Multicenter study investigating utilization of pharmacokinetic (PK)-guided docetaxel in senior adult breast cancer patients receiving docetaxel and cyclophosphamide (TC) chemotherapy

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H. LEE MOFFITT CANCER CENTER AND RESEARCH INSTITUTE
DEBARTOLO FAMILY PERSONALIZED MEDICINE INSTITUTE

Protocol #: 18118

Multicenter study investigating utilization of pharmacokinetic(PK)-guided docetaxel in senior adult breast cancer patients receiving docetaxel and cyclophosphamide (TC) chemotherapy

Coordinating Center: *H. Lee Moffitt Cancer Center and Research Institute*

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[redacted]

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Amendment #1 (10/2/2015)

MCC #: 18118
PI: Christine M. Walko, PharmD
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TREATMENT SCHEMA

Cycle 1: standard TC chemotherapy

1. Standard dose TC based on body surface area (docetaxel 75 mg/m^2 over 1 hour cyclophosphamide 600 mg/m^2 IV over 30 minutes)) administered in infusion clinic
2. Blood drawn (3-4mL each draw) for PK assessment to determine docetaxel plasma levels 5 minutes before the end of infusion and 30-60 min after the end of infusion
3. Docetaxel plasma concentration analysis and AUC calculation to be used for determining docetaxel dose for Cycle 2.

Cycle 2: PK-guided docetaxel (as part of TC)

1. Toxicity assessment in clinic
2. Docetaxel dose adjusted based on PK assessment from cycle 1 and toxicity (if present)
3. PK-guided dose of docetaxel and standard dose of cyclophosphamide administered in infusion clinic.
4. Blood drawn (3-4mL each draw) for PK assessment to determine docetaxel plasma levels 5 minutes before the end of infusion and 30-60 min after the end of infusion
5. Docetaxel plasma concentration analysis and AUC calculation to be used for determining docetaxel dose for Cycle 3.

If patient **was in range** from Cycle 2

Cycle 3 and 4: PK-guided docetaxel

1. Toxicity assessment in clinic
2. Docetaxel dose based on PK assessment from **previous in range cycle** (same dose as previous cycle) and toxicity (if present)
3. PK-guided dose of docetaxel and standard dose of cyclophosphamide administered in infusion clinic.
4. Blood drawn (3-4mL each draw) for PK assessment to determine docetaxel plasma levels 5 minutes before the end of infusion and 30-60 min after the end of infusion
5. Docetaxel plasma concentration analysis and AUC calculation to be used for determining docetaxel dose for Cycle 4
6. Continue 1 through 5 above for each cycle following a target AUC

If patient was **BELOW** range from Cycle 2

Cycle 3: PK-guided docetaxel

1. Toxicity assessment in clinic
2. Docetaxel dose adjusted based on PK assessment from **cycle 2** and toxicity (if present)
3. PK-guided dose of docetaxel and standard dose of cyclophosphamide administered in infusion clinic.
4. Blood drawn (3-4mL each draw) for PK assessment to determine docetaxel plasma levels 5 minutes before the end of infusion and 30-60 min after the end of infusion
5. Docetaxel plasma concentration analysis and AUC calculation to be used for determining docetaxel dose for Cycle 4

If patient **was in range** from Cycle 3

If patient was **BELOW** range from Cycle 3

Cycle 4: PK-guided docetaxel

1. Toxicity assessment in clinic
2. Docetaxel dose adjusted based on individualized PK assessment from **cycle 3** and toxicity (if present)
3. PK-guided dose of docetaxel and standard dose of cyclophosphamide administered in infusion clinic.
4. Blood drawn (3-4mL each draw) for PK assessment to determine docetaxel plasma levels 5 minutes before the end of infusion and 30-60 min after the end of infusion
5. Docetaxel plasma concentration analysis and AUC calculation

Continue steps for patients in range from cycle 2, except dose based on PK calculation from cycle 3

TABLE OF CONTENTS

Page

SCHEMA iv

1. OBJECTIVES 5

2. BACKGROUND 6
2.1 **Study Synopsis**
2.2 **Rationale**

3. PATIENT SELECTION 16
3.1 **Inclusion Criteria** 16
3.2 **Exclusion Criteria** 17
3.3 **Inclusion of Women and Minorities** 17
3.4 **Patient Registration** 18
3.5 **Removal of Patients from Study** 18

4. TREATMENT PLAN 19
4.1 **Chemotherapy Administration** 19
4.2 **Docetaxel PK Dose Adjustment** 19
4.3 **Supportive Care Guidelines** 20
4.4 **Duration of Therapy** 20

5. DOSING DELAYS/DOSE MODIFICATIONS 21

6. PHARMACEUTICAL INFORMATION 21

7. PHARMACOKINETIC ANALYSIS 22

8. STUDY CALENDAR 23

9. REGULATORY AND REPORTING REQUIREMENTS 25

10.1 **Reporting**
10.1.1 Unexpected and Serious Adverse Experiences 29
10.2 **Data Reporting** 29
10.2.1 Institutional Review Board 29
10.2.2 Data Management and Monitoring/Auditing 29
10.2.3 Informed Consent 30
10.2.4 Hospital/Clinical Records 30
10.2.5 Investigator Study Files 30

10.3 **Affiliate Site Required Documentation** 30

11. STATISTICAL CONSIDERATIONS.....31

REFERENCES 34

INFORMED CONSENT TEMPLATE .....

APPENDICES

APPENDIX A
ECOG Performance Status Criteria A-1

APPENDIX B
Docetaxel Pharmacokinetic Sampling Instructions.....B-1

APPENDIX C……...……..C-1
FACT-Breast version 4

APPENDIX D……...……..D-1
FACT-Taxane version 4

APPENDIX E……...……..E-1
Instrumental Activities of Daily Living (IADL) Scale

APPENDIX F……F-1
Mini-Mental State Examination (MMSE)

APPENDIX G……G-1
Mini Nutritional Assessment (MNA)

1. OBJECTIVES

1.1. Primary Objective:

To demonstrate that PK guided dosing of docetaxel chemotherapy improves the ability to achieve a targeted AUC (2.5-3.7 mg*hr/L) within 4 cycles of therapy in patients ≥ 65 years of age with breast cancer receiving TC (docetaxel and cyclophosphamide) as compared with historical non-PK guided therapy from patients receiving a similar regimen

1.2. Secondary Objectives:

To demonstrate that PK guided dosing of docetaxel chemotherapy decreases the incidence of grade 3 and 4 neutropenia and febrile neutropenia in cycles following PK adjustment (cycles 2-4) when compared with cycle 1 and historical non-PK guided therapy in patients ≥ 65 years of age with breast cancer receiving TC chemotherapy.

To assess whether a higher Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score at baseline is associated with a higher docetaxel AUC after cycle 1 and greater need for dose reductions based on the PK-guided dosing algorithm in patients ≥ 65 years of age with breast cancer receiving TC chemotherapy.

To assess whether a lower Instrumental Activities of Daily Living (IADL) total score at baseline is associated with a higher docetaxel AUC after cycle 1 and greater need for dose reductions based on the PK-guided dosing algorithm in patients ≥ 65 years of age with breast cancer receiving TC chemotherapy.

To assess whether a higher level of comorbidity, as defined by the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) total score, is associated with a higher docetaxel AUC after cycle 1 and greater need for dose reductions based on the PK-guided dosing algorithm in patients ≥ 65 years of age with breast cancer receiving TC chemotherapy.

To assess whether drug interactions, as measured by the total number of potential drug interactions (PDI) with docetaxel and the level of significance of each interaction, is associated with a higher docetaxel AUC after cycle 1 and greater need for dose reductions based on the PK-guided dosing algorithm in patients ≥ 65 years of age with breast cancer receiving TC chemotherapy.

To assess the relationship between the Function Assessment of Cancer Therapy (FACT) Taxane and Breast Cancer scores and docetaxel AUC results in patients ≥ 65 years of age with breast cancer receiving TC chemotherapy.

2. BACKGROUND

2.1 Study Synopsis

Docetaxel is a semisynthetic taxane that inhibits the microtubule network and is used in the treatment of many types of cancers. Standardized dosing of docetaxel, based on body-surface-area (BSA), is associated with significant variability in drug exposure (up to 10-fold variation in area under the concentration-time curve [AUC]).[1, 2] The clinical relevance of this is underscored given the correlation between AUC and both grade 4 neutropenia and febrile neutropenia.[1] Docetaxel AUC has also been correlated with efficacy endpoints. The AUC of docetaxel has been the parameter most associated with biologic effects.[1, 3] Validated limited sampling strategies have been developed that allow the AUC for docetaxel therapy to be estimated from two samples, one taken towards the end of the infusion and a second taken one hour after the end of infusion.[3-5] This provides practical support for the further evaluation of docetaxel AUC measurements to guide dosing in cancer patients.

The docetaxel and cyclophosphamide (TC) regimen has shown superior overall and disease free survival compared with doxorubicin and cyclophosphamide (AC) in early stage breast cancer patients receiving adjuvant chemotherapy.[6] The docetaxel and cyclophosphamide (TC) regimen is the preferred adjuvant treatment at Moffitt Cancer Center for early stage breast cancer patients ≥ 65 years of age and thus will be the regimen utilized in this trial. The risk of docetaxel toxicity is higher in patients ≥ 65 years of age. The rate of grade 4 neutropenia was 63% in patients ≥ 65 years of age compared with 30% in younger patients. Though docetaxel PK parameters were similar across ages, variability was higher in older patients (9.6-fold compared with 5-fold).[7]

Although it has been suggested that PK-guided drug dose adjustment may be necessary to optimize anticancer efficacy and minimize associated toxicities, the lack of a routinely available testing method has impeded its clinical adoption. Saladax Biomedical, Inc. (Saladax) develops novel diagnostic assays for the practical delivery of personalized medicine and companion diagnostics, delivering actionable diagnostic data to physicians to optimize the use of current and new pharmaceutical products. Saladax has developed a highly sensitive, accurate, reproducible and reliable homogeneous immunoassay for the

measurement of docetaxel levels in plasma samples, the MyDocetaxel™ assay [8].

The PK model used by Saladax to calculate AUC results for docetaxel was initially developed and validated by Bruno and colleagues [1], with data from 547 patients [5, 9] comprising multiple tumor types. The majority of patients received 75 mg/m^2 as 1-hour infusions. Using their population PK parameters and model, an optimal limited sampling strategy (LSS) was reported by Baille et al. [4] which allows calculation of the docetaxel AUC from only two plasma samples.

The purpose of this study is to demonstrate the value of PK-directed docetaxel therapy to decrease interpatient variability of the docetaxel AUC in breast cancer patients $\geq$ 65 years of age receiving TC. We will also compare the toxicity associated with PK-directed docetaxel dosing with historical data from patients $\geq$ 65 years of age receiving TC and assess the relationship between several geriatric focused functional assessments and the need for docetaxel dosing adjustments.[6] This will be a multicenter study, with Moffitt Cancer Center being the lead institution in collaboration with a select number of community oncology offices. Breast cancer patients $\geq$ 65 years of age who are scheduled to receive 4 cycles of adjuvant TC as their chemotherapy regimen will be enrolled on the study. Patients will initially receive TC dosed in the usual manner for the practice.

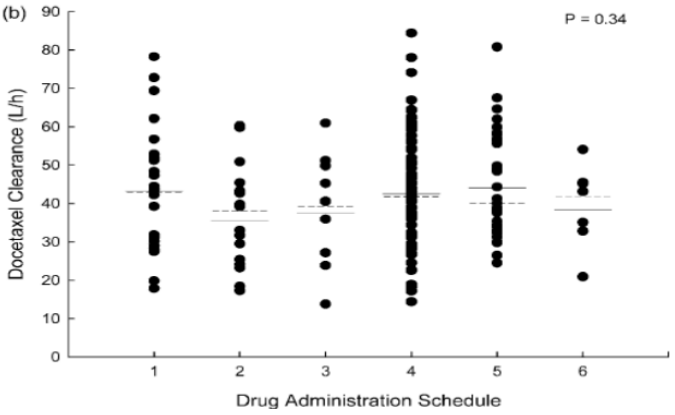
During cycle 1, a blood sample will be taken 5 $\pm$ 5 minutes prior the end of the docetaxel infusion and a second blood sample will be taken 45 $\pm$ 15 minutes after the end of the docetaxel infusion for assessment of docetaxel plasma concentrations. The MyDocetaxel™ assay results obtained from these blood samples will be used to calculate an AUC, which will then be used to determine what adjustments need to be made to the docetaxel dose for the second TC cycle to achieve a docetaxel AUC of 2.5 to 3.7 mg*hr/L. During cycle 2, a blood sample will again be taken 5 $\pm$ 5 minutes prior the end of the docetaxel infusion and a second blood sample will be taken 45 $\pm$ 15 minutes after the end of the docetaxel infusion to see if the patient achieved the target AUC range. If the patient is within range, the same docetaxel dose will be utilized for cycle 3 and blood samples will again be taken as previously described to ensure the patient remained in range. If the patient was not within range on cycle 2, the docetaxel dose for cycle 3 will again be appropriately adjusted using the docetaxel AUC value from cycle 2 to achieve an docetaxel AUC of 2.5 to 3.7 mg*hr/L as was done previously. These patients will also have blood samples drawn as previously described on cycle 3. This process will be repeated for cycle 4. Patients will be assessed for toxicity prior to each cycle of TC.

2.2 Rationale

Docetaxel is a semisynthetic taxane that inhibits the microtubule network and is used in many types of cancers including both locally advanced and metastatic breast cancer, lung

cancer, prostate cancer and gastric cancer. In clinical practice, the docetaxel dose is calculated according to a patient's estimated body surface area (BSA). Although convenient, significant interpatient variability in drug disposition makes this method inadequate for standardizing the optimal therapeutic outcome for a large proportion of patients. Variability in drug clearance and AUC of 10-fold and 7-fold, respectively means that some patients will be undertreated while others may be at higher risk for toxicity (Figure 1).[10] Docetaxel is metabolized to its primary metabolite, hydroxydocetaxel, via cytochrome P-450 (CYP) 3A4. This enzyme has demonstrated greater than 20-fold variability across populations and some data suggests that approximately 60-70% of the interpatient variability of docetaxel PK may be explained by differences in CYP3A4.[11] Other external factors may explain the remaining variability.[12]

Figure 1: *Clearance as a function of drug administration regimens for docetaxel. Solid line represents the mean and dotted line represents the median.*



Though Docetaxel clearance exhibits high interpatient variability when dosed by BSA (Figure 1), the intrapatient variability between cycles remains low.[13] Over the past decade, it has been increasingly recognized that the traditional concept of therapeutic drug monitoring (TDM) can be effectively applied to enhance the optimal use of anticancer agents. Successful examples in oncology practice include methotrexate, busulfan and fluorouracil.[14-16] The PK properties of docetaxel along with efficacy of TDM strategies support the idea that individualization of docetaxel therapy may be a worthy and feasible pursuit to optimize its use.

2.2.1 Docetaxel Systemic Exposure-Toxicity Relationship

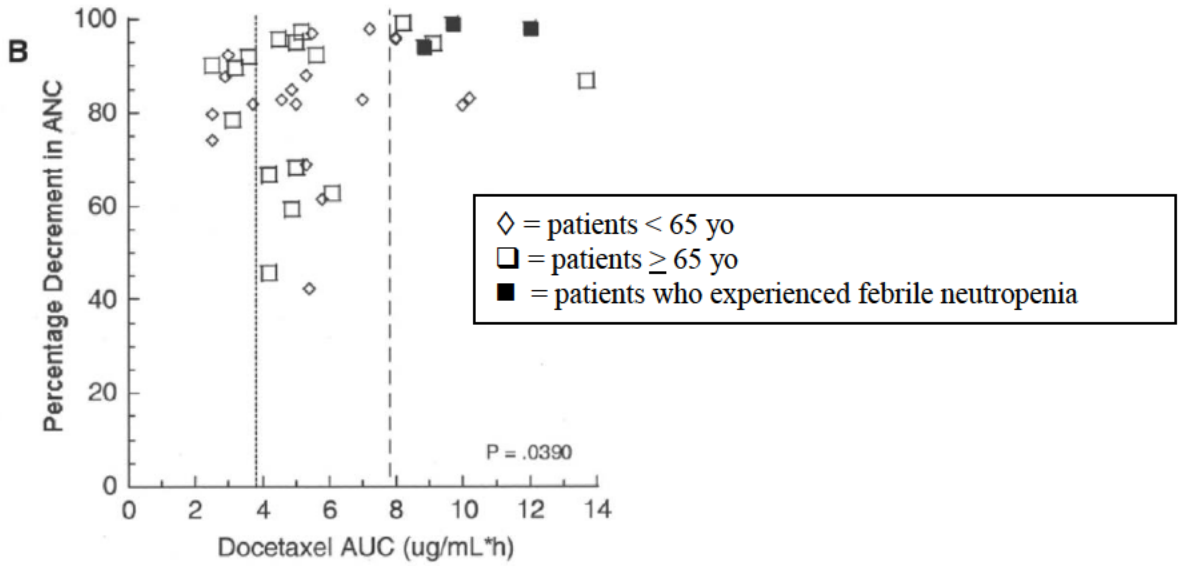
Correlation of plasma levels of docetaxel with hematologic toxicity, the major dose-limiting toxicity, has been well-established while associations of plasma levels and clinical efficacy have been reported less frequently. The docetaxel PK parameter that is most associated with biologic effects is total exposure, or AUC. Docetaxel AUC has been

correlated with both grade 4 neutropenia and febrile neutropenia.

This relationship was evaluated in 640 patients receiving docetaxel monotherapy as part of 24 different Phase II trials.[1] Docetaxel plasma levels were assessed using 4 different limited sampling strategies (each with 3 time points) and PK parameters were calculated using population PK and Bayesian estimation. The majority of patients (95%) received docetaxel 100 mg/m^2. Approximately 30% of patients had non-small cell lung cancer (NSCLC) and 36% had breast cancer. The median AUC was 4.81 mg*hr/L (95% range of 2.93-9.52). Docetaxel clearance was found to be a strong, independent predictor of both grade 4 neutropenia and febrile neutropenia ($p<0.0001$). The first course docetaxel AUC was found to be a predictor of time to tumor progression (TTP) in patients with NSCLC ($p=0.0232$), however there was not a clear association between any docetaxel PK parameter and response rate or TTP in the breast cancer patients. In a subset including the NSCLC patients, a change in AUC from 4.2 to 6.5 mg*hr/L was predictive of an approximate 2-fold increase in the odds of developing a severe adverse effect.[17]

The relationship between docetaxel PK and toxicity was also assessed in the older cancer patient population.[7] Single agent docetaxel 75 mg/m^2 every three weeks was administered to 20 patients $\geq$ 65 years of age or older (median was 71, range of 65-80) and 20 patients younger than 65 years of age (median was 53, range of 26-64). All patients had solid tumors with breast, lung, prostate and angiosarcoma being most common. The median AUC was 6.01 (1.54-13.7) mg*hr/L in the older patient population compared with 5.69 (2.47-10.2) mg*hr/L in the younger population. There were no significant differences in measures of docetaxel exposure parameters between the younger and older populations. However, the rates of grade 4 neutropenia and febrile neutropenia were higher in the patients $\geq$ 65 years of age (63% and 16%, respectively) compared with younger patients (30% and 0%, respectively). Though not statistically significant, there was a strong trend ($p=0.056$). The odds ratio for a patient $\geq$ 65 developing grade 4 neutropenia compared with a 50 year old patient was 1.98 ($p=0.091$). Overall, patients with grade 4 neutropenia did not have a significantly higher AUC value compared with patients who developed grade 3 or less neutropenia. However, the greatest percent decrease in ANC was in patients who had AUC values in the upper quartile compared with patients in the inter or lower quartiles ($p=0.0390$ for trend). (Figure 2) The frequency of non-hematologic toxicities including grade 1 or 2 alopecia, asthenia, nausea, oral mucositis, cutaneous toxicity, and neuropathy were not different between age groups. This suggests that use of PK-guided therapy in patients $\geq$ 65 years of age receiving docetaxel may be especially beneficial since this population has shown a higher risk of developing grade 4 neutropenia and febrile neutropenia. Additionally, the apparent lack of correlation between docetaxel PK parameters and outcomes in the breast cancer population suggests that dose adjustments may decrease toxicity without having a negative effect on drug efficacy.

Figure 2: *Relationship between percentage decrease in ANC and docetaxel AUC*



Numerous other trials have demonstrated the relationship between docetaxel AUC and toxicity. The results of several of these trials are summarized in the table below.

Authors	Indication(s)	Total n (PK n)	Regimen	AUC mg*h/L	Safety Outcomes
Ozawa et al. 2008[18]	Histologically confirmed malignancies indicated for docetaxel	200	20 to 60 mg/m^2 1 hour infusion every 3 weeks	Median = 1.8	Median AUC for FN = 3.30 Median AUC no FN = 1.78 Logistic regression for AUC for febrile neutropenia coefficient = 1.29, p<0.001
Alexandre et al. 2007[19]	Histologically confirmed malignancies indicated for	56	Either 75 or 100 mg/m^2 1 hour infusion every 3 weeks	Total = 4.4 Unbound = 0.19	AUC (total) predictor of febrile neutropenia (odds ratio = 2.51, p=0.01)

	docetaxel				
Minami et al., 2006[20]	Histologically confirmed solid tumor indicated for docetaxel	69	60 mg/m^2 1 hour infusion every 3 weeks	Median=2.68	Severe neutropenia, 34.8% Median AUC with neutrophils < 500 = 2.73 Median AUC with neutrophils ≥ 500 = 2.49
ten Tije et al., 2005[7]	Histologically confirmed solid tumor indicated for docetaxel	51	75 mg/m^2 1 hour infusion every 3 weeks	Age< 65 = 5.69 Age≥65=6.01	Grade 4 neutropenia Age< 65 = 30% Age≥65=63% Febrile neutropenia Age< 65 = 0% Age≥65=16%
Bruno et al., 1998[1]	Histologically confirmed solid tumor indicated for docetaxel	640	75 mg/m^2 1 hour infusion every 3 weeks	Median = 4.8	Logistic regression AUC of p=0.0232
Bruno et al., 2003[17]	NSCLC	180	100 mg/m^2 1 hour infusion every 3 weeks	Median = 4.98 Range 3.24 – 9.76	Change ins AUC from 4.2 to 7.2 increase odds of severe AE by ~2-fold
Goh et al., 2002[21]	Solid tumor indicated for docetaxel	31	Either 75 or 100 mg/m^2 1 hour infusion every 3 weeks	75 group = 5.1 100 group = 5.5	AUC significant correlated with ANC nadir (p = 0.001)
Extra et al., 1993[22]	Histologically confirmed malignancies not amenable to current therapy	65 23 for PK	Dose ranging from 5 – 115 mg /m2 1 hour infusion every 2 - 3 weeks	70 m/m^2 dose 2.79	Emax model fit of AUC with percent change in neutropenia (r = 0.672, p=0.001) AUC50 = 0.967

2.2.2 Outcomes From Studies Incorporating PK Guided Docetaxel

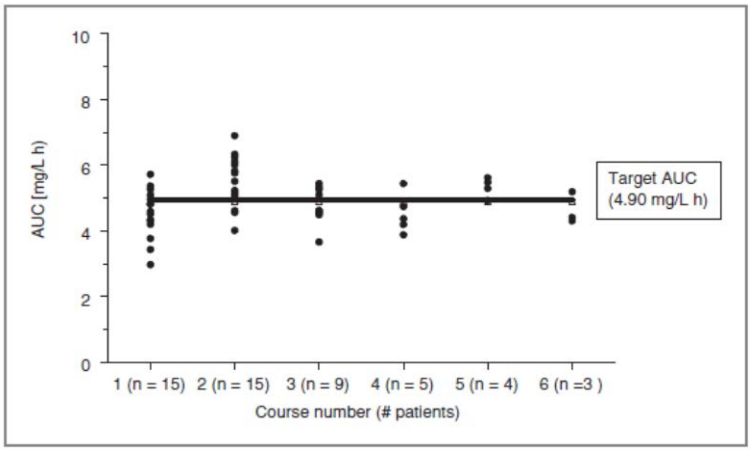
The implementation of PK-directed docetaxel dosing has used several different strategies. One method took advantage of the fact that docetaxel is primarily metabolized through CYP3A4 and used an assay assessing levels of exogenous cortisol metabolite in the urine.[23] The total amount of 24-hour urinary 6-beta-hydroxycortisol is significantly correlated with the clearance of docetaxel. The investigators aimed to demonstrate that application of this cortisol method to individualize docetaxel dosing could decrease PK and pharmacodynamics variability of docetaxel compared with BSA-based dosing. The target AUC was 2.66 mg*hr/L in the individualized arm and was based on the mean value from a previous study in which 29 patients were treated with 60 mg/m^2 of docetaxel. Fifty-nine patients with advanced NSCLC were randomized to standard BSA-based dosing arm and received docetaxel 60 mg/m^2 every 3 weeks or the individualized arm where dosing was based on estimated clearance. In individualized arm, the dose required to target the AUC

ranged from 37.4 to 76.4 mg/m^2 demonstrating the interpatient variability previously discussed. The mean AUC and standard deviation (SD) was 2.71 mg*hr/L (range 2.02 to 3.40 mg*hr/L) and 0.40 mg*hr/L in the BSA-based arm and 2.64 mg*hr/L (range 2.15 to 3.07 mg*hr/L) and 0.22 mg*hr/L in the individualized arm. The difference in SD was significantly less in the individualized arm ($p<0.01$). The percentage decrease in ANC was similar in both groups, though the SD was again smaller in the individualized arm. This trial supports the notion that individualized dosing of docetaxel can decrease interpatient variability.

A second trial used a limited sampling strategy in combination with a validated PK model and Bayesian analysis to compare BSA-dosing with PK-guided docetaxel.[3] A total of 30 patients were enrolled, 15 of whom receiving standard BSA-dosing (either 100 mg/m^2 or 75 mg/m^2) and 15 who received PK-guided docetaxel. The investigators aimed to evaluate the effect of PK-guided, AUC targeted, individualized docetaxel dosing on interindividual variability in exposure. The target AUC was 4.90 mg*hr/L for patients receiving 100 mg/m^2 and 3.68 mg*hr/L for those receiving 75 mg/m^2, based on the linearity of docetaxel PK. Approximately 40% of patients had breast cancer and 20% had prostate cancer, with other solid tumors making up the rest of the population. All 15 patients in the individualized group completed at least two PK-guided cycles of docetaxel and this group demonstrated a lower interpatient variability by 39% ($p=0.055$) compared with the standard BSA-dosed patients (Figure 3). Additionally, PK-guided patients had decreased interpatient variability in the percentage decrease in ANC by approximately 50%.

These two trials support the feasibility of using AUC to guide docetaxel therapy in the clinical setting and the ability of this technique to decrease interpatient variability.

Figure 3. *AUC values (mg*h/L) for all evaluated courses in the PK guided dosing group (course 1 and subsequent courses; N=51), specified per course number and extrapolated to a dose of 100 mg/m^2 for reasons of comparison[3]*

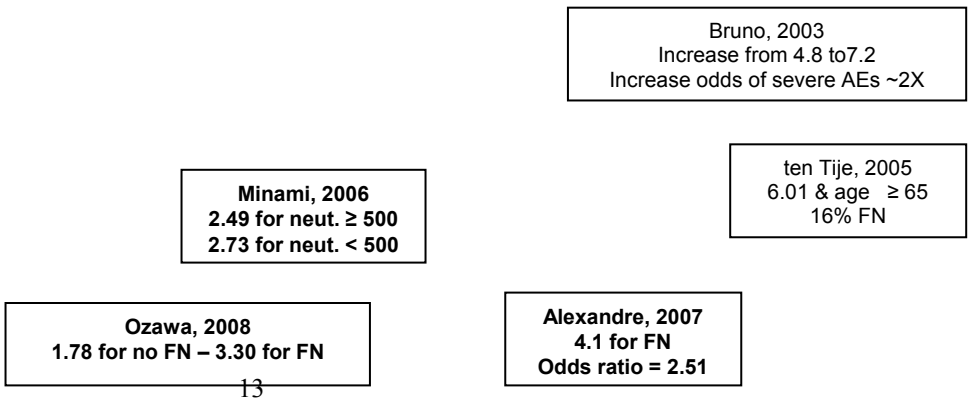


2.2.3 Practical Implementation of PK-Guided Docetaxel

Given the high interpatient variability of docetaxel and correlation between AUC and the primary toxicity of grade 4 neutropenia, the use of PK to guide docetaxel dosing is an attractive option. To translate this into clinical practice, a reliable assay as well as a defined therapeutic range to target is required along with an appropriate dose-adjustment strategy. This trial will use the *MyDocetaxel*™ assay (Saladax Biomedical, Inc., Bethlehem, PA).[8] Blood collection kits will be provided to the clinical sites and the plasma samples will be shipped to the [redacted] for analysis. The assay requires 2 blood samples to be drawn during each docetaxel infusion; the first drawn within 10 minutes before the end of infusion and the second between 30-60 minutes after the end of infusion. The freshly drawn blood samples will be processed and shipped to the laboratory by the Personalized Medicine Fellow. Based on established limited sampling and population PK modeling, the AUC will be calculated from these two points [1, 4, 13] and the AUC results reported back to the Personalized Medicine Fellow.

Given the lack of prospective data to validate an optimal therapeutic range for the docetaxel AUC, investigators have used retrospective data assessing the relationship between AUC and toxicity. The different thresholds for docetaxel dose adjustments based upon the AUC are illustrated below in the context of the relationship with toxicity (Figure 4). The relationship between AUC and the primary hematologic toxicity of neutropenia across a variety of tumor types and dose ranges is shown. The targeted AUC range of 3.1 +/- 20% (or 2.5-3.7 mg*hr/L) for patients receiving docetaxel 75 mg/m^2 was empirically derived from the apparent "cutpoints" for these trials, specifically from the published work of Minami, Alexandre and Ozawa, along with ongoing trials with the same assay in China and internal review by Saladax of the results from their CLIA lab.[18-20].

Figure 4: *Schematic representation of relationship with AUC and pharmacodynamic endpoints from the literature[7, 17-20]*



AUC < 1.4, ↑ 20%	1.5<AUC< 2.4 ↑ 10%	2.5< AUC < 3.7 none	3.8<AUC< 4.8 ↓ 15%	AUC > 4.9 ↓30%

AUC mg*h/L ***FN = febrile neutropenia; AEs = adverse events***

A dose adjustment algorithm for docetaxel has been constructed and is based on toxicity and on the results of plasma concentrations from the preceding applications **(Figure 5)**. This algorithm was developed using the information pulled from the literature (i.e. the range of AUCs observed, the relationship with toxicities, etc.). [1-5, 7, 9-11, 13, 17-24]

Figure 5: *Proposed literature derived dose adjustment algorithm in the context of reported PK/PD relationships.*

AUC (mg.h/L) from Previous Cycle	**Suggested % Dose Adjustment Algorithm (Assumes initial dosing of 75 mg/m^2) ***	
	Toxicity Grade 0 - 2	**Toxicity Grade 3 - 4**
> 4.8	**- 30%**	**- 30%**
3.8 - 4.8	**- 15%**	**Follow package insert instructions: Do not administer drug with neutrophil counts <1500 cells/mm^2. With grade 4 toxicity, reduce next dose by 25%.**
2.5 - 3.7	**No Change**	
1.5 - 2.4	**+ 10%**	
< 1.5	**+ 20%**	

* The information presented provides an algorithm adapted from dose adjustment recommendations published in:
Engels FK, et al. *Clin Cancer Res* 17(2): 353-362, 2011 [3]
Extra JM, et al. *Cancer Res* 53(5): 235-252, 1993 [18]
Bruno R, et al. *J Clin Oncol* 16(1):187-196, 1998 [1]
Baker SD, et al. *Clin Cancer Res* 10(6):1976-1983, 2004 [2]
Baker SD, et al. *Clin Pharmacokinet* 45(3): 235-252, 2006 [25]

The suggested dosing algorithm for docetaxel presented above will be incorporated into the present trial for the AUC concentrations below the recommended range. Given the adjuvant nature of the trial and the treatment goal of cure for these patients, dose

reductions for concentrations above the recommended range will only be performed in the event of toxicity as described in section 4.2 below.

2.2.4 Use of the TC Regimen in Older Breast Cancer Patients

The combination of doxorubicin and cyclophosphamide (AC) is one of the most common adjuvant chemotherapy regimens for breast cancer patients with operable disease. Based on the efficacy of docetaxel in the metastatic breast cancer setting and the potential for toxicities from AC, including cardiac toxicity, the combination of docetaxel and cyclophosphamide (TC) was attractive. The two regimens were compared in 1016 operable breast cancer patients with stage I, II, or III disease. Patients received either AC or TC every 3 weeks for 4 cycles. Dexamethasone 8 mg orally twice daily x 5 doses, starting the day before chemotherapy, was given as a premedication for patients receiving docetaxel. Prophylactic growth factors were not permitted. After 7 years of follow up, the disease free survival (DFS) was 75% in the AC arm compared to 81% in the TC arm (HR 0.74, 0.56-0.98, p=0.033). The OS was 82% in the AC arm compared to 87% in the TC arm (HR 0.69, 0.50-0.97, p=0.032). Patients who received AC had higher rates of nausea and vomiting while those who received TC had higher rates of myalgia, arthralgia, edema and febrile neutropenia.[6, 25]

Of the total 1016 patients, approximately 17% were 65 years of age or older. The median age in the older population was 69 with range of 65-77 compared with a median age of 50 (range 27-64) for the younger patients. The benefit of TC over AC was similar in the older population in terms of both DFS and OS. Older patients had higher rates of febrile neutropenia compared with younger patients (8% compared with 4%). Other common grade 3 or 4 toxicities of TC are listed in the table below.[6]

	< 65 years old (%)	≥ 65 years old (%)
Neutropenia	60	52
Thrombocytopenia	<1	0
Febrile neutropenia	4	8
Asthenia	3	6
Edema	1	0
Myalgia	2	0
Arthralgia	1	<1
Nausea	2	3
Vomiting	1	0

Patients ≥ 65 years of age and older with operable breast cancer are commonly given the TC regimen at Moffitt Cancer Center and many other sites. The higher rate of febrile neutropenia in the older population and the 52% rate of grade 3 or 4 neutropenia suggest

that PK-guided therapy may be helpful to optimize dosing of this regimen in patients ≥ 65 years of age. Given that the PK profile of docetaxel did not differ between older and younger patients and the fact that older patients may be more susceptible to the neutropenic effects of docetaxel, the commercially available *MyDocetaxel*™ assay may be helpful in individualizing the drug for this older population. The present study will evaluate the use of PK-guided docetaxel chemotherapy to achieve a target AUC of 2.5-3.7 mg*hr/L within 4 cycles of therapy in patients ≥ 65 years of age with breast cancer receiving adjuvant TC in both academic and community practice oncology settings.

2.2.5 Geriatric Assessments

The relationship between docetaxel exposure and several validated methods of predicting toxicity outcomes in the older cancer population will also be assessed as part of this trial. These will include the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH), Instrumental Activities of Daily Living (IADL) and the Cumulative Illness Rating for Geriatrics (CIRS-G).

The CRASH score has been shown to distinguish several toxicity risk levels into the following categories: low, intermediate-low, intermediate-high, or high. It includes chemotherapy risk, hematologic risk factors (diastolic BP, IADL, and LDH) and non-hematologic risk factors (ECOG PS, Mini-mental status score and mini-nutritional assessment score. In a prospective, multicenter study in 518 patients ≥ 70 years of age who were starting a new chemotherapy regimen, twenty-four different parameters were assessed with the purpose analyzing a large number of likely variable to create and then validate a clinically relevant tool to predict risk of chemotherapy toxicity. The final CRASH score consists of two subscores, one to predict for hematologic and the other for nonhematologic toxicity. The best model for hematologic toxicity included IADL, lactate dehydrogenase level, diastolic blood pressure and toxicity of the chemotherapy regimen (Chemotox). The best model for nonhematologic toxicity included ECOG performance status, Mini-Mental Status score, Mini-Nutritional Assessment score, and Chemotox. Bootstrap internal validation and independent sample validation supported stable risk categorization and P trend < 0.001.[26] The CRASH scoring tool is available through the Moffitt Cancer Center website at: http://moffitt.org/cancer-types--treatment/cancers-we-treat/senior-adult-oncology-program-tools. The IADL scale assesses the patient's ability to perform on 9 different functional domains and is incorporated into the CRASH score discussed above.[27]

The CIRS-G measures chronic illness burden in the elderly. This is a 14 category scale measuring the cardiovascular, respiratory, gastrointestinal, genitourinary, musculo-skeletal-integumentary, neuropsychiatric, and general systems. For each of the 14 systems, the illness burden is rated on a 5 point scale (none, mild, moderate, severe, extremely severe). The total score (out of 65) is then calculated with higher numbers being

more indicative of higher disease burden. The feasibility and reliability of the CIRS-G rating scale was assessed in 141 elderly outpatients who received comprehensive physical examinations, reviews of symptoms and laboratory testing. This data was then used by nurse practitioners, physician's assistants and geriatric psychiatrists to determine the CIRS-G ratings of chronic illness burden. The interrater reliability was 0.78-0.88 (intraclass correlations) for the scores.[28] This scale is also available as an online tool at the above Moffitt Senior Adult Website.

3. PATIENT SELECTION

3.1 Inclusion Criteria

Patients meeting all of the following criteria will be considered for enrollment in the study:

- Patients must have histologically confirmed localized or locally advanced breast cancer for which the treatment plan includes chemotherapy with 4 cycles of standard TC (docetaxel 75 mg/m^2 and cyclophosphamide 600mg/m^2)
- Age $\geq$ 65 years (Senior adult focused study given increased risk for toxicity)
- Patients must be female
- ECOG performance status $\leq$2. (Appendix A)
- Patients must have normal organ and marrow function as defined below:
  - leukocytes $\geq$3,000/μL
  - absolute neutrophil count $\geq$1,500/μL
  - platelets $\geq$100,000/μL
  - total bilirubin within normal institutional limits
  - AST(SGOT)/ALT(SGPT) $\leq$1.5 x institutional upper limit of normal
  - alkaline phosphatase $\leq$ 2.5 x institutional upper limit of normal
- No pre-existing neuropathy grade > 1 per the NCI CTCAE version 4.0
- Be postmenopausal (defined as amenorrheic for at least 12 months)
- All patients must be informed of the investigational nature of this study and be willing to provide written informed consent in accordance with Institutional guidelines and GCP indicating that they understand the purpose of and procedures required for the study and are willing to participate prior to the beginning of any specific study procedures.

3.2 Exclusion Criteria

Any patient meeting any of the following criteria will be excluded from participating:

- Have uncontrolled illness (including, but not limited to, ongoing or active infection, congestive heart failure, angina pectoris, or cardiac arrhythmia) that would limit compliance with study requirements.
- Have psychiatric illness that would limit compliance with study requirements
- Have history of allergic reactions attributed to compounds of similar chemical or biologic composition to taxanes (docetaxel or paclitaxel) or cyclophosphamide.
- Have known seropositivity for human immunodeficiency virus, hepatitis C virus, hepatitis B surface antigen, or syphilis. Does not require serologic confirmation as a study procedure.
- Not willing to follow protocol requirements or to give informed consent

3.3 Inclusion of Women and Minorities

Women of all races and ethnic groups are eligible for this trial. Inclusion criteria is restricted to women in an effort to decrease overall patient variability.

3.4 Patient Registration

Once clinical eligibility is confirmed, patients must sign an informed consent prior to registration indicating awareness of the investigation nature of the study and its inherent risks in keeping with the policies of the hospital and Federal regulations (Code of Federal Regulations Part 1X, Subpart B, Sections 50.20-50.27). Once the informed consent is signed and patient eligibility is confirmed, the patient will be assigned a unique Patient ID number consisting of the site identification number (for example 01, 02, etc.) and an ascending sequential number assigned by the site (001, 002, 003, etc.). For example, site 01's first subject will be 001, so the Patient ID number for that subject will be 01-001.

All subjects must be registered with the MCRN Coordinating Center to be able to participate in a trial. The participating site must fax or email the completed study specific eligibility checklist and registration forms, supporting documents and signed informed consent to the Coordinating Center. Unsigned or incomplete forms will be returned to the site. Once documents are received, the MCRN Research Coordinator will review them to confirm eligibility and to complete the registration process. If eligibility cannot be confirmed, the research coordinator will query the site for clarification or additional documents as needed. Subjects

failing to meet all study eligibility requirements will not be registered and will be unable to participate in the trial.

Upon completion of registration, the MCRN Research Coordinator will provide the participating site with the study sequence number. Within 24-48 hours after registration, it is the site's responsibility to enter the demographic and on-study patient information into the Oncore database.

It is the responsibility of the participating Investigator or designee to inform the subject of the research treatment plan and to conduct the study in compliance with the protocol as agreed upon with Moffitt Cancer Center and approved by the site's IRB.

To register a patient send the completed signed eligibility checklist along with supporting documentation to the MCRN [redacted]

3.5 Removal of Patients From Study

Patients may be removed from the study for any of the following reasons:

1. Progression of disease
2. Significant protocol violation
3. Patient non-compliance: defined as any deviation from the protocol without prior agreement of the principal investigator
4. Investigator non-compliance: defined as any significant medical or non-medical deviation from the protocol without agreement of the sponsor
5. Patient's request to withdraw from the study or refusal of further therapy
6. Unacceptable toxicity. A patient may be removed from the study for any complication of treatment that the investigator feels is life threatening.

4. TREATMENT PLAN

4.1 Chemotherapy Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 6. Appropriate dose modifications for docetaxel based on toxicities are described in Section 5.

All patients will receive TC for cycle 1 given as indicated below with subsequent cycles repeated every 3 weeks for a total of 4 cycles. All initial dosing will be based on actual body weight and height.

Chemotherapeutic Agent	Dose	Route	Day	Infusion Duration
Docetaxel (Taxotere®)	75 mg/m^2	IV	1	60 minutes
Cyclophosphamide (Cytoxan®)	600 mg/m^2	IV	1	30 minutes

4.2 Docetaxel PK-Guided Dose Adjustment

Beginning with cycle 2, the docetaxel dose will be individually adjusted before each cycle. The cyclophosphamide dose will not be changed unless dictated by toxicity. The docetaxel dose will be adjusted, if necessary, and the dose adjustment will be determined using the AUC results from the preceding cycle and the dose adjustment algorithm detailed below. The dose may also be adjusted downward for clinical toxicity as described in section 5 below. In the event that a patient experiences a docetaxel related toxicity ≥ grade 2, but has an AUC value that is below the target, the toxicity and subsequent dose reduction would take precedence over the PK-guided dose escalation recommendation. For patients with toxicity grade ≤ 1 on the day of treatment, the dose adjustment for cycle 2 will be made according to the following docetaxel dose-adjustment algorithm in consultation with the treating oncologist.

Docetaxel Dose Adjustment Algorithm

Toxicity Grade = 0/1		Docetaxel Toxicity Grade ≥2[a]
AUC (mg*hour/L)	**Dose Adjustment (± % of previous dose)**	**Toxicity Considerations**
AUC ≤ 1.4	+ 20%	Grade 2: Physician discretion Grade 3[a]: Delay until recovery to < grade 2, and resume with 15% dose reduction unless patient's AUC is ≥ 4.9. Grade 4 hematologic: Delay until recovery to < grade 2, and resume with 30% dose reduction Grade 4 non-hematologic: Discontinue Treatment
1.5 – 2.4	+ 10%	
2.5 – 3.7	Unchanged	
3.8 – 4.8	-15% only in the event of grade 3 or higher toxicity	
AUC ≥ 4.9	-30% only in the event of grade 3 or higher toxicity	

[a] Asthenia, edema, myalgia/arthralgia, mucositis, neuropathy

For patients who achieve the target AUC in any given cycle, the docetaxel dose will remain the same for the next cycle, with continued PK samples drawn per protocol to assure the target AUC was maintained. In the event the AUC falls below the target range, the docetaxel dose for the subsequent cycle will be readjusted based on the out-of-range AUC and the dose adjustment algorithm above. Given the adjuvant nature of the trial and the treatment goal of cure for these patients, dose reductions for concentrations above the recommended range will only be performed in the event of grade 3 or higher toxicity as indicated above.

The patient's required participation on the trial is completed after the post-cycle 4 assessment for toxicity. All dosing decisions will be made in consultation with and at the discretion of the primary treating medical oncologist.

The dose of cyclophosphamide will remain the same unless dose reductions for toxicity are required (see Section 5).

4.3 Supportive Care Guidelines

Supportive care therapy, including antiemetic prophylaxis, should follow institution specific guidelines for a moderately emetogenic chemotherapy regimen. Hydration should also follow institution standards. Dexamethasone 8 mg twice daily is recommended by the manufacturer the day before, day of, and day after the docetaxel infusion to prevent edema and infusion reactions, though may be adjusted by the primary treating physician based on patient specific factors. All patients should receive either pegfilgrastim 6 mg SC x 1 or equivalent therapy (i.e. filgrastim, sargramostim, or tbo-filgrastim) 24 to 72 hours following the end of the docetaxel infusion as primary prophylaxis for febrile neutropenia.

4.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment should continue for four cycles or until one of the following criteria applies:

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

5. DOSING DELAYS/DOSE MODIFICATIONS

All toxicities experienced during the course of each cycle will be assessed on the day of treatment, and graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. In the event of grade 2 non-hematologic toxicity associated with docetaxel (asthenia, edema, myalgia/arthralgia, neuropathy or mucositis), the dose of docetaxel will be decreased at the primary treating oncologist's discretion. In the event of grade 3 non-hematologic toxicity or grade 4 hematologic toxicity attributed by treating medical oncologist to docetaxel, docetaxel treatment will be withheld until recovery of the toxicity to grade < 2 and then restarted with a 15-20% dose reduction of docetaxel as described in section 4.2. Treatment will be discontinued in cases of grade 4 non-hematologic toxicity. In the event that a patient experiences a docetaxel related toxicity, but has an AUC value that is below the target, the toxicity and subsequent dose reduction would take precedence over the PK-guided dose escalation recommendation.

Any cyclophosphamide dose modifications secondary to toxicity will be at the discretion of the primary treating medical oncologist.

6. PHARMACEUTICAL INFORMATION

Commercially available supplies of the agents that comprise TC will be used for this study. Please see the prescribing information for each agent for complete details on safety, formulation, preparation, administration, storage and stability and handling and disposal: Docetaxel (http://products.sanofi.us/Taxotere/taxotere.html) and cyclophosphamide (http://packageinserts.bms.com/pi/pi_cytoxan.pdf)

Reported Adverse Events and Potential Risks
The most common toxicities seen with docetaxel therapy include infections, neutropenia, anemia, febrile neutropenia, hypersensitivity reactions, thrombocytopenia, neuropathy, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions and myalgia. The toxicity severity and frequencies differ depending on the dose and schedule of the docetaxel. When given with cyclophosphamide as part of the TC regimen, as is being used in this trial, the frequencies of these common side effects for patients ≥ 65 are listed in the table below:

Frequency of Grade 3-4 Toxicity in Patients ≥ 65yo Receiving TC

	%
Anemia	<1
Neutropenia	52
Thrombocytopenia	0
Febrile neutropenia	8
Asthenia	6

Edema	0
Fever	6
Myalgia	0
Arthralgia	<1
Stomatitis	0
Diarrhea	5
Nausea	3
Vomiting	0

Availability
Docetaxel is commercially available as a sterile, nonpyrogenic injectable solution for intravenous administration. Each 10 mL contains 200 mg of docetaxel (20 mg/mL) in 50/50 ratio with polysorbate 80/dehydrated alcohol. The product should be further diluted for intravenous administration in 5% Dextrose for Injection USP or in 0.9% Sodium Chloride, USP to produce a final concentration of 0.3 mg/mL to 0.74 mg/mL.

Storage and Stability
Intact vials should be stored at room temperature between 2° and 25°C (36° and 77°F) and should be protected from light. Docetaxel final dilution for infusion is stable at room temperature for 6 hours (including the 1 hour infusion time) and stable up to 48 hours if in a non-PVC bag and stored between 2° and 8°C.

7. PHARMACOKINETIC ANALYSIS

Saladax Biomedical's *MyDocetaxel*™ Assay will be used to measure and report the AUC of docetaxel (see http://www.mycaretests.com/health-care-professionals/mycare-product-information/mydocetaxel/ for complete details) based on the blood samples drawn for docetaxel plasma testing. The *MyDocetaxel*™ proprietary assay is a homogenous two-reagent nanoparticle agglutination immunoassay used for detection of docetaxel in human plasma. During each cycle (i.e. each administration of docetaxel), two blood samples, each consisting of 2 – 3mL of whole blood, must be collected from a peripheral port or venous draw for determination of the docetaxel plasma levels. The first blood sample will be collected 5 $\pm$ 5 minutes before the end of the docetaxel infusion and a second sample will be collected 45 $\pm$ 15 minutes after the end of the docetaxel infusion. The AUC is calculated from the measured concentrations of docetaxel using a Bayesian population PK model. This AUC result assumes the sample was drawn peripherally (i.e. not drawn from a portacath) and that the sample was handled according to the laboratory instructions provided in the collection kit. The plasma samples collected for docetaxel PK testing will be tested for docetaxel levels in the CLIA licensed Johns Hopkins University Chemistry Reference Laboratory using IUO labeled *MyDocetaxel*^{TM} assay kits provided by Saladax. Each

report will provide the calculated AUC in comparison to the target range of 2.5-3.7 mg.hr/L. It is expected that results will be provided to the study team within 10 days following sample draw.

8. STUDY CALENDAR

Baseline evaluations are to be conducted within 1-week prior to start of protocol therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. The assessments listed for each Cycle should be completed on +/-3 days from the first day of that cycle.

Evaluations and Procedures	Pre-study	Cycle 1-4		Off Study[8]
		D1	D8-10	
Informed Consent	X			
History and physical exam	X	X	X	X
Medication history	X			
Concurrent medications		X		
ECOG Performance Status	X	X		X
Height and weight	X			
CBC with diff[1]	X	X[2]	X[2]	X[2]
AST/ALT/Alkaline phosphatase/Total Bilirubin/LDH	X			
CRASH Score[3] and IADL Assessment, MMSE and MNA[4]	X			
CIRS-G[5]	X			
FACT-Taxane and Breast Assessment	X	X		X
Adverse Events and Toxicity Assessment (CTCAE v 4)	X	X		X
Docetaxel PK sample #1 and #2[6,7]		X		
Pegfilgrastim or equivalent[9]		X		

[1]WBC, RBC, hemoglobin, hematocrit %, platelets count, neutrophils %, lymphocytes %, ANC and ALC to be recorded
[2]CBC with differential at baseline, prior to each cycle of chemotherapy and then once **between days 8-10** following chemotherapy administration during each cycle.
[3]Chemotherapy Risk Assessment Scale for High-Aged Patients
[4]Instrumental Activites of Daily Living 9 functional domain scale in addition to Folstein Mini-Mental State Assessment (MMSE) and Mini-Nutritional Assessment (MNA), which are all part of the CRASH score
[5]Cumulative Illness Rating Scale for Geriatrics
[6]First blood sample (2-3mL) to be taken 5 $\pm$ 5 minutes prior to the end of the docetaxel infusion and second blood sample (2-3mL) to be taken 45 $\pm$ 15 minutes following the end of the docetaxel infusion.
[7]See Appendix C for detailed instructions on collecting, storing and shipping blood samples
[8]Assessment and physical exam to be done 3-5 weeks following cycle 4 of TC or following the last cycle in which PK monitoring was be performed.
[9]All patients should receive either pegfilgrastim 6 mg SC x 1 or equivalent therapy (i.e. filgrastim, sargramostim, or tbo-filgrastim) 24 to 72 hours following the end of the docetaxel infusion as primary prophylaxis for febrile neutropenia

Pre-study Assessments

A complete medical history, medication history, , demographics, physical examination (including height and weight for determination of body surface area [BSA, m^2]) and performance status (ECOG) will be documented when patients are identified as being candidates for this study. The following laboratory values will be recorded: WBC, RBC, hemoglobin, hematocrit %, platelets count, neutrophils %, lymphocytes %, ANC, ALC, AST, ALT, total bilirubin, and alkaline phosphatase. The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH), Instrumental Activities of Daily Living (IADL), and Cumulative Illness Rating Scale for Geriatrics (CIRS-G) assessments will be performed at baseline for each patient. Additionally, the LDH will be assessed and the Folstein Mini Mental Status (MMS) Assessment and Mini-Nutritional Assessment (MNA) will also be performed at baseline since they are required to complete the CRASH score, Patients will also complete the FACT-Taxane and FACT-Breast quality of life assessment written surveys at baseline. Prior to starting their TC treatment, patients will also be assessed for any pre-existing toxicity using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.

Treatment Assessments

Prior to the start of each cycle, the patient performance status will be assessed and their weight recorded for the determination of their BSA (in m^2). During cycle 1, a blood sample (2-3mL drawn into a 4mL lavender top K_2EDTA Vacutainer® tube) will be taken 5 $\pm$ 5 minutes prior the end of docetaxel infusion and a second blood sample will be taken 45 $\pm$ 15 minutes following the end of the docetaxel infusion for assessment of docetaxel plasma levels. Please see Appendix B for detailed instructions on collecting, handling, storing and shipping the blood samples. The docetaxel plasma concentrations determined in these blood samples will be used to calculate the docetaxel dose for the second TC cycle to achieve a docetaxel area-under-the-concentration-time curve (AUC) of 2.5 to 3.7 mg*hr/L or higher without the presence of toxicity. During cycles 2-4, blood samples will again be taken 5 $\pm$ 5 minutes prior the end of docetaxel infusion and 45 $\pm$ 15 minutes following the end of the docetaxel infusion for assessment of docetaxel plasma levels and calculation of a docetaxel AUC. Prior to each cycle of chemotherapy while the patient is on study, the following laboratory values will be assessed and recorded: WBC, RBC, hemoglobin, hematocrit %, platelets count, neutrophils %, lymphocytes %, ANC, ALC, AST, ALT, total bilirubin, and alkaline phosphatase. Any changes to the patient's current medications will also be recorded (concurrent medications). Additionally, prior to each cycle of chemotherapy while the patient is on study, patients will be assessed for toxicity using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Patients will also complete the FACT-Taxane and FACT-Breast quality of life assessment written surveys during each chemotherapy cycle . Pegfilgrastim 6 mg SC x 1 or equivalent therapy (i.e. filgrastim, sargramostim, or tbo-filgrastim) will be given 24 to 72 hours following the end of the docetaxel infusion as primary prophylaxis for febrile neutropenia to all patients.

An additional CBC with differential will be drawn once between days 8-10 following each cycle of chemotherapy. The WBC, RBC, hemoglobin, hematocrit %, platelets count, neutrophils %, lymphocytes %, ANC and ALC will be recorded. The purpose of this additional CBC is to closely monitor patients given their age and risk of neutropenia with docetaxel based regimens.

Post-treatment/Follow-up Assessments
3-5 weeks following the 4th and last cycle of TC (or last cycle in which PK monitoring was performed), the patient will be assessed for toxicity and performance status and will have their WBC, RBC, hemoglobin, hematocrit %, platelets count, neutrophils %, lymphocytes %, ANC and ALC assessed. A final FACT-Taxane and FACT-Breast quality of life assessment will also be completed by the patient. The patient will officially be off study following this assessment.

9. ADVERSE EVENTS AND REPORTING REQUIREMENTS

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

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy. During the collection of blood samples, patients may experience pain and/or bruising at the needle site, lightheadedness and/or fainting during or shortly after the blood draw, and in rare cases, localized clot formation and infections at the collection site. These events are expected and should not be recorded as an AE.

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9.1 Adverse Events (AE) Procedures

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A list of adverse events that have occurred or might occur (Reported Adverse Events and Potential Risks) can be found in Section 6 (Pharmaceutical Information). A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/reporting/ctc.html).

Beginning at the time of subject consent, at each subject's visit, the investigator will assess and document the occurrence of any adverse events. The information on all adverse events CTCAE grade ≥2, whether reported by the subject or discovered by the investigator as a result of general questioning, during a physical examination, or in laboratory or other tests, will be recorded on the appropriate AE CRF in Oncore. All AE, regardless of CTCAE grade, will be reported on the case report AE log which will be reviewed by the Primary Investigator for verification of CTCAE grading. Any AE CTCAE grade ≥2 will then be reported appropriately in Oncore. Those illnesses/medical conditions present prior to starting the study treatment will only be considered AEs if they worsen after initiating the study treatment. Abnormal laboratory or other test results will only be considered AEs if they cause clinical symptoms or signs or if they require treatment.

As far as possible, each adverse event should be described in terms of:

- Its duration (date of onset and resolution)
- Severity - worst grade experienced during the interval (evaluated according to NCI-CTCAE criteria, version 4)
- Relationship to the study treatment
- Action(s) taken
- Outcome

Causality Assessment

The investigator will assess the causal relationship between the investigational product and all AEs. The investigator will use his/her clinical expertise and judgment to select the category below that best fits the circumstances of the AE:

Definite

- Temporal relationship to the administration of the study drug and,
- Course following a known reaction pattern and,
- Improvement of the symptoms after dose reduction or discontinuation of the drug and,
- Recurrence of the symptoms after re-administration of the drug;

Probable

- Temporal relationship to the administration of the drug and;
- At least one of the following criteria is met:
  - Course following a known reaction pattern,
  - Improvement of the symptoms after dose reduction,
  - The subject's current health status provides no other explanation for the event;

Possible

- Temporal relationship to the administration of the drug and
- At least one of the following criteria is met:

- Course following a known reaction pattern,
- The event may also have been caused by other factors;

Unlikely
- No temporal relationship to the administration of the drug or,
- Other factors are more likely to have caused the event;

Not Related
- No temporal relationship to the administration of the drug or
- Other factors have caused the event;

9.2 Suspected Adverse Events

For reporting purposes, the categories of "Definite", "Probable" and "Possible" will be summarized as "suspected" adverse events. A suspected adverse event is an adverse event for which there is a reasonable possibility that docetaxel caused the adverse event.

Information about all suspected adverse events should be recorded on the Adverse Event CRF in Oncore and will be appropriately followed up.

9.3 Serious and Unanticipated Adverse Events

A serious adverse event (SAE) is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening,
- results in required or prolonged hospitalization,
- results in persistent or significant disability/incapacity,
- constitutes a congenital anomaly or a birth defect (not applicable for this study), or
- is medically significant (i.e. may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above).

Events **not** considered to be serious adverse events are hospitalizations for the:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition,
- treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen, and
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

An AE observed during the conduct of the study should be considered an unanticipated problem involving risk to human subjects only if it were unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually

safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, or informed consent).

SAEs must be followed until resolution or deemed irreversible. All relevant follow-up information must be promptly reported and recorded on the appropriate eCRF for that patient.

9.4 Adverse Event Reporting Responsibility and Procedures

All adverse events must be recorded on the appropriate CRF. Non-serious Adverse Events will be recorded using the Adverse Event CRF in Oncore and will be monitored by the Primary Investigator on an on-going basis during the study.

Information about all serious adverse events (SAE) will be collected and recorded. To ensure patient safety, each serious adverse event must be reported to the PI expeditiously. Moffitt Cancer Center and all participating sites will report SAEs by completing an SAE report in Oncore, the electronic data capture system. The SAE must be reported by email [redacted] to the MCRN within 2 working days. If applicable, the site should also follow protocol guidelines for additional reporting to government agencies. These toxicities will also be reviewed by the investigator and appropriate measures taken in terms of delaying or reducing or omitting the next cycle of therapy.

The Primary Investigator will notify the IRB within 7 days after receipt of an Unanticipated SAE report in compliance with GCP and local requirements. The Primary Investigator will also be in charge to inform all other concerned investigators of findings that could affect adversely the safety of the subjects, impact on the conduct of the trial or affect the favourable opinion to continue the trial. All information on Suspected, Serious and Unanticipated Adverse Events will be reported by the investigators on the appropriate CRFs during the treatment phase up to 30 days after the end of the study treatment.

Follow-up information about a previously reported Serious or Unanticipated Adverse Event must also be reported to the Primary Investigator within 24 hours of the investigator receiving this new information. A new Serious Adverse Event CRF should be used, stating that this is a follow-up to the previously reported Serious or Unanticipated Adverse Event and giving the date of the original report. Each re-occurrence, complication or progression of the original event should be reported as a follow-up to that event. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or discontinued study participation.

Serious unexpected adverse events related to the use of docetaxel or other study medication occurring from the time of administration of the first dose of study drug until 30 days after the final dose of study drug must be promptly reported to the FDA on a MedWatch form following Commercial Drug Reporting Guidelines. Any serious unexpected adverse event must be reported to the Primary Investigator within 24 hours of the investigator receiving this new information so the appropriate reporting can be done in the 48 hour time frame. Any SAE occurring after this time that is thought to be possibly related to prior treatment with

study drug should also be reported and recorded on the appropriate Electronic Case Report Forms (eCRF) for that patient.

An Unanticipated Adverse Event that has not been previously documented (new occurrence) and is thought to be related to the study drugs (or therapy) may require further information from the investigator for FDA reporting.

UNEXPECTED EVENT		EXPECTED EVENT	
GRADES 3 **Attribution of Possible, Probable or Definite**	**GRADES 4 and 5** **Regardless of Attribution**	**GRADES 1 - 3**	**GRADES 4 and 5** **Regardless of Attribution**
Grade 3 - Report by phone to PI within 24 hrs. Expedited report to follow within 10 working days. (**Grade 1 and 2** – Adverse Event Expedited Reporting NOT required.)	Inform PI within 24 hrs. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.	Adverse Event Expedited Reporting NOT required.	Inform PI within 24 hrs. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.

For reasonable cause the Investigator and/or sponsor may terminate this study prematurely. Conditions that may warrant termination include, but are not limited to: the discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study or if the accrual goals are met. A written notification of termination will be issued

10.1 Data Reporting

10.2.1 Institutional Review Board

No subject is to be enrolled on this protocol until the Center's Institution Review Board has approved it.

10.2.2 Data Management and Monitoring/Auditing

Data will be captured in Oncore, Moffitt's Clinical Trials Database. Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly to verify data

is accurate, complete, and verifiable from source documents; and the conduct of the trial is in compliance with the currently approved protocol/ amendments, Good Clinical Practice (GCP), and applicable regulatory requirements. The Primary Investigator and study team will regularly assess the accuracy, management, and quality control of the data.

To obtain access to Oncore, the site research staff must complete an Oncore Access Request Form and a Moffitt Information Systems Confidentiality Agreement (provided in the MCRN Handbook at the site initiation visit) and submit both to the Coordinating Center. Once the completed forms are received, the site coordinator will receive VPN access, logon/password, and information on how to access Oncore using the VPN. The MCRN Coordinating Center will provide Oncore training to the site once initial access is granted and on an ongoing basis, as needed.

10.2.3 Informed Consent

The investigator is responsible for patient care and for obtaining consent by the patient. Written informed consent must be obtained prior to entry of any patient.

10.2.4 Hospital/Clinic Records

Hospital records for patients on this study are the responsibility of the investigator. They will be available for review by the sponsors of the trial, health care personnel involved in this study, the IRB, DHHS, and the FDA.

10.2.5 Investigator Study Files

The Principal Investigator is responsible for maintaining study files for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. The following documents should be kept in the study files:

A completed, signed FDA Form 1572 (Statement of Investigator) and copies of all current curricula vitae of all sub investigators listed on the Statement of the Investigator.

- The original protocol and all amendments
- Final IRB approval, annual renewals and all IRB correspondence
- Blank Case Report Forms
- Copy of all IRB approved Informed Consent forms with applicable version date
- Updated laboratory certification and laboratory values (covering entire time of study)
- Copy of all patient's signed informed consent forms
- The final completed case report form for all patients

10.3 Affiliate Site Required Documentation

Before the study can be initiated at any site, the site will be required to provide regulatory documentation to the Moffitt Clinical Research Network (MCRN) at Moffitt Cancer Center. Sites must provide a copy of their informed consent to the MCRN coordinating center for review and approval prior to submission of any documents to the site's IRB. Any changes requested by the site's IRB must be provided to the MCRN staff for review and approval prior to resubmission to the IRB.

The MCRN Coordinating Center must receive the following trial specific documents either by hardcopy, fax, or email before a site can be activated for any trial:

1. IRB Approval Letter that includes the protocol version and date
2. FDA Related Forms 1572/1571/310 as appropriate
3. Signed Protocol Title Page
4. IRB Approved Consent Form
5. Site Delegation of Authority Log
6. Signed Financial Interest Disclosure Forms (principal and sub investigators)
7. Updated Investigator/Personnel documents (CVs, licenses, Conflict of Interest statements, etc.) as needed
8. Updated Laboratory Documents (certifications, normal ranges, etc.) as needed
9. Signed protocol specific Task Order

A study initiation teleconference will be held prior to the start of any study related activity at the site. Attendance is required for:

- The site PI and appropriate research staff
- Moffitt PI and MCRN research coordinator

The requirements of the protocol and all associated procedures and processes will be reviewed and agreed upon prior to the activation of the study. The MCRN utilizes the EDC system, Oncore. Oncore training will be scheduled, if indicated, with the appropriate staff from the site.

10.4 Protocol Monitoring Committee (PMC)

The PMC meets once a month. The PMC reviews and evaluates safety and/or efficacy data for all physician authored clinical intervention trials. The PMC ensures the safety of patients and the validity and integrity of data. PMC reviews SAEs, deviations, Interim analysis, interim and final reports from the external Data Monitoring Committee (DMC) as well as audits both internally and externally. The PMC can make the following determinations, Accepted, Acceptable with Corrective Action and Tabled.

Investigators of studies, which are designated to be reviewed by the PMC for data and safety monitoring, shall provide an interim analysis report of the study's progress and summary of

adverse events and deviations based on the phase of the study and the associated risk of the study or more often if applicable. The external DSMB (if applicable) shall forward its report for high-risk studies designated for external review at least annually or more often if applicable.

The PMC and/or the IRB may vote to suspend or terminate approval of a research study not being conducted in accordance with the IRB, the Cancer Center and/or regulatory requirements or that has been associated with unexpected problems or serious harm to subjects. The PMC/IRB will notify the PI in writing of such suspension or terminations. It is the responsibility of the PMC/IRB Chairperson to ensure prompt written notification of any suspensions or terminations of PMC/IRB approval to the relevant Federal Agencies, including OHRP, FDA, the study sponsor/funding source and if applicable, the Affiliate Program.

11. STATISTICAL CONSIDERATIONS

11.1 Study Design/Endpoints

This is a non-randomized trial assessing the impact of PK-guided docetaxel therapy in breast cancer patients $\geq$ 65 years of age receiving TC. All comparisons will be made using historical data. The primary objective in this study is to demonstrate that PK guided docetaxel chemotherapy improves the ability to achieve a targeted AUC within 4 cycles of therapy in patients $\geq$ 65 years of age with breast cancer receiving docetaxel as part of the standard TC regimen.

11.2 Sample Size/Accrual Rate

Historical data suggest that 23% of patients receiving non-PK guided docetaxel achieve the targeted AUC within 4 cycles. We wish to detect an improvement with suitable power in those patients receiving docetaxel as part of TC. We estimate 50% of patients in the targeted AUC range after cycle 4 using the PK-guided dose adjustment of docetaxel. The level of significance is 0.05. A sample size of 52 evaluable patients achieves 97% power to detect a difference of 27% using the two-sided binomial test. A sample size of 26 evaluable patients achieves 84% power to detect a difference of 27% using the two-sided binomial test. We will enroll 52 patients so at least 26 patients will be fully evaluable for all 4 cycles of therapy (based on drop out and sample mishandling from previous multicenter PK-directed therapy trials conducted by the investigators).

11.3 Analysis of Secondary Endpoints

The incidence of grade 3 and 4 neutropenia and febrile neutropenia in cycles following PK adjustment (cycles 2-4) will be compared with cycle 1 and historical non-PK guided therapy using the Wilcoxon-Rank sum assessment.

The association between the CRASH score, IADL total score, and CIRS-G score at baseline and the docetaxel AUC after cycle 1 will be assessed as a secondary endpoint along with the greater need for dose reductions based on the PK-guided dosing algorithm. The CRASH score will be reported as ordinal data (low, intermediate-low, intermediate-high, or high risk). The IADL will be reported as binomial data. (greater or less than 26 based on how it is incorporated into the CRASH score). The CIRS-G will be reported as discrete data out of a possible score of 65. The Wilcoxon-Rank sum and Chi-squared tests will be used as appropriate.

Additionally, the relationship between PK-guided docetaxel patient profiles and the Function Assessment of Cancer Therapy (FACT) Taxane and Breast Cancer scores will be described.

12.0 Publications

The study of these patients and results of all laboratory studies are considered private and confidential. The progress and results of this study will not be presented without approval by the principal investigator. The principal investigator prior to submission will review all abstracts and publications.

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Appendix A
Eastern Cooperative Oncology Group Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

2	Ambulatory and capable of all self-care but unable to carry out any work activities. UP and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.
This scale was developed by the ECOG, Robert Comis, MD, Group Chair

MCC #: 18118
PI: Christine M. Walko, PharmD
March 5, 2015

Appendix B

Docetaxel Pharmacokinetic Sampling Instructions Using Saladax Biomedical's *MyDocetaxel*™ Test

Samples for Pharmacokinetic (PK) Measurements: For each chemotherapy application, two blood samples will be collected, with the first blood sample for PK assessment being collected 5 minutes before the end of docetaxel infusion and the second blood sample being collected ~30 to 60 minutes after the end of the docetaxel infusion.

- **DO NOT collect blood samples from the infusional IV line**. Rather, collect blood samples by venipuncture or through a peripheral IV line to avoid contamination by the infusing drug.
- **Freeze gel packs a minimum of 24 hours prior to use for shipment of plasma samples**.
- Samples collected on a Friday must be stored at 2 – 8°C immediately after processing and shipped to the laboratory on the following Monday.
- Samples collected the day before a holiday must be must be stored at 2 – 8°C immediately after processing and shipped to the laboratory on the day following the end of the holiday, unless that is a Friday, in which case the sample should be shipped on the following Monday.

The following procedure shall be followed for the collection, processing and shipment of PK blood specimens to The Johns Hopkins University Chemistry Reference Laboratory for evaluation with the MyDocetaxel™ assay:

1. One patient blood sample of 2 – 3mL will be collected ~**5 minutes before the end of docetaxel infusion and a second sample will be collected ~30 to 60 minutes after the end of the docetaxel infusion** from a peripheral port or venous draw. Standard phlebotomy techniques to collect venous blood specimens in 4.0mL lavender top K_2EDTA tubes will be used. Venous blood specimens will be collected by qualified medical personnel. Universal Precautions when collecting blood specimens will be observed.
2. The following patient-specific information must be recorded on the Laboratory Requisition Form which includes information such as:

   a. Patient ID
   b. Sample collection date and time
   c. The treatment regimen, drug dose and unit of concentration
   d. Cycle number
   e. Infusion start date and time
   f. Infusion end date and time

3. The whole blood samples must be centrifuged within 10 minutes of the blood draw or immediately be placed on ice or refrigerated at 2-8°C and then centrifuged within 1 hour of the draw. Centrifuge samples for 10 minutes (preferred speed of 4,000g). Samples not centrifuged per these instructions will not be tested.
4. After centrifugation, carefully draw off the plasma from the top of the K_2EDTA tube, avoiding the cell layer, and transfer to a secondary cryotube. The plasma must be free of cells. Squeeze the bulb of the disposable pipette before inserting the tip into the plasma. Insert the pipette tip just beneath the top of the clear plasma layer and slowly release the bulb. Track down as plasma is being drawn. Aspirate only once to avoid disturbing the buffy coat/cellular layer between the plasma and red blood cells.
5. Transfer the plasma sample into one of the supplied, 4mL graduated sample tubes. Mark the provided label with the patient's study identification number. Attach the label lengthwise on the plasma tube. Store the plasma sample at 2 – 8°C until shipment (must send sample to laboratory within 24-48Hr after collection).

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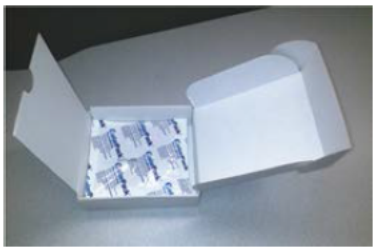

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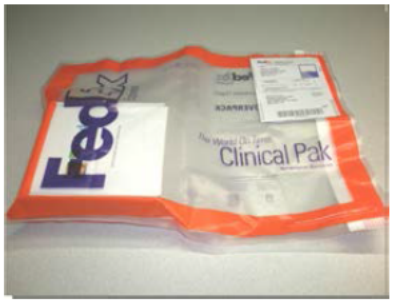

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MCC #: 18118
PI: Christine M. Walko, PharmD
March 5, 2015

APPENDIX C: FACT-B version 4

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

MCC #: 18118
PI: Christine M. Walko, PharmD
March 5, 2015

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
B1	I have been short of breath	0	1	2	3	4
B2	I am self-conscious about the way I dress	0	1	2	3	4
B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4

MCC #: 18118
PI: Christine M. Walko, PharmD
March 5, 2015

APPENDIX D: FACT-Taxane version 4 additional questions to be added to the FACT-B

Below is a list of statements that other people with your illness have said are important**.**

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4
NTX 5	I have joint pain or muscle cramps	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
NTX 6	I have trouble hearing	0	1	2	3	4
NTX 7	I get a ringing or buzzing in my ears	0	1	2	3	4
NTX 8	I have trouble buttoning buttons	0	1	2	3	4
NTX 9	I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4
Tax1	I feel bloated	0	1	2	3	4
Tax2	My hands are swollen	0	1	2	3	4
Tax3	My legs or feet are swollen	0	1	2	3	4
Tax4	I have pain in my fingertips	0	1	2	3	4

Tax5	I am bothered by the way my hands or nails look	0	1	2	3	4

MCC #: 18118
PI: Christine M. Walko, PharmD
March 5, 2015

APPENDIX E: Instrumental Activities of Daily Living (IADL) Scale (Lawton 1988)

Name_____Rated_____Date_____

1. Can you use the telephone?	
1. Without help	3
2. With some help, or	2
3. Are you completely unable to use the telephone?	1
2. Can you get to places beyond walking distance?	
1. Without help	3
2. With some help, or	2
3. Are you completely unable to travel unless special arrangements are made	1
3. Can you go shopping for groceries?	
1. Without help	3
2. With some help, or	2
3. Are you completely unable to do any shoppping	1
4. Can you prepare your own meals?	
1. Without help	3
2. With some help, or	2
3. Are you completely unable to prepare any meals?	1
5. Can you do your own house work?	
1. Without help	3
2. With some help, or	2
3. Are you completely unable to do any housework?	1
6. Can you do your own handyman work?	
1. Without help	3
2. With some help, or	2
3. Are you completely unable to do any handyman work?	1
7. Can you do your own laundry?	
1. Without help	3
2. With some help, or	2
3. Are you completely unable to do laundry at all?	1
8a. Do you take medicines or use any medications?	
Yes (if yes, answer question 8b) No (if no, answer question 8c)	
8b. Do you take your own medicine?	
1. Without help (in the right doses at the right times)	3
2. With some help (if someone prepares it for you and/or reminds you to take it)	2
3. You are completely unable to take your own medicine?	1
8c. If you had to take medicine, could you do it?	
1. Without help (in the right doses at the right times)	3
2. With some help (if someone prepares it for you and/or reminds you to take it)	2 1
3. You would be completely unable to take your own medicine?	
9. Can you manage your own money?	
1. Without help	3
2. With some help, or	2
3. Are you completely unable to manage money?	1

Appendix 2 **- INSTRUMENTAL ACTIVITIES OF DAILY LIVING (IADL) SCALE (Lawton 1988)**
The IADL Scale evaluates more sophisticated functions than the ADL Index. Patients or caregivers can complete the form in a few minutes. The first answer in each case except for 8a indicates independence; the second, capability with assistance; and the third, dependence. In this version, the maximum score is 29, although scores have meaning only for a particular patient, as when declining scores over time reveal deterioration. Questions 4-7 tend to be gender-specific. Modify them as you see fit.
Ref: Lawton MP. Scales to measure competence in everyday

APPENDIX F: Mini-Mental State Examination (MMSE)

MINI-MENTAL STATE EXAMINATION

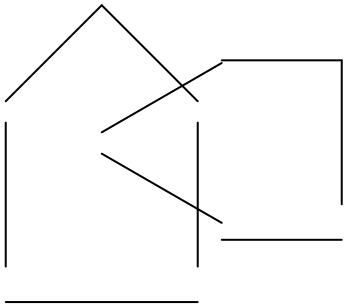
Patient Score	Maximum Score	
		ORIENTATION
_____	**5**	**What is the (year) (date) (day) (month)?**
_____	**5**	**Where are we (country) (state) (county) (city) (clinic)?**
		REGISTRATION
_____	**3**	**Name three objects, allotting one second to say each one. Then ask the patient to name all three objects after you have said them. Give one point for each correct answer. Repeat them until he hears all three. Count trials and record number.**
		APPLE....BOOK.....COAT Number of trials_____
		ATTENTION AND CALCULATION
_____	**5**	**Begin with 100 and count backwards by 7 (stop after five answers): 93, 86, 79, 72, 65. Score one point for each correct answer. If the patient will not perform this task, ask the patient to spell "World" backwards (DLROW). Record the patient's spelling:_____ Score one point for each correctly placed letter.**
		RECALL
_____	**3**	**Ask the patient to repeat the objects above (see Registration). Give one point for each correct answer.**
		LANGUAGE
_____	**2**	**Naming: Show a pencil and a watch, and ask the patient to name them.**
_____	**1**	**Repetition: Repeat the following: "No ifs, ands, or buts."**
_____	**3**	**Three-Stage Command: Follow the three-stage command, "Take a paper in your right hand; fold it in half, and put it on the table.**
_____	**1**	**Reading: Read and obey the following: "Close your eyes" (show the patient the item written on page 2).**
_____	**1**	**Writing: Write a sentence (on page 2).**
_____	**1**	**Copying: Copy the design of the intersecting pentagons (on page 2).**
_____	**30**	**Total Score Possible**

Mini-Mental State Examination (continued from previous page)

C L O S E Y O U R E Y E S

W R I T E A S E N T E N C E

C O P Y D E S I G N



APPENDIX G: Mini Nutritional Assessment (MNA)

PROTOCOL #

Center# _____ Subject # _____ Initials: _____Date: _____ CRA _____

Complete the screen by filling in the boxes with the appropriate numbers.

SCREENING

A Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
0 = severe loss of appetite
I = moderate loss of appetite
2 = no loss of appetite

B Weight loss during the last 3 months
0 = weight loss greater than 3 kg (6.6 lbs)
I = does not know
2 = weight loss between I and 3 kg (2.2 and 6.6lbs)
3 = no weight loss

C Mobility
0 = bed or chair bound
I = able to get out of bed/chair but does not go out
2 = goes out

D Has suffered psychological stress or acute disease in the past 3 months
0 = yes 2 = no

E Neuropsychological problems
0 = severe dementia or depression
I = mild dementia
2 = no psychological problems

F Body Mass Index (BMI) (weight in kg) / (height in m)^2
0 = BMI less than 19
1 = BMI 19 to less than 2I
2 = BMI 21 to less than 23
3 = BMI 23 or greater

Screening score (subtotal max. 14 points)
12 points or greater Normal
II points or below Possible malnutrition

ASSESSMENT

G Lives independently (not in a nursing home or hospital)
0 = no 1 – yes

H Takes more than 3 prescription drugs per day
0 = yes I = no

I Pressure sores or skin ulcers
0 = yes 1 = no

J How many full meals does the patient eat daily?
0 = 1 meal
1 = 2 meals
2 = 3 meals

K Selected consumption markers for protein intake
-At least one serving of dairy products (milk, cheese, yogurt) per day yes ☐ no ☐
-Two or more servings of legumes or eggs per week? yes ☐ no ☐
-Meat fish or poultry every day yes ☐ no ☐
0.0 = if 0 or I yes
0.5 = if 2 yes
1.0 = if 3 yes

L Consumes two or more servings of fruits or vegetables per day?
0 = no 1 = yes

M. How much fluid (water, juice, coffee, tea, milk) is consumed per day?
0.0 = less than 3 cups
0.5 = 3 to 5 cups
1.0 = more than 5 cups

N Mode of feeding
0 = unable to eat without assistance
I = self-fed with some difficulty
2 = self-fed without any problem

0 Self view of nutritional status
0 = views self as being malnourished
1 = is uncertain of nutritional state
2 = views self as having no nutritional problem

P In comparison with other people of the same age, how does the patient consider his/her health status?
0.0 = not as good
0.5 = does not know
1.0 = as good
2.0 = better

Q Mid-arm circumference (MAC) in cm
0.0 = MAC less than 21
0.5 = MAC 21 to 22
1.0 = MAC 22 or greater

R Calf circumference (CC) in cm
0 = CC less than 31
1 = CC 31 or greater

Assessment (max. 16 points)
Screening score
Total Assessment (max. 30 points)

Malnutrition Indicator Score
17 to 23.5 points = at risk of malnutrition
Less than 17 points = malnourished