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TITLE: **Age-Related Changes in Nanoparticle Albumin Bound (nab) Paclitaxel Pharmacokinetics and Pharmacodynamics**

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In Memory of Dr. Arti Hurria

SYNOPSIS

Study Objectives

The primary objective of the study is to determine age-related changes in the pharmacokinetics and pharmacodynamics of weekly nab-paclitaxel. The secondary objectives are to determine response and time to progression, to explore predictors of the need for dose reduction, dose delays, or grade 3 or 4 toxicity, and to explore how the factors captured in a geriatric assessment (called "self-assessment measure for this protocol) are associated with changes in the pharmacokinetics and pharmacodynamics of cancer therapy

Eligibility:

Metastatic breast cancer, first or second line chemotherapy treatment for metastatic disease, age ≥18 years., KPS ≥70%, resolution of grade ≥ 2 toxicity from prior therapy (other than alopecia), peripheral neuropathy ≤ grade 1, hematologic inclusion (white blood cell count ≥3,000cells/mm^3, absolute neutrophil count ≥1,500/mm^3, platelets ≥100,000cells/mm^3, and Hb ≥ 9.0g/dl), 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 absent of liver metastases, bilirubin ≤ 1.5mg/dl, CrCl ≥ 30ml/min) and negative pregnancy test in patients of childbearing potential, 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

Pharmacokinetic sampling:
Pharmacokinetic sampling will be obtained cycle 1, week 1 at the following time points: 0,0.25,0.5,1,1.5,2,4,6,8,24, and 48 hours.

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 3.0.

Sample size: 40 patients

TABLE OF CONTENTS

1.0. OBJECTIVES

1.1. Primary objective:

1.1.1 To determine age-related changes in the pharmacokinetics of weekly nab-paclitaxel

1.1.2 To determine age-related changes in the pharmacodynamics (toxicity) of nab-paclitaxel

1.2. Secondary objectives:

1.2.1. To determine response and time to progression

1.2.2. To explore predictors of pK parameters

1.2.3. To explore predictors of the need for dose reduction, dose delays, or grade 3 or 4 toxicity

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. Docetaxel

In a population pharmacokinetic analysis of 640 patients who received docetaxel, the impact of age on docetaxel clearance was modest, estimated at a 7% decrease in clearance for a patient 71 years of age. Docetaxel clearance decreased in patients with abnormal liver function. A 27% decrease in clearance was noted among patients with elevated transaminases (SGOT or SGPT > 1.5 times upper limit of normal) and alkaline phosphatase (> 2.5 times upper limits of normal). A decrease in docetaxel clearance was a strong predictor of grade 4 neutropenia and febrile neutropenia (a 50% decrease in clearance was associated with a 4.3-fold increased risk of grade 4 neutropenia and a 3-fold increased risk of febrile neutropenia). Based on this, the authors recommended no specific dose adjustments in older patients; however, dose adjustment in patients with liver impairment was recommended.[20]

The pharmacokinetics and toxicity of docetaxel at 75 mg/m^2 every 3 weeks was evaluated in a cohort of 20 patients age 65 and older (median 71 years; range 65 to 80), and 20 patients less than age 65 (median 53 years; range 29 to 64). There was no significant difference in docetaxel pharmacokinetics between these 2 groups. In particular, there was no association between age and docetaxel clearance or age and the AUC of docetaxel. Older patients were more likely to experience grade 4 neutropenia (63% $\geq$ age 65 vs 30% < age 65) and febrile neutropenia (16% $\geq$ age 65 vs 0% < age 65). There was no significant difference in AUC values between patients with grade 4 neutropenia and patients with less than grade 4 neutropenia. Among the 10 patients with an AUC in the upper quartile, 3 out of 6 patients > age 65 experienced febrile neutropenia compared with zero out of 4 patients < age 65. The frequency of nonhematologic toxicity was similar between the older and younger patients.[21]

The pharmacokinetics of weekly docetaxel was evaluated in 2 studies that also included the Erythromycin Breath Test, a surrogate measure of cytochrome 3A4 activity, which is the main enzyme responsible for docetaxel metabolism. In a study by Salviero and colleagues, the pharmacokinetics of docetaxel 40 mg/m^2 was evaluated in a cohort of 54 patients with advanced cancer (median age 63; range 40 to 83). There was no significant association between age and clearance. However, there was a significant correlation between Erythromycin Breath Tests results, liver function enzymes, and docetaxel clearance.[22] Hurria and colleagues studied the pharmacokinetics and toxicity of weekly docetaxel 35 mg/m^2 for 3 weeks followed by a 1-week break in a cohort of 20 patients age 65 and older (median age 75; range 66 to 84). In this cohort, 19 patients were evaluable for pharmacokinetic analysis. There were no significant age-related pharmacokinetic differences in this cohort of older patients. There was a statistically significant association between decreased cytochrome 3A4 activity (as measured by the Erythromycin Breath Test) and decreased docetaxel clearance and increased AUC; however, there was no significant association between either the Erythromycin Breath

Test results or docetaxel pharmacokinetic parameters and the frequency of grade ≥ 3 toxicity.[23]

The pharmacokinetics and pharmacodynamics of weekly docetaxel (for 3 out of 4 weeks) in combination with cisplatin (25 mg/m^2 every 4 weeks) was evaluated in 27 patients age 75 and older and 25 patients under age 75. Patients under age 75 received a docetaxel dose of 35 mg/m^2 and patients age 75 and older received 20 mg/m^2. There was no significant difference in the clearance or volume of distribution of docetaxel in older and younger patients. In comparison with younger patients, older patients had a smaller AUC of docetaxel; however, both groups experienced similar rates of neutropenia, suggesting that older patients were more sensitive to docetaxel exposure than younger patients.[24]

2.3. 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.

2.3.1. 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]

2.3.2. Clinical Studies with Nab-paclitaxel

2.3.2.1. 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 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.

2.3.2.2. 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]

2.3.2.3. 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.

2.3.2.4. Potential Risks of Abraxane

Toxicities
Myelosuppression, nausea and vomiting, diarrhea, mucositis, infections, hypotension, abnormal ECG changes, cough, dyspnea, edema, sensory neuropathy, bilirubin/liver enzyme elevations, 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 #1 below:

Table 1: Frequency[a] of Important Treatment Emergent Adverse Events in the Randomized Study on an Every-3-Weeks Schedule

Percent of Patients		
Nab-Paclitaxel 260/30min[b] (n=229)		**Paclitaxel Injection 175/3h[c,d] (n=225)**
Bone Marrow		
Neutropenia < 2.0 x 109/L < 0.5 x 109/L	 80 9	 82 22
Thrombocytopenia < 100 x 109/L < 50 x 109/L	 2 <1	 3 <1
Anemia < 11 g/dL < 8 g/dL	 33 1	 25 <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 1 (continued): Frequency[a] of Important Treatment Emergent Adverse Events in the Randomized Study on an Every-3-Weeks Schedule

Percent of Patients		
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 Abraxane 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.

2.4. Rationale and Goals of this Study: Pharmacokinetics of Nab-Paclitaxel

The goal of this study is to determine the age-related changes in the pharmacokinetics of nab-paclitaxel. The rationale for exploring weekly dosing is based on the hypothesis that more frequent dosing minimizes tumor regrowth and decreases the emergence of drug resistance. This hypothesis is supported by clinical data from CALGB 9840.[35] In this randomized study, patients with metastatic breast cancer treated with weekly paclitaxel had a superior response and time to progression in comparison to patients treated with every three week paclitaxel. In addition, there is a lower risk of grade 3 or 4 neutropenia with weekly dosing, an important consideration for older patients who have decreased bone marrow reserve. In a phase I trial of weekly nab-paclitaxel, the MTD for heavily treated patients was 100mg/m^2 and the MTD for lightly pre-treated patients was 150mg/m^2.[31] Gradishar et al. evaluated the efficacy and toxicity of weekly verses every 3-week nab-paclitaxel. Patients receiving the weekly nab-paclitaxel dose had a statistically significant higher response rate than patients receiving the every three week dosing. Two different weekly schedules were evaluated: 100mg/m^2 verses 150mg/m^2 delivered 3 weeks in a row followed by a 1 week break. The 100mg/m^2 dose was associated with a lower risk of peripheral neuropathy, neutropenia, fatigue, and arthralgias.[36] Based on all of this data, the 100mg/m^2 3 week on, 1 week off dosing schedule will be used in this study. The specific aims of this study are to: 1) to determine age-related changes in the pharmacokinetics of weekly nab-paclitaxel; 2) to determine age-related changes in the pharmacodynamics (toxicity) of nab-paclitaxel

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 all ages in order to identify factors other than chronological age which can predict toxicity to cancer therapy. Therefore, we will replace the term "Comprehensive Geriatric Assessment" with the term "Self-Assessment Measure"

3.0. PATIENT SELECTION

3.1. Inclusion Criteria

3.1.1 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 ≥18 years.
Because no dosing or adverse event data are currently available on the use of nab-paclitaxel in patients <18 years of age, children are excluded from this study.
To be assured of getting adequate variability in age, we will define 4 age strata <50, 50-60, 60-70, and >70 years of age and require at least 10 patients in the <50 age group, at least 5 patients in the > 70 age group, the two groups we expect to be the most difficult to accrue.

3.1.5 KPS ≥70%

3.1.6 Resolution of grade ≥ 2 toxicity from prior therapy (other than alopecia)

3.1.7 Peripheral neuropathy ≤ grade 1

3.1.8 Hematologic inclusion:

- white blood cell count ≥3,000cells/mm3
- absolute neutrophil count ≥1,500/mm3
- platelets ≥100,000cells/mm3
- Hb ≥ 9.0g/dl

3.1.9 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 metatasis are present in the absent of liver metastases)
- bilirubin	$\leq$ 1.5mg/dl
- creatinine clearance (calculated or 24 hour)	$\geq$ 30ml/min

3.1.10 Negative pregnancy test in patients of childearing potential. Patients with reproductive potential must use an effective method to avoid pregnancy for the duration of the trial

3.1.11 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 Women who are lactating

3.2.6 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, or research team. Potential subjects will be contacted by their treating physician and will be referred to the investigator/research staff of the study.

The principal investigator 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 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 may also review portions of their medical records at COH 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.

In most cases, 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. 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.

To be assured of getting adequate variability in age, we will define 4 age strata <50, 50-60, 60-70, and >70 years of age and require at least 10 patients in the <50 age group, at least 5 patients in the > 70 age group, the two groups we expect to be the most difficult to accrue.

4.2. Registration Processes

All eligible patients will be registered at the City of Hope. Once the signed informed consent has been obtained, all pretreatment evaluations have been performed, patients will be entered on study. To register a patient, the research nurse or CRA must complete

the Eligibility Checklist. The research nurse or CRA will register the patient onto the study and assign a patient accession number.

4.3. Procedures for On-Study and Treatment Deviations

Any waivers or deviations from the study protocol need to be approved by the IRB

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 2.3.2.4**. 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.Pharmacokinetic Sampling

Peripheral blood samples (each in a 7 ml sodium or lithium heparin containing Vacutainer® tube) will be collected from a site distal to the site of drug infusion during cycle 1, week 1 at the following time points: 0, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 24, and 48

hours. A separate pharmacokinetic flow sheet will be used to record the actual times of blood draws and pertinent dosing information (Appendix III). Blood samples will be kept on ice and processed within 1 hour of drawing. Processing will consist of separation of plasma from whole blood by centrifugation at 1500 x rpm for 10 minutes at 4°C. Plasma will be transferred to appropriately labeled polypropylene tubes and stored at < -70°C until analysis in the City of Hope Analytical Pharmacology Core laboratory;

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5.3. 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 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 the white blood cell count returns to $\geq$3,000cells/mm^3, absolute neutrophil count $\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 white blood cell count returns to ≥3,000cells/mm^3, absolute neutrophil count ≥1,500/mm^3, platelets ≥100,000cells/mm^3, and Hb ≥ 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. 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:

Use of G-CSF and Dose Reductions for Hematologic Toxicity

Adverse Event	Occurrence	Action to be Taken

ANC < 500 cells/mm3 (nadir count) with neutropenic fever > 38° OR Delay of next cycle due to persistent leukopenia (WBC <3,000cells/mm^3) or neutropenia (ANC < 1500 cells/mm^3) OR For patients on weekly treatment whose next treatment within the cycle (Day 8 or Day 15) is omitted persistent leukopenia (WBC <3,000cells/mm^3) or neutropenia (ANC < 1500 cells/mm^3) OR Neutropenia < 500 cells/mm3 for > 1 week	Any Occurrence	At the first occurrence of a hematological toxicity (as outlined in the Adverse Event column), 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. If G-CSF is given concurrently with weekly nab-paclitaxel, administration may begin the day after nab-paclitaxel is given and should stop at least 48 hours prior to when nab-paclitaxel is given the following week.
Thrombocytopenia Grade 3 or Grade 4*	1st Occurrence	Dose reduction to next lower level
	Recurrence	Dose reduction to next lower level

*See NCI Toxicity Criteria 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).

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 Table 2) 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, treatment should be withheld until resolution to ≤ grade 1 or baseline if baseline was greater than grade 1, then reinstituted, if medically appropriate, at the next lower dose level (see Table 2). Patients who present with grade 2 toxicities may have their treatment held 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 Abraxis BioScience, LLC, 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 Abraxis BioScience, LLC. 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 Abraxis BioScience, LLC at 908-393-8304.

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.

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 (aka "Self-Assessment Measure")

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: Hospital Anxiety and Depression Scale
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 in follow-up

The following information will be collected at each clinic visit via the toxicity tool (see Appendix III):

1) Grade 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

Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) is a 14-item self-administered measure that has been well tested in cancer populations.[56] It has two 7-item subscales that assess depression and anxiety. The scale is considered particularly appropriate for use with medically ill patients because of the absence of somatic items which often confound the determination of psychiatric problems in a medically ill population. Reported anxiety and depression cutoff scores on the HADS have varied from 8 to 11.[57, 58] The total cutoff score for psychological distress has ranged from 13, reflecting adjustment disorder, to 19, reflecting major depressive disorders.[59] Ibbotson and colleagues found that an overall cutoff score of 15 or greater resulted in 80% sensitivity, 76% specificity, and a positive predictive value of 41% for psychological distress.[60]

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:

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

9.0. STUDY CALENDAR

SCHEDULE OF EVALUATIONS / STUDY CALENDAR

Parameter	Pre-study	PK Sampling with First Dose***	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, differential, platelet count	X		X	X	X			
CMP*	X		X		X			
CEA, CA15-3	X		X					
CT Chest, Abdomen, Pelvis	X						X	
Bone scan	X						X	
Pharmacokinetic Sampling***		X						
Self-Assessment Questionnaire**	X					X		X

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

**+/- 2 weeks

*** Pharmacokinetic sampling will be obtained cycle 1, week 1 at the following time points: 0,0.25,0.5,1,1.5,2,4,6,8,24, and 48 hours.

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.

  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 with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

  Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.

- 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.

- 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

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.

- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.

- 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.

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	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- 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. Special Considerations for Laboratory Results

Any CTCAE grade 3 or 4, or any clinically significant grade 1 or 2 hematology or biochemistry laboratory values not solely considered a result of disease progression will be considered an AE.

11.2.4. Treatment Non-Response as an Adverse Event

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

11.2.5. Types of Adverse Events

In the clinical study setting, adverse events are most often subcategorized as either SERIOUS or NON-SERIOUS. This distinction is critical, as SERIOUS AEs require additional documentation that is both time-sensitive and detailed.

11.2.5.1 Serious Adverse Events (SAE)

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

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

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations; for example, important medical events may not be immediately life-threatening or result in death or

hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Hospitalization that do not meet this criteria are:

- reasons described in the protocol, e.g., drug administration, protocol-required testing
- social reason in the absence of an AE
- surgery or procedure planned prior to entry into the trial

11.2.5.2. "Serious" Versus "Severe" Adverse Events

There will be an acknowledged distinction between serious and severe AE's. Assessment of seriousness will be made solely by the serious criteria listed above. Severity of AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events v3.0. Therefore, serious events will not be automatically considered severe. For example, a stroke that results in only a limited degree of disability may be considered a mild (not severe) stroke, but it would still meet serious criteria and thus, be captured as an SAE. Similarly, severe events may not always be serious. An example would be an episode of severe, transient nausea which persists for several hours. This would be classified as a "severe" episode of nausea, but if it did not require treatment, intervention, or somehow meet other serious criteria, it would not be considered an SAE.

11.2.5.3. Nonserious Adverse Events

Any adverse event that is not an SAE is, by default, a non-serious AE.

11.3. Documentation of Adverse Events Observed during the Study Period

All AEs (serious and nonserious) will be documented. Any experience or condition that is identified from the signing of the informed consent through the 30-day follow-up period must be captured as an adverse event (AE). Information collected will include a description of the event, date of onset and resolution, assessment of serious (SAE) criteria, any action taken (e.g., changes to study treatment), final outcome, and the investigator's assessment of causality (i.e., the relationship to the study treatment[s]).

11.3.1. AE Term Selection

To facilitate proper analysis of any observed adverse events within the study, consistent and medically accurate standards of AE term selection will be applied. Whenever possible, an AE term will be the formal diagnosis or disease term

experienced by the patient. If the final diagnosis remains differential or is pending, then the presenting signs, symptoms and/or abnormal laboratory results will be captured as AEs until a diagnostic term can be applied.

11.3.2. Causality

For each adverse event an investigator will assess the possibility that a study drug or regimen may have caused or contributed to an adverse event as described in the previous section entitled "Definition and Types of Adverse Events."

11.3.3 Deaths

ANY deaths occurring within the trial period or within 30 days after discontinuing protocol treatment will be captured without exception, regardless of perceived causal relationship to study drug. A single AE term will be selected, the event will be considered an SAE, and "death" will serve as the positive criteria applied to the seriousness assessment. If the cause of death is unknown, then "death" will be captured as the sole AE term. Whenever possible the underlying cause, not the specific mechanism, of death will be selected as the SAE term, unless the investigator feels the specific mechanism of death is clinically relevant or offers significance that might otherwise be lost if not captured.

11,3.4. Follow up Procedures for Adverse Events Observed During the Study Period

All adverse events (serious and non-serious) that are unresolved or unimproved since initial presentation will be followed until resolution or improvement of the AE. With respect to AEs that are abnormal laboratory or investigational results, an unresolved or persistent CTCAE grade 3 or 4 laboratory abnormality at study completion or withdrawal will be followed until the laboratory abnormality has either returned to a comparable baseline value, or is judged to have a severity of grade 2 or better.

If, in the investigator's medical judgment, any AE noted in the study is not likely to resolve or improve, the investigator will document that opinion in the patient's medical record. Should the patient become lost to follow-up or further information is otherwise unattainable, the investigator will note this in the patient's medical record.

11.4. Adverse Events Emerging Subsequent to Study Cessation

For 30 days subsequent to study completion or withdrawal, new onset adverse events will be captured. Follow up of these events will follow the same procedure as described above for AEs observed during the study period.

11.5. Safety Reporting Requirements and Timelines

The Sponsor-Investigator will utilize the FDA voluntary 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/).

All serious adverse events regardless of severity or relationship must be reported to Abraxis BioScience and Abraxis Oncology within 24 hours of the investigational staff's knowledge (using the Abraxis Bioscience SAE form).

Abraxis BioScience, LLC.
Drug Safety and Surveillance Department
4505 Emperor Blvd, Suite 400
Durham, NC 27703
Ph: 919-433-8515 (8am-5pm EST, normal business days and hours)
Ph: 919-606-1832 (24hr hotline)
Fax: 919-433-8402
E-mail: SAE-REPORTING@abraxisbio.com

AbraxisBioScience, LLC.
200 Somerset Corporate Blvd - Suite 8000
Bridgewater, NJ 08807
Office: 908-393-8248
Fax: 908-393-8304
Cell: 267-337-2720
Email: AbraxisMedAffairs@abraxisbio.com

In addition, the Sponsor-Investigator will adhere to the safety reporting requirements and timelines described in the Research Funding Agreement with Abraxis BioScience.

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

11.6. 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.infosci.coh.org/ocrqa/forms/guidance.doc 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 3 & 4 toxicities**.** Reporting of data and safety to the DSMB will occur at intervals of 6 months using the PMT report.

C) Adverse Events

Reporting: Adverse events must be reported to the COH DSMB and IRB and GCRC according to definitions and guidelines at http://www.infosci.coh.org/ocrqa/forms/guidance.doc and http://iris.coh.org, which are defined below. AEs will be monitored by the PMT. Less than serious adverse events will be reported only at the time of protocol continuation reports.

Adverse Event - An adverse event (AE) 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.

Serious Adverse Event - All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be recorded on the City of Hope National Medical Center Adverse Events (COH AER) form (http://iris.coh.org)**.**

A serious adverse event (SAE) is defined as *any expected or unexpected adverse event* (AE, generally equivalent to CTCAE grades 3, 4 or 5) that is *related or unrelated* to the intervention that results in any of the following outcomes:

- Death
- A life-threatening event
- 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
- Causes cancer
- Is an overdose

Certain medical events that may not result in death, be life-threatening, or require hospitalization, may also be considered a serious adverse event when appropriate medical or surgical intervention is necessary to prevent one of the outcomes listed above.

Unexpected Adverse Event - Any event in which the severity or specificity is not consistent with the risk information described in the protocol, and the event is not anticipated from the subject's disease history or status.

Expected Adverse Event - Any event in which the severity or specificity is consistent with the risk information described in the protocol or is anticipated based on the subject's medical history.

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. This is recorded using the Adverse Event Report (COH AER) form (http://iris.coh.org) in one of five categories scored as the following: 5=related, 4=probably related, 3=possibly related, 2=unlikely related, and 1=unrelated. The attribution is subject to change as follow-up information becomes available and it can be changed by the DSMB or by the IRB in the process of review.

11.7. Human Subjects Issues

11.7.1. 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.

11.7.2. Alternatives

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

11.7.3. Confidentiality

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.

11.7.4. 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

12.1 Primary objectives

12.1.1. To determine age-related changes in the pharmacokinetics of weekly nab-paclitaxel

12.1.2. To determine age-related changes in the pharmacodynamics (toxicity) of nab-paclitaxel

12.1.1 Statistical Rationale

Linear regression analysis will be used to examine the strength of the relationship between the explanatory variable age and the pharmacokinetic response variables such as log transformation of clearance (log(Cl)) and log transformation of area under the curve (log(AUC)).

Generalized linear models assuming a binomial distribution and implementing a logit link will be used to examine the strength of the relationship between age and the PD variables (i.e., dose reductions, dose delays and grade 3 & 4 toxicities)

Descriptive statistics including means, medians and modes as measures of location and standard deviation and quartiles as measures of the dispersion will be provided for the PK parameters, such as log(Cl) and log(AUC). Counts and percentages will be provided for dose reductions, dose delays and grade 3 & 4 toxicities.

12.2. Statistical Power Calculation

The calculation of sample size for this study focuses on r, the coefficient of correlation, and its square, the coefficient of determination, R^2, from a linear regression analysis examining the strength of the relationship between the explanatory variable age and the response variable log(Cl). Note below the formula for r.

$r = ß * \sigma_{age} / \sigma_{log(Cl)}$

As this formula shows, r, the correlation coefficient, is based on three components: the linear regression coefficient, β, and the variation in the predictor age as measured by the standard deviation(σ_{age}), and the variation in the response variable log(Cl) as measured by the standard deviation($\sigma_{log(Cl)}$). This means that r and thus R^2 increase with increasing slope or increasing variation in the predictor value age, or by minimizing variation of the response variable log(Cl).

To be assured of getting adequate variability in age, we will define 4 age strata <50, 50-60, 60-70, and >70 years of age and require at least 10 patients in the <50 age group, at least 5 patients in the > 70 age group, the two groups we expect to be the most difficult to accrue.

Table 1 provides information on the variability of log(Cl) Nab-Paclitaxel.
Table1.

Drug of interest	$\sigma_{log(Cl)}$
Nab-Paclitaxel (100, 150 mg/m^2)	.32, .62[31]

We have selected a sample size of 40 subjects which would provide at least 80% power with an alpha level of 0.05 (R^2 can only increase – this study is powered to be comparable to a two-tailed r) to find a relationship between age and log(Cl) if age predicts at least 17% of the variation in log(Cl).

12.3. Secondary objectives:

12.3.1. To determine response and time to progression: Counts and percentages will be provided for categories of response criteria examining both target and non-target lesions based on the definitions provided in section 10.4. Median time to progression and associated confidence limits will be calculated using a Kaplan Meier method.

12.3.2. To explore predictors of pK parameters. After the initial examination of univariate relationship between the pK parameters (log(Cl), log(AUC)) and age, we will refine our linear model(s) by examining the effects of including variables associated with disease stage, cancer diagnosis, nutritional status, physical functioning level and the geriatric assessment measures. We will limit our study to a select set of models based on the current knowledge base. Models will be compared using a small sample Akaike information criteria (AIC).

12.3.2. To explore predictors of the need for dose reduction, dose delays, or grade 3 or 4 toxicity. We will use the same general approach to modeling the PD response variables as the pK parameters but we will implement a generalized linear model with a binomial distribution and logit link.

In the case that we have multiple drugs in a class we can extend our model to recognize the hierarchical structure of the data using generalized estimating equations.[62] Combining the data on multiple drugs will boost the sample size thus providing a more full range in the variables of interest for modeling the pharmacokinetics and pharmacodynamics.

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