	Neutropenia g3 (19%) Neutropenia g4 (75%) Sensory Neuropathy g3 (12%)

2.2.2.2.5 Phase III Studies of *Nab*-Paclitaxel in Metastatic Breast Cancer

In a phase III trial performed by Gradishar and colleagues[30], 454 patients with metastatic breast cancer received 260 mg/m^2 *nab*-paclitaxel or 175 mg/m^2 standard paclitaxel every three weeks. The average age of participants in the study was 53.2 years, range 26-83 years. 13% of participants receiving *nab*-paclitaxel and 14% of participants receiving standard paclitaxel were ≥ 65 years old. Median time to progression was 23.0 weeks with *nab*-paclitaxel and 16.9 weeks with standard paclitaxel. Overall response rate was 33% with *nab*-paclitaxel and 19% with standard paclitaxel. Reported adverse events were similar in patients less than 65 years old and patients ≥ 65 years old in both groups. Among all patients, the incidence of grade 3 sensory neuropathy was 10% in the *nab*-paclitaxel group v. 2% in the standard paclitaxel group, and incidence of grade 4 neutropenia was 9% in the *nab*-paclitaxel group v. 22% in the standard paclitaxel group, despite the higher dose of *nab*-paclitaxel administered. Among patients ≥ age 65, the main adverse events in the *nab*-paclitaxel versus standard paclitaxel groups included: neutropenia (23% v. 59%, respectively), leucopenia (10% v. 31%, respectively), nausea (20% v. 38%, respectively), hyperglycemia (0% v. 19%, respectively), and flushing (0% v. 16%, respectively).

This phase III trial was used by Celgene Corporation to gain FDA approval for the drug. Based on this study, the ABRAXANE package insert states, "Geriatric use: Of the 229 patients in the randomized study who received ABRAXANE, 11% were at least 65 years of age and <2% were 75 years or older. No toxicities occurred notably more frequently among elderly patients who received ABRAXANE."

Table 2. Phase III studies of *nab*-paclitaxel

Author	**Regimen**	**# of Patients**	**Median Age**	**Efficacy Profile (Overall Response Rate, %)**	**Toxicity**
Gradishar et al[30]	*Nab*-paclitaxel 260 mg/m^2 q3w	229	53.1	33	Sensory Neuropathy g3 (10%) Neutropenia g4 (9%) \
	Standard paclitaxel 175 mg/m^2 q3w	225	53.3	19	Sensory Neuropathy g3 (2%) Neutropenia g4 (22%)

Examining these six major phase II studies and one major phase III study with *nab*-paclitaxel, the number of patients ≥ age 65 is not specified in three of the six studies. In the three studies where age breakdown was specified, the patients ≥ age 65 were a

minority, constituting 22% in the phase II study by Blum et al, 17% in the phase II study by Gradishar et al, and 14% in the phase III study by Gradishar et al. With low representation of the geriatric population in the studies, there exists a knowledge gap of the toxicity and efficacy of *nab*-paclitaxel specifically in patients ≥ age 65. This study addresses this issue in its objectives to evaluate tolerability, efficacy, and predictors of the need for dose reduction, dose delays, or grade 3-5 toxicity and sensory neuropathy grade 2 and higher for patients ≥ age 65 receiving *nab*-paclitaxel as treatment for locally advanced or metastatic breast cancer.

2.2.2.2.6 Potential Risks of *nab*-Paclitaxel

Toxicities

Myelosuppression, nausea and vomiting, diarrhea, mucositis, infections, hypotension, abnormal ECG changes, cough, dyspnea, edema, sensory neuropathy, bilirubin/liver enzyme elevations, pneumonitis, allergic reactions, alopecia, asthenia, arthralgia, and myalgia. During post marketing surveillance, rare cases of severe hypersensitivity reactions have occurred. The frequency of important treatment related adverse events are detailed in Table #3 below:

Table 3: Frequency[a] of Important Treatment Emergent Adverse Events in the Randomized Study on an Every-3-Weeks Schedule

Percent of Patients		
Adverse Event	***Nab*-Paclitaxel 260/30min[b] (n=229)**	**Paclitaxel Injection 175/3h[c,d] (n=225)**
Bone Marrow		
Neutropenia		
< 2.0 x 109/L	80	82
< 0.5 x 109/L	9	22
Thrombocytopenia		
< 100 x 109/L	2	3
< 50 x 109/L	<1	<1
Anemia		
< 11 g/dL	33	25
< 8 g/dL	1	<1
Infections	24	20
Febrile Neutropenia	2	1
Bleeding	2	2
Hypersensitivity Reaction[e]		
All	4	12
Severe[f]	0	2
Cardiovascular Vital Sign Changes[g]		
Bradycardia	<1	<1
Hypotension	5	5
Severe Cardiovascular Events[f]	3	4
Abnormal ECG		
All patients	60	52
Patients with Normal Baseline	35	30
Respiratory		
Cough	7	6
Dyspnea	12	9
Sensory Neuropathy		
Any Symptoms	71	56
Severe Symptoms[f]	10	2
Myalgia / Arthralgia		
Any Symptoms	44	49
Severe Symptoms[f]	8	4

Table 3 (continued): Frequency[a] of Important Treatment Emergent Adverse Events in the Randomized Study on an Every-3-Weeks Schedule

Percent of Patients		
Adverse Event	***Nab*-Paclitaxel 260/30min[b] (n=229)**	**Paclitaxel Injection 175/3h[c,d] (n=225)**
Asthenia		
Any Symptoms	47	39
Severe Symptoms[f]	8	3
Fluid Retention/Edema		
Any Symptoms	10	8
Severe Symptoms[f]	0	<1
Gastrointestinal		
Nausea		
Any symptoms	30	22
Severe symptoms[f]	3	<1
Vomiting		
Any symptoms	18	10
Severe Symptoms[f]	4	1
Diarrhea		
Any Symptoms	27	15
Severe Symptoms[f]	<1	1
Mucositis		
Any Symptoms	7	6
Severe Symptoms[f]	<1	0
Alopecia	90	94
Hepatic (Patients with Normal Baseline)		
Bilirubin Elevations	7	7
Alkaline Phosphatase Elevations	36	31
AST (SGOT) Elevations	39	32
Injection Site Reaction	<1	1

a Based on worst grade
b *nab*-Paclitaxel dose in mg/m2/duration in minutes
c paclitaxel injection dose in mg/m2/duration in hours
d paclitaxel injection pts received premedication
e Includes treatment-related events related to hypersensitivity (e.g., flushing, dyspnea, chest pain, hypotension) that began on a day of dosing.
f Severe events are defined as at least grade 3 toxicity
g During study drug dosing.

2.3 COH IRB 07157: Age-related changes in the pharmacokinetics (pK), response, and toxicity of weekly *nab*-paclitaxel in patients with metastatic breast cancer

The goals of this study were 1) to evaluate the age-related changes in the pharmacokinetics and pharmacodynamics of weekly *nab*-paclitaxel in patients with metastatic breast cancer; 2) to determine response rate; and 3) to explore the relationship of age with pK and pD parameters (i.e., dose reductions, dose delays and grade $\geq$ 3 toxicities). Forty patients with MBC, receiving 1st or 2nd line chemotherapy, entered an IRB approved protocol to evaluate the age-related changes in the pK of weekly *nab*-paclitaxel administered at 100 mg/m^2 IV for 3 weeks followed by a 1-week break. Patients were accrued from 4 age strata <50, 50-60, 60-70, and >70 years of age. Blood samples were collected for pK analysis with the first dose of *nab*-paclitaxel. Response was assessed every 2 cycles. Toxicity was graded using the NCI Common Toxicity Criteria for Adverse Events (v 3.0) and was adjudicated as attributable to *nab*-paclitaxel if it was possibly, probably, or definitely related. Linear regression analysis was used to examine the strength of the relationship between patient age and natural logarithm of 24 hour area under the curve (AUC). Two-sided two-sample t-tests were used to assess if there was a difference in mean age based on the presence of pD variables (i.e., dose reductions, dose delays and grade $\geq$ 3 toxicities). The significance level was set to 0.05.

Of the 40 patients who entered the study, 39 (98%) were evaluable with a mean age of 60 (SD=13.4; min=30; max=81). Patients were accrued in the following age cohorts: <50 (n= 10; 26%), 50-60 (n= 5; 13%), 60-70 (n= 15; 38%), and >70 (n= 9; 23%) years of age. The median number of courses completed was 4 (min=1, max=21). The response rate was: 0% (n=0) CR, 31% (n=12) PR, 38% (n=15) SD. Grade 3 toxicity was experienced by 26% (n=10). We observed 8% (n=3) grade 3 hematological toxicities [neutrophils (n=1; 3%), leukocytes (n=2; 5%)] and 18% (n=7) grade 3 non-hematological toxicities [nausea and hypophosphatemia (n=1; 3%), diarrhea and infection without neutropenia (n=1; 3%), fatigue (n=2; 5%), hyponatremia (n=1; 3%), and infections without neutropenia (n=2; 5%)]. There were no cases of grade 4 or 5 toxicity. Grade 2 sensory neuropathy was experienced by 8% (n=3; no cases in the 70+ age cohort). Dose reductions or course delays were experienced by 62% (n=24) and 21% (n=8), respectively. There was a borderline significant positive association between age and natural logarithm of total *nab*-paclitaxel 24 hour AUC (coef=.01; se=.006; p=0.055; n=36). There were no differences in the mean ages based on the presence of grade 3 or higher toxicity (p =0.75), need for dose reductions (p=0.48), or need for dose delays (p=0.61).

In summary, this study demonstrated that here is a borderline statistically significant relationship between age and 24 hour AUC but no differences in mean age based on pD variables (i.e., dose reductions, dose delays and grade $\geq$ 3 toxicities) were identified. The treatment was well-tolerated across all age groups.

2.4 Rationale and Goals of this Study

The goal of this study is to build upon the prior study (which accrued patients of all ages) by specifically focusing on the older adults with breast cancer. Older adults have been under-represented on therapeutic clinical trials. This study will help to address this knowledge gap by evaluating the tolerability (grade 2-5 toxicity, sensory neuropathy grade 2 and higher, need for dose reductions, or delays) of weekly *nab*-paclitaxel in older adults with metastatic breast cancer. The rationale for exploring tolerability of weekly *nab*-paclitaxel is based on the observation that physiological changes with aging can affect drug disposition and tolerability to chemotherapy treatment. *Nab*-paclitaxel is a particularly attractive drug for an older patient population. The therapy is efficacious and in contrast with paclitaxel, no pre-medications are required with *nab*-paclitaxel.[30] In

addition, previous studies have shown a favorable toxicity profile.[30] This study will help further our knowledge regarding the tolerability and efficacy of *nab*-paclitaxel in older patients.

2.5 Evaluating Factors Other Than Chronological Age Which May Affect Treatment Tolerance: The Role of Geriatric Assessment

Aging is a heterogeneous process. While certain declines in organ function are universal as the human body ages, the rate of this decline and the consequences of this decline on everyday function proceeds at a unique pace in each individual. Therefore, chronologic age tells us relatively little about the specific individual. A more detailed evaluation of an older adult patient is needed in order to capture factors other than chronological age that predict for morbidity and mortality. A comprehensive geriatric assessment may serve this purpose. The comprehensive geriatric assessment includes an evaluation of functional status, comorbid medical conditions, cognitive function, nutritional status, social support and psychological state, and a review of medications. Conclusions from several studies are emerging regarding the benefits of performing a comprehensive geriatric assessment for older patients with cancer:

(1) Factors evaluated in a comprehensive geriatric assessment predicts survival; [37]
(2) Factors evaluated in a comprehensive geriatric assessment predicts toxicity to chemotherapy; [38]
(3) A comprehensive geriatric assessment uncovers problems not detected by routine history and physical in initial consultation and in follow-up care; [39-41]
(4) Patients undergoing a comprehensive geriatric assessment and intervention based on the results had improved pain control; [42]
(5) A comprehensive geriatric assessment and intervention improves an older patient's mental health and well-being. [42]

Consensus guidelines recognize these benefits and recommend the inclusion of a geriatric assessment as part of the evaluation of an older patient. [43, 44] In this study we will capture this information in patients of age 65 or greater.

3.0. PATIENT SELECTION

3.1. Inclusion Criteria

3.1.1 Locally advanced or metastatic breast cancer

3.1.2 Any ER, PR, or Her2neu status as long as the patient will receive *nab*-paclitaxel alone

3.1.3 First or second line chemotherapy treatment for metastatic disease

3.1.4 Age $\geq$65 years.

3.1.5 KPS $\geq$70%

3.1.6 Resolution of grade $\geq$ 2 toxicity from prior therapy (other than alopecia)

3.1.7 Peripheral neuropathy ≤ grade 1

3.1.8 Hematologic inclusion:

– absolute neutrophil count	≥1,500/mm3
– platelets	≥100,000cells/mm3
– Hb	≥ 9.0g/dl

3.1.9 Hepatic and renal inclusion:

- AST and ALT	≤ 2.5 x institutional upper limit of normal
- alkaline phosphatase	≤ 2.5 x upper limit of normal unless bone metatasis are present in the absence of liver metastases
- bilirubin	≤ 1.5mg/dl
- creatinine clearance (calculated or 24 hour)	≥ 30ml/min

3.1.10 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients may not be receiving any other investigational agents.

3.2.2. Untreated CNS metastases or symptomatic CNS metastases requiring escalating doses of corticosteroids

3.2.3 Known history of allergic reactions to paclitaxel

3.2.4 Presence of any serious or uncontrolled infection

3.2.5 Receipt of a taxane for adjuvant therapy or metastatic disease in the last 12 months

3.3. Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial; however, we anticipate that the majority of patients will be female based on the demographics of breast cancer

4.0. RECRUITMENT AND REGISTRATION PROCEDURES

4.1. Subject Identification and Recruitment:

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator (at the participating site), or research team (at the participating site). Potential subjects will be contacted by their treating physician and will be referred to the investigator/research staff of the study.

The principal investigator (at the participating site) may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff (at the participating site) and the patient; the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff (at the participating site) may also review portions of their medical records in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

The initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team at the participating site. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (*partial*) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

Eligible patients will be given the opportunity to participate in the study. The goals of the study will be described and the patient will be given a copy of the informed consent to review. The interested patient will sign the consent form and retain a copy.

4.2. Registration Processes

The following person(s) at City of Hope may obtain informed consent: Arti Hurria, M.D., George Somlo, M.D., FACP, Joanne Mortimer, M.D., Joseph Chao, M.D., Warren Chow, M.D., Yuan Yuan, M.D., and Stephen Koehler, M.D.

Confirm in the electronic medical record that the patient has received the Notice of Privacy Practice. This must be obtained before the eligibility confirmation and obtaining of the research informed consent.

4.2.1 <u>Registration Process (City of Hope patients)</u>

- Registrations for this protocol must be made through the CTO office at the City of Hope between the hours of 8:30 a.m. to 4:30 p.m., Monday through Friday (except holidays).
- Patients must be registered within 2 weeks prior to initiation of protocol therapy.
- A patient failing to meet all protocol requirements may not be registered. If you have any questions regarding eligibility, contact (626) 256-4673 ext. 62468 and ask for the CRA in charge of this study.
- Prestudy laboratory tests, scans and x-rays must be completed prior to registration according to the study calendar.
- Patients must sign an informed consent prior to registration.
- Confirm that the patient meets all inclusion and exclusion eligibility criteria for the protocol.
- Complete the Eligibility Checklist.
- Verify that all required pre-study tests were performed.
- Fax the completed Eligibility Checklist and the signed, dated informed consent to CTO. The FAX number is (626) 301-8393.
- Call CRA at (626) 256-4673 x 62468 to confirm the FAX arrival. If the Coordinator is not in the office, have her paged.
- If the patient qualifies, the City of Hope Coordinator will assign the patient's study ID number.
- Once a patient has been registered, CRA will confirm registration of the patient.

The outside institution patient registration process will be handled by the Department of Clinical Research Information Support (CRIS) Data Coordinating Center (DCC) at City of Hope. Documentation of current IRB approval must be on file with the DCC prior to registration of patients on this study for participating institutions.

The steps below are to be taken when registering a **patient at a participating institution**:

4.2.2 Registration Process (Participating Institutions)

The participating institution's research staff must assure they have the most current and updated version of the protocol and informed consent prior to enrolling a patient. If a question arises, please contact the Data Coordinating Center at 626-256-4673 extension 63968 or via pager at 626-423-6486.

The participating institution must assure that all pre-study laboratory tests, scans and x-rays have been completed prior to registration according to the study calendar.

The participating institution must assure that the patient has signed an approved informed consent prior to registration, including Experimental Subject Bill of Rights (if applicable) and appropriate HIPAA authorization.

The participating institution must confirm that the patient meets all inclusion and exclusion eligibility criteria for a protocol. The eligibility checklist must be completed in its entirety.

A patient failing to meet all protocol requirements may not be registered. Patients must be registered within 2 weeks prior to initiation of protocol therapy.

Once a patient is eligible, all the pre-study requirements have been fulfilled, and the informed consent obtained, the research nurse or the data manager (study coordinator) at the participating center will inform the Data Coordinating Center (626-

256-4673, ext 63968; pager 626-423-6486) and FAX (fax number 626-301-8422) a copy of the signed informed consent, patients' Bill of Rights, signed HIPPA consent, completed eligibility checklist and corresponding source documentation confirming eligibility (including pathology reports, lab reports, x-ray reports, etc.).

4.2.3 The Data Coordinating Center will:

- Review all materials received to ensure the patient is eligible.
- Ensure the consent form is valid and is signed correctly by all parties. If additional information is needed or should there be any questions, the Data Coordinating Center will immediately contact the participating institution and registration will not occur until all issues are resolved. No exceptions will be granted.
- The patient will be registered centrally at City of Hope.
- Confirmation of Registration will be emailed/faxed to the participating institution noting study number as well as assigning the dose (if applicable) within 24 hours via fax or email.
- The Data Coordinating Center will call the research nurse or data manager (study coordinator) at the participating site and verbally confirm registration.

- If a patient does not receive protocol therapy following registration, the patient's registration on the study may be cancelled. The Data Coordinating Center should be notified of cancellations as soon as possible.

4.3. Procedures for On-Study and Treatment Deviations

Any amendments to the study protocol need to be approved by the IRBs at both the study sponsor site as well as at all participating centers. All deviations or single subject exceptions to the study protocol must be reported to the primary IRB of the participating site, and to Dr. Arti Hurria, the study PI at the sponsoring institution.

5.0. TREATMENT PLAN

5.1.Guidelines for *Nab*-Paclitaxel Administration

Nab-paclitaxel (ABI-007, *nab*-paclitaxel, albumin-bound 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.

NOTE: It is not a requirement to use filter needles in the preparation of, or in-line filters during the administration of *nab*-paclitaxel. In any event, filters of pore-size less than 15 micrometers must not be used.

5.1.1 *Nab*-paclitaxel Premedication

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

5.1.2. Treatment Plan

Nab-paclitaxel 100mg/m^2 will be administered on a 3 week on +/- 1 day from indicated dates, 1 week off schedule. Treatment will be administered on an outpatient basis. Comprehensive adverse events and potential risks for *nab*-paclitaxel are described in **Section 2.2.2.2.6**. Appropriate dose modifications for *nab*-paclitaxel are described in **Section 6**. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.2. Duration of Therapy

Protocol therapy will continue until one of the following criteria applies:

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

Restaging will be performed after every two cycles. All patients who enter the trial will undergo a comprehensive assessment consisting of an evaluation of the individual's functional status, comorbid medical conditions, cognition, nutritional status, psychological state, and social support. The assessment will be repeated at the end of 2 cycles of therapy and upon completion of therapy. Data regarding grade 2, 3 or 4 toxicity, dose delays, and dose reductions will be recorded.

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

6.0. DOSING DELAYS/DOSE MODIFICATIONS

6.1. Administration of Study Drug to Patients with Abnormal Hematologic Function

Nab-paclitaxel dosing should not be administered at the start of each cycle until absolute neutrophil count is $\geq$1,500/mm^3, platelets are $\geq$100,000cells/mm^3, and Hb is $\geq$ 9.0g/dl. If the ANC is below threshold, GCSF can be given per physician discretion and GCSF must be administered with subsequent cycles. Treatment will be held until ANC $\geq$1500/mm^3. In the event that day 1 is held, the day 8 criteria for treatment must be: ANC $\geq$1,500/mm^3, platelets $\geq$100,000cells/mm^3, and Hb $\geq$ 9.0g/dl. If days 1 and day 8 are held, the day 15 criteria for treatment must be: ANC $\geq$1,500/mm^3, platelets $\geq$100,000cells/mm^3, and Hb $\geq$ 9.0g/dl.

For patients receiving weekly *nab*-paclitaxel, for each subsequent dose of *nab*-paclitaxel within a cycle (Days 8 and 15), patients must have an absolute neutrophil count $\geq$1,000/mm^3, platelets $\geq$100,000cells/mm^3, and Hb $\geq$ 9.0g/dl. If the counts are not adequate for treatment on Day 8 and/or 15, the dose will be omitted and the total cycle length remains the same. Upon a grade 2 ANC (<1500 to 1000/mm^3) on day 8 or day 15 of treatment, treatment will be administered and GCSF support will be initiated. Treatment will be held for a grade 3 ANC (<1000 to 500/mm^3) and GCSF support would be initiated and continued on all subsequent cycles, support following the day 15 dose may be held based on physician discretion. Patients who experience hemoglobin below 9.0 g/dl may receive a blood transfusion to stimulate counts. Normal treatment may be given if counts are then documented as adequate and the patient falls in the +/-1 day window but will remain on the original treatment schedule.

6.2. Administration of Study Drug to Patients with Abnormal Hepatic Function

Study drug should only be administered if hepatic function is within the parameters established in the eligibility criteria. Hepatic toxicity from taxanes may occur but it is uncommon. Therefore, hepatic dysfunction that occurs while the patient is on study should prompt an evaluation to determine the cause, including the possibility of progressive metastatic disease and hepatotoxicity from concurrent medications.

6.3. Dose Modification

Dose Level	*Nab*-Paclitaxel Dose
0	100
-1	80
-2	60

Patients who require dose modifications will be allowed to continue on study for 2 dose modifications (down to dose level -2). If the patient experiences any further toxicity necessitating a dose reduction beyond dose level -2, they will be removed from the study protocol.

6.4. Dose Reductions and Guidelines for Use of Growth Factors for Hematologic Toxicity

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

Table 4:Use of G-CSF and Dose Holds for Hematologic Toxicity

Day 1*		
	If counts are…	Action to be Taken
ANC	<1500 mm^3	Hold treatment and initiate GCSF for subsequent doses (GCSF can be initiated following the dose hold per MD discretion)
Platelets	< 100,000cells/mm^3	Hold treatment
Hemoglobin	≤ 9.0g/dl.	Hold treatment. Patient may receive a blood transfusion. Treatment may be given if counts are then documented as adequate and the patient is +/- 1 day from the original treatment date.
Day 8 and 15		
ANC	<1000 mm^3	Hold treatment and initiate GCSF
	<1500 to 1000/mm^3	Treatment is given and GCSF support is initiated for this cycle and all subsequent cycles
Platelets	< 100,000cells/mm^3	Hold treatment
Hemoglobin	≤ 9.0g/dl.	Hold treatment. Patient may receive a blood transfusion. Treatment may be given if counts are then documented as adequate and the patient is +/- 1 day from the original treatment date.

* These criteria will be applied for day 8 if the day 1 dose is omitted and applies for day 15 if days 1 and 8 doses are omitted.
Note: Once GCSF support is initiated, it must be continued on all subsequent doses. Support following day 15 may be held based on physician discretion.

*See NCI Toxicity Criteria 4.0 Scale for definition of Grade 3 and Grade 4 events.
** Treatments skipped due to toxicity will be omitted and total cycle length remains the same.

6.4.1. G-CSF Administration

For weekly study drug administration administer G-CSF 5 mcg/kg/day (rounded to the nearest vial size per investigator/institution's standard of care). The number of days of G-CSF is up to the discretion of the treating MD; however, the patient must start at least 24 hours after the dose of chemotherapy and be held at least 48 hours prior to the next dose. The dose of the G-CSF can be adjusted based on the investigator's discretion. The delivery of G-CSF following week #3 of any cycle is per investigator discretion (since the patient will have a 2 week break prior to the next dose). At the first occurrence of a hematological toxicity (as outlined above), the same dose is maintained and G-CSF is given as outlined below. In the event that a hematological toxicity re-occurs in the face of G-CSF, dose reduction to the next lower level will be required for subsequent cycles once ANC is ≥ 1500 cells/mm3.

6.4.2. Sensory Neuropathy

Nab-paclitaxel should be withheld in patients who experience ≥ Grade 2 sensory neuropathy. Treatment may be resumed at the next lower dose level (see Section 6.3) in subsequent cycles after the sensory neuropathy improves to ≤ Grade 1. The time to resolution to Grade ≤ 1 should be the adverse event duration used for adverse event reporting. 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 Level -2; see Table 2) in subsequent cycles after the sensory neuropathy improves to ≤ Grade 1.

6.4.3. 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 reactions to *nab*-paclitaxel should not be re-challenged.

6.4.4. Other Toxicities

If toxicities are ≥ grade 3, except for anemia, any pre-existing comorbidities, or toxicities deemed unrelated to cancer or cancer treatment (such as hypertension, hyperglycemia, decreased lymphocyte count, non-cancer related pain, fracture or orthopedic surgery), treatment should be withheld until resolution to ≤ grade 1 or baseline if baseline was greater than grade 1, then reinstituted, if medically appropriate, at the next lower dose level (see Section 6.3). Patients who present with grade 1-2 toxicities may have their treatment held at the discretion of the treating physician. Patients may also have their dose reduced to the next lower level based on grade 1-2 toxicities at the discretion of the treating physician. Treatments skipped due to toxicity will be omitted and total cycle length remains the same.

6.4.5. Concomitant Medications

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. Erythropoietin and G-CSF may be administered at the discretion of the investigator, consistent with institutional guidelines.

7.0. PHARMACEUTICAL INFORMATION

7.1. Availability / Distribution

Nab-paclitaxel will be supplied by Celgene Corporation, in single-use vials. Each single-use 50 mL vial will contain paclitaxel (100 mg) and approximately 900 mg human albumin (HA) as a stabilizer. Each vial will be labeled according to country-specific regulatory requirements for labeling of investigational products.

Investigational sites will be supplied with *nab*-paclitaxel upon identification and screening of a potential trial subject. No supplies will be shipped until regulatory approval has been obtained. Upon identification of a potential subject, sites must fax a completed Drug Request Form to Celgene Corporation. Allow at least 5

working days for drug shipment. There are no shipments on Fridays or holidays. For re-supply of drug, complete and fax the Drug Request Form to Celgene Corporation at 908-673-2779.

7.2. Storage and Stability

Unreconstituted *nab*-paclitaxel should be stored at controlled room temperature (20° to 25°C or 68° to 77°F) in its carton. Retain in the original package to protect from bright light. Unopened vials of albumin-bound paclitaxel are stable until the date indicated on the package when stored at the above temperatures in the original package. Reconstituted albumin-bound paclitaxel should be used immediately, but may be refrigerated at 2°C to 8°C (38°F to 46°F) for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion. Also, the suspension for infusion (reconstituted as recommended) is stable in an IV bag at room temperature 20°C to 25°C (68-77°F) and ambient lighting conditions for up to 8 hours if necessary.

7.3. Study Medication Administration

Albumin-bound paclitaxel should be administered by IV over 30 minutes. **NOTE: It is not a requirement to use filter needles in the preparation of, or in-line filters during the administration of *nab*-paclitaxel. In any event, filters of pore-size less than 15 micrometers must not be used.**

7.3.1. Reconstitution and use of *Nab*-paclitaxel

1. Calculate the patient's body surface area at the beginning of the study and if the weight changes by > 10%. If the patient's weight changes by >10%, a new body surface area will be calculated and used to determine Total Dose for subsequent chemotherapy administrations.

2. Calculate the total dose (in mg) to be administered by:

$$\text{Total Dose (mg)} = \text{BSA} \times (\text{study dose mg/m}^2)$$

3. Calculate the total number of vials required by:

$$\text{Total Number of Vials} = \frac{\text{Total Dose (mg)}}{\text{100 (mg/vial)}}$$

Round up the number of vials to be reconstituted to the next higher whole number when a fractional number of vials is obtained by the above formula (eg, if the total number of vials = 4.05 or 4.5, then 5 vials would be reconstituted).

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

5. Swab the rubber stoppers with alcohol.

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

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

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

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

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

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

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

7. Calculate the exact total dosing volume of 5 mg/ml suspension required for the patient:

Dosing volume (ml) = Total dose (mg) / 5 (mg/ml)

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

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

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

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

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

8.0. QUESTIONNAIRES

Appendix I and II describe the data which will be captured as a part of this study. Appendix I is data gathered by the research interviewer. Appendix II is the "Self-Assessment Measure" is completed by the patient. If the patient requires assistance, a member of the healthcare or research team will assist them. Appendix I and II will be completed at three time points (+/- 2 weeks):

1) prior to initiation of cycle #1

2) prior to the 3rd cycle
3) end of the study

8.1. Data to be gathered by the research interviewer (Appendix I):

1) Medical Characteristics:
    a) Cancer diagnosis*
    b) Disease stage*
    c) Chemotherapy regimen*
    d) Labs: Hemoglobin, Creatinine, LFTs, albumin
2) Functional Status:
    a) Physician rated KPS (to be obtained from the primary MD)
    b) Timed Up and Go
3) Cognition: Blessed Orientation-Memory-Concentration*
4) Nutrition
    a) Body Mass Index
    b) Percent Unintentional Weight Loss*

*Time point #1 only

8.2. Data to be completed by study participants: (Appendix II: Geriatric Assessment Measures)

1) Demographics (Age, Marital status, Educational Status, Household composition, Employment status, Race, Ethnicity)
2) Functional Status:
    a) Older American Resources and Services (OARS): Instrumental Activities of Daily Living (IADL)
    b) Medical Outcomes Study (MOS): Physical Functioning
    c) Karnofsky Performance Status (KPS): Patient Rated
    d) Number of falls in last 6 months
3) Comorbidity: OARS Physical Health Sub-scale
4) Psychological status: Mental Health Inventory - 17
5) Social functioning and support:
    a) MOS Social Activity Limitation:
    b) Medical Outcomes Study (MOS) Social Support Subscale
6) Nutritional Status:
    a) Amount of involuntarily weight loss over the past 6 months
    b) Baseline weight
7) Questions Concerning the Geriatric Assessment

8.3. Data to be collected at each clinic visit while on treatment:

The following information will be collected at each clinic visit
    1) Grade 2, 3 or 4 toxicity
    2) Hospitalization
    3) Dose delay or reduction
    4) Discontinuation of chemotherapy course because of toxicity

8.4. Description of Questionnaire Measures

8.4.1. Functional Status

a) Activities of Daily Living: [subscale of Medical Outcomes Study (MOS) Physical Health]
The MOS Physical Health Scale contains measures of higher levels of physical functioning than those described in other activities of daily living scales. The variation in functioning among healthier patients in the study will be examined through asking about higher order functioning. The scale includes items on vigorous activities (running, lifting heavy items) as well as basic activities (bathing and dressing). Items are rated on a three-point Likert scale of independent performance of the activity. The sum of the scores is divided by the total number of items responded to in that scale. The scale score is then transformed into a 0-100 score. Internal consistency of the physical function score is high at 0.92.[45]

b) Instrumental Activities of Daily Living (IADL): [subscale of the Older American Resources and Services (OARS)]
The OARS Multidimensional Functional Assessment Questionnaire (MFAQ) was developed to provide a profile of the level of functioning and need for services of older persons who live at home but may have some degree of impairment. The MFAQ has been tested on over 6,000 older community residents.[46] The Instrumental Activities of Daily Living (IADL) subscale consists of 7 questions rated on a three-point Likert scale of degree to which the activity can be performed independently. Norms are available for the MFAQ based on 2,146 elderly community residents.[47]

c) Karnofsky Physician-Rated Performance Rating Scale (KPS)
The Karnofsky Performance Status, has been widely used in the evaluation of cancer patients.[48] It is a general measure of patient independence in carrying out normal activities. Patients are given a score on a numerical scale of 0-100 as a global indicator of functional status. Studies on inter-rater reliability between nurse and social worker KPS ratings indicate good correlation ($r = 0.69$, $p<.001$). KPS was most strongly correlated with variables related to physical functioning (difficulty with stairs: $r = 0.63$; difficulty with balance: $r = 0.61$).[49]

d) Karnofsky Self-Reported Performance Rating Scale
A patient self-report version of the Karnofsky Performance Scale was developed by several researchers to assess the patient's perception of performance status.[50] The Wingard version is chosen for this study because it is significantly related to survival. Items range from severely disabled, requiring continuous nursing care, to normal activities requiring no assistance.[51]

e) Timed Up & Go
The timed "up and go" is a test of physical mobility. The test, measured in seconds, is the time it takes for an individual to stand up from a standard arm-chair (approximate seat height of 46 cm), walk a distance of 3 meters (10 feet), turn, walk back to the chair, and sit down again. Intra-rater and inter-rater reliability was extremely high (intra-class correlation 0.99). Performance on the timed "up and go" test significantly correlated with scores of other performance measures including Berg Balance Scale ($r = -0.81$), gait speed ($r = -0.61$), and Barthel Index of ADL ($r = -0.78$).[52]

f) Number of Falls in Last 6 Months
Older patients are at risk for falls and injury secondary to falls because of gait and balance impairments. In patients with cancer the risk is even greater for a number of reasons. First, bony metastases may place them at

risk of a pathologic fracture with falls. Secondly, patients receiving chemotherapy may have a low platelet count which puts them at greater risk of hemorrhage. Lastly, commonly used chemotherapy drugs may have neurologic complications resulting in falls. For example, paclitaxel and cisplatin may cause neuropathy, fluorouracil and cytarabine may cause cerebellar toxicity. For these reasons, knowing a patient's risk of falling before treatment could help providers make treatment decisions.[53]

8.4.2. Comorbidity

Physical Health Section [subscale of The Older American Resources and Services Questionnaire (OARS)]:
The OARS Physical Health Section is a comorbidity scale which contains a list of concurrent illnesses and the degree to which they impair daily activities, rated on a three-point scale of "not at all" to "a great deal." Medication use is recorded. Test-retest reliability was excellent (r = .66) over a five-week period. In terms of validity, the Physical Health subscale correlated significantly with health professional ratings (Kendall's tau co-efficient =.75).[46]

8.4.3. Cognition

Blessed Orientation-Memory-Concentration Test
The BOMC consists of 6 questions designed to screen for gross cognitive impairment. A score >11 signifies cognitive impairment. The test-retest reliability is high (Spearman Rank Correlation 0.96; $p < 0.001$).[54] The BOMC has excellent validity as a screening instrument, correlates highly with clinicians' ratings of dementia severity (r=0.89), predicts results from a longer (26 item) mental status questionnaire, and discriminates between patients with mild, moderate, and severe cognitive deficits.[55]

8.4.4. Psychological

Mental Health Inventory - 17
The Mental Health Inventory (MHI) (Revised General Well-Being Scale) is based upon the General Well-Being Scale, developed by Dupuy for the National Health Interview Survey, and was included in a battery of health measures in the Rand Health Insurance Study.[64] The full length MHI consists of 38 items grouped into five subscales (anxiety, depression, general positive effect, emotional ties, and loss of behavior control) and three global scores (Psychological Distress – negative effect, Psychological Well-Being – positive effect, and the MHI total score). The MHI-17, a 17 item version of the full 38 item MHI, will be used in this study to measure psychological health, in order to reduce respondent burden, The MHI-17 will yield three global scores of Psychological Distress, Psychological Well-Being, and MHI total score, as in the original 38 item MHI.[61] Each score is on a scale of 0-100: a higher Psychological Distress score indicates higher distress, a higher Psychological Well-Being score indicates greater well-being, and a higher MHI score indicates greater mental health. The MHI has demonstrated an excellent external consistency (alpha coefficient = .96).[61]

8.4.5. Social Functioning

Medical Outcomes Study (MOS) Social Activity Limitations Measure

The impact of cancer on patients' social functioning will be assessed by the Social Activity Limitations scale from the Medical Outcome Study (MOS).[61] As with all MOS measures, the Social Activity Limitations scale was developed from a national sample of medically ill patients being treated in outpatient facilities. The four-item scale assesses the extent to which physical or emotional problems have interfered with social activities. All items are rated on a 5-point Likert scale, with response categories varying with each item. The mean of the total score is transformed to a scale of 0-100, with a higher number indicating greater support. Internal consistency was good (alpha coefficient = .77). The scale correlates significantly with a range of measures: role limitations due to physical (r= .52) and emotional (r = .49) health, psychological distress (r= .64) and pain (r = .55).

8.4.6. Social Support

Medical Outcomes Study (MOS) Social Support Survey: Emotional/Information and Tangible Subscales
This is a 20-item measure of social support, with four subscales: emotional/informational, tangible, affectionate, and positive social interactions. The scale was developed as part of the Medical Outcome Study, tested on 2987 patients, and designed to assess quality of life across medical conditions. In this study, we use the Tangible (access to material aid or behavioral assistance) and Emotional/Information (the expression of positive affect and empathetic understanding; the offering of advice, information, guidance, or feedback) subscales. All but one item is rated on a five-point Likert scale from "None of the Time" to "All of the Time." Internal consistency of the subscales and total score are excellent (alpha coefficient $\geq$ 0.91). Convergent validity was demonstrated by significant correlations of social support total score with measures of mental health (r =.45).[61]

8.4.7. Nutrition

a) % Unintentional Weight Loss
Patients will be asked to quantify the amount of unintentional weight loss in the past 6 months and to record their baseline body weight 6 months ago.

The following is the calculation for % unintentional weight loss:

$$\%\ \text{unintentional weight loss} = 100 \times \frac{\text{unintentional weight lost in last six months}}{\text{baseline body weight}}$$

b) Body Mass Index
Weight and height will be measured in order to calculate body mass index, by the following formula:

$$\text{BMI} = \frac{\text{Weight in kg}}{\text{Height in m}^2}$$

9.0. STUDY CALENDAR

SCHEDULE OF EVALUATIONS / STUDY CALENDAR

Parameter	Pre-study	Prior to the 1st dose of each cycle	Prior to the 2st dose of each cycle	Prior to the 3rd dose of each cycle	Prior to the 3rd cycle	After every 2 cycles	Study Termi-nation
MD Visit	X	X		X			
Physical examination	X	X		X			
Vital signs	X	X		X			
CBC, ANC, platelet count	X	X	X	X			
CMP*	X	X		X			
CEA, CA15-3**		X					
CT Chest, Abdomen, Pelvis	X†					X	
Comprehensive Geriatric Assessment***	X				X		X

*CMP = comprehensive biochemical screening profile (which includes electrolytes, BUN, creatinine, AST, ALT, total bilirubin, total protein, albumin, alkaline phosphatase, and glucose)

**CEA, CA15-3 baseline tumor marker evaluations are to be conducted within 2 weeks of administration of protocol therapy

***+/- 2 weeks

† For baseline evaluations, if a PET-CT was done within the 4 week window prior to start of therapy, the study team will review with the study radiologist to see if the CT portion is sufficient to measure baseline target lesions. With the study radiologist's confirmation, the PET-CT will then be utilized for the baseline radiologic evaluation.

Baseline evaluations are to be conducted within 2 weeks prior to administration of protocol therapy. Scans and x-rays must be done within 4 weeks prior to the start of therapy. Tests indicated for the following weeks may be performed within ± two days of the indicated dates. Cycles consist of three weeks of therapy +/- 1 day from indicated dates followed by a one week break.

10.0 MEASUREMENT OF EFFECT

In this protocol, assessment of response and TTP will be a secondary objective. We will use RECIST criteria to assess response; however, due to limited resources, confirmatory scans will not be performed. RECIST criteria are described below.

10.1 Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.
- Key criteria for assessing tumor burden is taken verbatim from RECIST. For full reference, see the Revised RECIST guideline by Eisenhauer et al.

  Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology**.**

  Measurable lesions - lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
  - 10 mm caliper measurement by clinical exam
  - 20 mm by chest X-ray

  Non-measurable lesions - all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and also abdominal masses/abdominal organomegaly that are identified by physical exam but are not measurable by reproducible imaging techniques.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. A PET-CT may be used for the baseline evaluation if done within the specified window and the study radiologist confirms that the CT portion of the PET-CT is adequate for baseline tumor measurements.

- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

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

10.2. Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. 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. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

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

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

- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

10.3. Baseline documentation of "Target" and "Non-Target" lesions

- When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as ***target lesions*** and will be recorded at baseline (this means in instances where patients have only one or two organ sites involved a *maximum* of two and four lesions respectively will be recorded)..

- Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

- Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum.

- A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. The baseline sum diameters will be used

as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form.

10.4. Response Criteria

Evaluation of target lesions

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

Evaluation of non-target lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

(1) Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

10.4.1. Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	NE	No	PR

PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

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

10.4.2. Confirmation

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

- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

10.4.3. Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

10.4.4. Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two

measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

10.4.5. Response review

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

10.5. Reporting of results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

- All conclusions should be based on all eligible patients.

- Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.

- The 95% confidence intervals should be provided.

11.0 REGULATORY AND REPORTING REQUIREMENTS

11.1 Identification, Recording, and Handling Adverse Events

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

11.2 Definitions and Types of Adverse Events

11.2.1 Adverse Event (AE)

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

11.2.2 Causality

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

11.2.3. Adverse Events Grading and Data Collection

Adverse events will be graded according to the CTCAE v4.0. Any CTCAEgrade 2-5 will be considered an AE an collected on the CRFs.

11.3. Additional Criteria for COH Data and Safety Monitoring

A) Definition of Risk Level

This is a Risk Level 3 study, as defined in the "Guidance, Policy and Procedures for Data and Safety Monitoring for In-House Trials at City of Hope", http://www.coh.org/dsmc/Pages/forms-and-procedures.aspx because it is a Phase II/ Pharmacokinetics clinical trial where the risks are at least balanced by the potential benefit to subjects and the importance of the knowledge that may result.

B) Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT) consisting of the PI, Collaborating Investigator, CRA, protocol nurse, and statistician is responsible for monitoring the data and safety of this study, including implementation of any stopping rules for safety and efficacy.

Data and safety will be reported to the COH DSMB. Protocol specific data collection will include the following items: dose reductions, dose delays and grade 2, 3 & 4 toxicities**.** Reporting of data and safety to the DSMB will occur at intervals of 6 months using the PMT report.

C) Definitions **Adverse event (AE) -** An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Attribution - For reporting purposes, attribution is the assessment of the likelihood that an AE is caused by the research agent or protocol intervention. The attribution is assigned by the Principal

Investigator after considering the clinical information, the medical history of the subject, and past experience with the research agent/intervention. The attribution is subject to change as follow-up information becomes available, and it can be changed by the DSMC or by the IRB during the process of review.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event

Serious Adverse Event (SAE) [21 CFR 312.32] is defined as *any expected or unexpected adverse event* that results in any of the following outcomes:

- Death
- Is life-threatening event (places the subject at immediate risk of death from the event as it occurred);
- Requires in-patient hospitalization (not required as part of the treatment) or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect
- Secondary Malignancy, or
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasisas of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated problem (UP) – Any incident, experience or outcome that <u>meets all three</u> of the following criteria:

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

Unexpected Adverse Event [21 CFR 312.32 (a) – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

D. Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems: Unanticipated problems must be reported to the COH DSMC and IRB **within 5 calendar days** according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx. Any unanticipated problem that occurs during the study conduct will be reported to the DSMC and IRB by submitting electronically in iRIS (http://iris.coh.org).

Serious Adverse Events - All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be reported according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx and Table 5 below. Those SAEs that require expedited reporting will be submitted electronically in iRIS (http://iris.coh.org/).

Adverse Events - Adverse events will be monitored by the PMT. Adverse events that do not meet the criteria of serious adverse event or are not unanticipated problems will be reported only at the time of protocol continuation reports (see Table 5 below).

Table 5: City of Hope Adverse Event Reporting Timelines for the IRB and DSMC

Required Reporting Timeframe to IRB of Record		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grades 3 and 4 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grade 1 and 2 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual

Required Reporting Timeframe to DSMC		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	5 calendar days	
Unlikely, Unrelated		
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	5 calendar days	No reporting required*
Unlikely, Unrelated	No reporting required*	No reporting required*
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	5 calendar days	5 calendar days
Unlikely, Unrelated	5 calendar days	5 calendar days
	Grade 1 and 2 AND resulting in "hospitalization"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	10 calendar days	10 calendar days

*Such events are not required to be reported to the DSMC. These events should be included with the SAE/AE summary provided in the IRB Annual Continuation reports.

11.4. Safety Reporting Requirements and Timelines – City of Hope Process

The Sponsor-Investigator will utilize the FDA MedWatch program for the reporting of adverse events and follow up information to those events. Full information regarding these procedures is described on the FDA website. (http://www.fda.gov/medwatch/).

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

All serious adverse events regardless of severity or relationship must be reported to Celgene Corporation within 24 hours of the investigational staff's knowledge.

Celgene Corporation
Drug Safety Department
86 Morris Avenue
Summit, NJ 07901
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

and

Industry Contact:
Norma Powers
Director, Medical Operations
Celgene Corporation
86 Morris Avenue
Summit, NJ 07901
Mobile: 267-337-2720
Fax: 908-673-2779
Email: npowers@celgene.com

11.5 Safety Reporting Requirements and Timelines – Participating Sites

The guideline is to provide a procedure for accurate and timely reporting of serious adverse events (SAEs) from the participating institution to the Principal Investigator (PI) at City of Hope (COH). The participating institution, participating PI and/or study coordinators are responsible for reporting all serious adverse events immediately (within 24 hours after learning of the event) to their local IRB, the PI at City of Hope, and the Data Coordinating Center at COH.

The participating investigator must report each serious adverse event, regardless of attribution, to the Principal Investigator within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event.

Report to City of Hope all serious adverse events by telephone (to Dr. Hurria and the DCC) and send via fax a copy of the following forms:

- Participating sites internal serious adverse event form.
- FDA MedWatch Form 3500A
- Notification of Toxicity Form (Appendix IV)

SAE Notification Contact Numbers:

Dr. Arti Hurria	Phone: 626-471-9200	Fax: 626-301-8233
Data Coordinating Center	Phone: 626-256-4673x63968	Fax: 626-301-8422

The participating institution will notify their local IRB as per their local established guidelines, and include a copy of the completed FDA MedWatch Form 3500A.

The Data Coordinating Center at City of Hope will send a copy of the participating institutions serious adverse event (reported via FDA MedWatch Form) to the following internal departments:

- City of Hope IRB
- Celgene Corporation.

Any supporting documentation to the reports (i.e., laboratory, pathology, progress notes, discharge summary, autopsy, etc.) explaining the adverse event should also be submitted to the Data Coordinating Center at City of Hope. The Data Coordinating Center will then submit to our COH IRB as well as submit to Celgene in a timely manner.

Drug Return and Destruction

If the investigational site does not have a policy, procedure or SOP detailing the process to follow for study drug destruction, the study drug must then be returned to Celgene using the Drug Return Form provided in the package containing the study drug. The following information must be recorded on the site's pharmacy drug accountability log: quantity of vials to be returned, expiration date and lot number. A copy of the Drug Return Form and the study drug should be returned to Celgene Clinical Supplies Dept. using the mailing address on the packaging slip that came with the original study drug order. A copy of the Drug Return Form should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records (drug dispensing log, drug accountability log and any destruction memos) must be mailed to Celgene Medical Operations.

If the investigational site has a policy, procedure or SOP detailing the process to follow for study drug destruction, the pharmacist or designee can choose to destroy the study drug on site. The following information must be recorded on the site's pharmacy drug accountability log: quantity of vials destroyed, expiration date and lot number. The pharmacist must document that the study drug was destroyed in accordance with their institution's drug destruction policy or SOP. A drug destruction memo and the site's drug destruction SOP/policy should be sent to Celgene Medical Operations Dept. A copy of the drug destruction memo should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records (drug dispensing log, drug accountability log and any destruction memos) must be mailed to Celgene Medical Operations.

In addition, the Sponsor-Investigator will adhere to the safety reporting requirements and timelines described in the Clinical Trial Agreement with Celgene Corporation.

The Sponsor-Investigator will provide full and timely cooperation with any requests from Celgene, governing IRB, institution, or regulatory agency with any requests regarding reports of individual reports of adverse events.

11.6. Human Subjects Issues

11.6.1. Informed Consent Process

Ethical standards for human subjects will be strictly followed. The purpose of the study will be thoroughly explained to potential subjects. It will be emphasized that participation is totally voluntary. Patients may choose to withdraw at any time without adverse consequence to medical care. Patients will be informed of the research nature of this project and that while their participation may enable improvements in patient care, there is no guarantee of personal benefit. Procedures for assuring confidentiality will be discussed. Informed consent will be contingent upon patient's full awareness and affirmation of these ethical standards. Once all questions have been addressed, informed consent will be obtained. A consent document will be signed and maintained in their medical record.

11.6.2. Alternatives

Participation in this study is voluntary. Participants may choose to participate or decline. There are no adverse consequences to not participating.

11.6.3. Confidentiality and Storage of Records

The original data collection forms will be submitted into Medidata Electronic Data Collection (EDC). Data will be stored in encrypted, password protected, secure computers that meet all HIPAA requirements. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed. Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. They will be made available for review, as required by the FDA, HHS, or other authorized users such as the NCI, under the guidelines established by the Federal Privacy Act and rules for the protection of human subjects

The study protocol will strictly adhere to all HIPAA and COH IRB regulations. Confidentiality of the subjects will be maintained. No data will be linked to a particular name or personal identifiers. The individual results will not be disclosed. The de-identified dataset will be provided to the investigators for analysis. The composite results will be analyzed and summarized for presentation and publication.

11.6.4. Financial Compensation and Obligation to be Incurred by the Research Subject

There will be no financial compensation for participating in this study.

12.0 STATISTICAL CONSIDERATIONS

The study will be an open label, single arm, phase IIA toxicity study to describe the toxicity profile of *nab*-paclitaxel in patients age 65 and older with locally advanced or metastatic breast cancer who are receiving first or second line treatment. We plan to study 40 subjects, using a stratification factor based on patient age (at least 5 patients age 75 years or older and no more than 15 patients age 65-70 years)

There will be one interim analysis after 20 subjects have completed one cycle of drug.

12.1 Primary Objective

12.1.1. To evaluate the tolerability (grade 2-5 toxicity, neuropathy grade 2 or higher, dose reductions, delays, or interruptions) of weekly *nab*-paclitaxel in older adults with locally advanced or metastatic breast cancer

12.2 Secondary Objectives:

12.2.1. To evaluate the efficacy (response and time to progression) of weekly *nab*-paclitaxel in older adults with locally advanced or metastatic breast cancer.

12.2.2. To explore predictors of the need for dose reduction, dose delays, or grade 2-5 toxicity and neuropathy grade 2 or higher based on a cancer-specific geriatric assessment.

Sample Size Justification: Given a sample size of 40 subjects the widest half-width of the 95% confidence limits for the rate of grade 2 or higher neuropathy and grade 2 or higher other toxicities will be less than or equal to 0.16. For example if we saw a toxicity rate of 0.2 (8 subjects/40) the 95% lower and upper confidence limits would be .09 and .36, respectively.

Interim Analysis: After approximately 20 subjects have completed one full cycle, the study team will review the data and assess if the dose being studied is too high, that is requiring too many patients, in the opinion of the team, to experience a dose reduction. If so, a reduction of the dose will be considered, otherwise the study will continue to completion at the planned dose.

Analysis: Rates and associated 95% exact Clopper and Pearson binomial confidence limits will be estimated for 1) grade 2 or higher neuropathy and grade 2 or higher other toxicities, and 2) dose reductions, delays, and interruptions, 3) objective response rate (CR+PR) and 4) clinical benefit rate (CR+PR+SD) as determined by RECIST. Progression free survival will be estimated using the product limit method of Kaplan and Meier.

Tables will be created to summarize the toxicities and side effects by course, organ and severity for all patients. We will describe all toxicities on a patient by patient basis. Numbers of cycles received and dose reductions will be tabulated. Descriptive statistics will be provided for study patient demographics, including tumor characteristics. General linear models and graphical methods will be used to explore factors as identified by a cancer-specific geriatric assessment that may be predictive of toxicity/dose reduction or dose delays.

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APPENDIX I and II: Geriatric Assessment Survey

Please contact the Principal Investigator (Dr. Arti Hurria) or listed Protocol Personnel to obtain a copy of the Geriatric Assessment Survey.

APPENDIX III: Eligibility Checklist

Efficacy and Tolerability of Nanoparticle Albumin Bound (nab) Paclitaxel in Patients 65 and Older with Metastatic Breast Cancer

Eligibility Checklist*

Question	Yes	No
Does this patient have locally advanced or metastatic breast cancer?	☐	☐
Will the patient be receiving nab-paclitaxel as a single agent?	☐	☐
Is this first or second line chemotherapy treatment for metastatic disease?	☐	☐
Is the patient age ≥65 years?	☐	☐
Is the patient's KPS ≥70%?	KPS %:	☐
Has the patient had resolution of grade ≥ 2 toxicity from prior therapy (other than alopecia)?	☐	☐
Does the patient have peripheral neuropathy ≤ grade 1?	☐	☐
Does the patient have the ability to understand and the willingness to sign a written informed consent document?	☐	☐

Eligibility Checklist*

Question	Yes	No
Is the absolute neutrophil count $\geq$1,500/mm^3?	☐ ANC: Date:	☐
Is the platelet count $\geq$100,000cells/mm^3?	☐ Plt count: Date:	☐
Is the Hb $\geq$ 9.0g/dl?	☐ Hb: Date:	☐
Is the AST and ALT $\leq$ 2.5 x institutional upper limit of normal?	☐ ALT: AST: Date:	☐
Is the alkaline phosphatase $\leq$ 2.5 x upper limit of normal (unless bone metatases are present in the absent of liver metastases)?	☐ Alk phos: Date:	☐
Is the bilirubin $\leq$ 1.5mg/dl?	☐ Bilirubin: Date:	☐

Question	Yes	No
Is the creatinine clearance ≥ 30ml/min? (24 hour collection or Cockcroft-Gault Equation*) Please attach a sheet with your calculations.	☐	☐
	Creatinine Clearance:	
	Date:	
Will the patient be receiving any other investigational agents?	☐	☐
Does the patient have untreated CNS metastases or symptomatic CNS metastases requiring escalating doses of corticosteroids?	☐	☐
Does the patient have a known history of allergic reaction to paclitaxel?	☐	☐
Does the patient have the presence of any serious or uncontrolled infection?	☐	☐
Did the patient receive a taxane for adjuvant therapy or metastatic disease in the last 12 months?	☐	☐

**Shaded boxes must be checked/marked for patient to be eligible*

*Cockcroft-Gault equation:

Creatine clearance (ml/min) = ([{140 – age in years} x body weight in kg]/{72 x Cr in mg/dl}) x 0.85 (female gender)

Signatures:

Consenting MD:_____ Date:_____

Protocol RN:_____ Date:_____

APPENDIX IV

Data Coordinating Center
Department of Clinical Research Information Support
City of Hope

NOTIFICATION OF TOXICITY

THIS FORM ALONG WITH A COPY OF LOCAL IRB REPORT and MEDWATCH 3500A FORM MUST BE FAX'D (626-301-8422) TO THE DATA COORDINATING CENTER WITHIN 24 HOURS OF KNOWLEDGE OF ONSET OF SERIOUS ADVERSE EVENT

COH IRB #11139
INSTITUTIONAL IRB # _____

Efficacy and Tolerability of Nanoparticle Albumin Bound Paclitaxel (Abraxane) in Patients 65 and Older with Locally Advanced or Metastatic Breast Cancer

Participating/Treating Institution: _____
Reporter: _____ Phone #:_____
Email: _____

PATIENT INFORMATION

Patient Name_____ Pt Study ID: _____

SERIOUS ADVERSE EVENT INFORMATION

Serious Adverse Event: _____ Start Date of SAE: ____/____/____

REPORTING INFORMATION

Has the event been reported to the following?

Via Phone/Fax to Dr. Arti Hurria? Phone: 626-471-9200/Fax: 626-301-8233	__ No	__ Yes	Date: __ __ / __ __ / __ __
Institutional IRB?	__ No	__ Yes	Date: __ __ / __ __ / __ __
Report sent to Data Coordinating Center (COH)? Fax: 626-301-8422	__ No	__ Yes	Date: __ __ / __ __ / __ __

APPENDIX V: Multicenter Guidelines

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with sponsoring organization. The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to the FDA and Celgene are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to the FDA and Celgenewith a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to Celgene and the FDA. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the study sponsor chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions through the Coordinating Center.