TITLE: A Phase 2 Feasibility Study of Abraxane and Carboplatin in Epithelial Neoplasms of the Uterus

NYU Study #: s15-01156

Version date: Version 10, December 19, 2017

Coordinating Center: NYU Langone Medical Center
Cancer Institute
160 East 34th St
New York, NY 10016

***Principal Investigator:** *Name: Franco Muggia, MD*
462 First Avenue, Building CD, Room 556
New York, NY 10016
Telephone: 212-263-6485
Fax: 212-263-8210
Email address: franco.muggia@nyumc.org

Co-Principal Investigator: *Name: Bhavana Pothuri, MD*
550 First Ave
New York, NY 10016
Telephone: 212-731-6455
Fax: 212-263-8210
Email address: bhavana.pothuri@nyumc.org

Co-investigator/Biostatistician: *Name: Judith D. Goldberg, Sc.D.*
650 First Avenue, 534
Division of Biostatistics
Telephone: 212-263-0314
Fax: 212-263-8570
Email address: jd.goldberg@nyumc.org

Contents

1.0 Background

1.1 Endometrial Cancer:

Endometrial cancer is the most common gynecologic cancer in the United States, affecting more than 60,000 women annually [1]. This disease generally afflicts women that are postmenopausal with median ages older than those seen with ovarian cancer. Importantly, the disease is increasing in incidence as its etiology is linked to obesity, diabetes, and hypertension. Although 80% of women are diagnosed at an early stage and are curable with locoregional treatment [1], few effective treatment options exist for women who recur, which occurs with frequency in high-risk histologic subtypes (papillary serous carcinoma, clear cell carcinoma, grade 3 endometrioid carcinomas and carcinosarcomas). Chemotherapy has become a key part of the treatment for patients diagnosed with advanced disease, as well as for those with high-risk disease in both the adjuvant and recurrent disease settings. Trials that improve the 'chemotherapy backbone' with a focus to decrease potential toxicity and improve outcomes are important in parallel with the development of new therapies. This protocol describes a feasibility trial to verify the tolerability of a more optimal taxane schedule and formulation in endometrial cancer.

1.2 Experience with Carboplatin and Paclitaxel:

The systemic treatment of endometrial carcinoma was first developed around progestins and Adriamycin (doxorubicin) and then mostly evolved from Phase III studies by the Gynecologic Oncology Group (GOG) performed since the 1970s [2]. An additional study, GOG122, demonstrating the superiority of one of these regimens, doxorubicin + cisplatin, to whole abdominal radiation [3], served as a powerful stimulus for extending the curative potential of adjuvant systemic therapy to earlier stages of this disease. The rationale to treat endometrial cancer with systemic chemotherapy is supported by recent data from the Cancer Genome Atlas (TCGA), which characterizes high-risk subtypes of endometrial cancer as carcinomas marked by genetic instability and hypermutations, not unlike subsets of ovarian and breast cancers that are highly susceptible to chemotherapy [4]. In addition, the use of taxanes in endometrial cancer is associated with markedly improved survival for women with recurrent disease [5].

More recently, GOG 209 demonstrated the non-inferiority and more favorable toxicity profile of the doublet of **carboplatin + paclitaxel** over doxorubicin, cisplatin and paclitaxel (plus G-CSF) in a phase III study of advanced endometrial cancers (references with Table 1: summary of GOG studies in advanced stage and recurrent endometrial cancers). Since then, carboplatin and paclitaxel have been considered the standard systemic chemotherapy backbone for patients with advanced presentations or recurrent disease [2]. Data in ovarian cancer (replicating prior data in breast cancer) is supportive of weekly dosing of paclitaxel as being associated with an improved survival benefit over every 21 day dosing (JGOG3016) albeit at greater myelosuppression

(requiring blood transfusions) and neurotoxicity leading to greater dose attenuation and discontinuation [6]. Divided dose paclitaxel has been studied in the endometrial cancer population in a phase II study published by the Leuven Group [7]. This group utilized dose-dense day 1, 8 of both paclitaxel (90 mg/m^2) and carboplatin (AUC 4) administered every 21 days to 42 patients. The median age was 63.9 years (range, 41-81 years). The main histopathologic types were serous/clear cell (n = 27) and endometrioid (n = 13). The patients were divided in 2 groups: chemotherapy-naïve group (n = 28, group 1) and a group with previous chemotherapy (n = 14, group 2). The responses for group 1 were as follows: 11 (39 %) complete response, 9 (32%) partial response, and 2 (7%) stable disease. The responses for group 2 were 1 (7%) complete response, 2 (14%) partial response, and 6 (43%) stable disease. Treatment-related death occurred in 1 patient (7%) because of neutropenia and nephrotoxicity. Progression-free survival for group 1 was 10 months (range, 4-19 months). At time of analysis, 57% of the patients were still alive after a median follow-up of 10 months (range, 4-21 months). Progression free survival for group 2 was 11 months (range, 4-19 months). *Because of grade 3 and 4 hematologic toxicity, treatment adjustments were as follows: 49 (18%) and 18 (19%) dose reductions (carboplatin AUC, 2-3), 35 (13%) and 14 (15%) dose delays, and 8 (3%) and 6 (6%) treatments were not administered on day 8 for groups 1 and 2, respectively.* The authors concluded that while activity was impressive, the regimen was not suitable for eventual phase III study. Our proposed study employs a similar 'divided dose' for nab-paclitaxel only with carboplatin at the customary AUCs every 3 weeks – a regimen we have analyzed retrospectively [Musa F, Kudlowitz D, Velastegui A et al 2014 SGO abstract, manuscript in preparation].

1.3 Abraxane

Abraxane is a novel formulation of paclitaxel, where nanoparticles of the parent drug are bound to albumin. The smart nanoparticle formulation of paclitaxel uses tumor biology against itself, promoting the direct delivery of paclitaxel to the tumor and concentrating the drug where it is most needed. The pharmacokinetics of Abraxane are favorable over paclitaxel given its 43% higher clearance rate, no need for co-administration with the solvent Cremophor (responsible for Taxol-associated reactions, which limit its use) and 53% higher volume of distribution [8]. The combination of Abraxane and carboplatin has been studied in non-small cell lung cancer, metastatic breast cancer and metastatic pancreatic cancer leading to the FDA approval of Abraxane for these indications. Data from phase III trials suggest the combination is safe and effective with significantly decreased grade ≥ 3 neuropathy, neutropenia, arthralgia and myalgia in the Abraxane arm. Importantly, with the high prevalence of glucose intolerance and diabetes in our study population, obviating glucocorticoid pre-medication would be expected to remove or reduce complications associated with chemotherapy. In addition, the decreased neuropathy seen with Abraxane would be especially important to patients with pre-existing diabetic neuropathy.

Every-Three-Week (Q3W) Schedule in Metastatic Breast Cancer
In a phase I study, the maximum tolerated dose (MTD) of Abraxane was determined to be 300 mg/m^2 by 30 minute infusion Q3W, without premedication or G-CSF support[9]. **No severe hypersensitivity reactions occurred with Abraxane despite the absence of premedication.** Dose-limiting toxicities included sensory neuropathy, stomatitis, and superficial keratopathy, which occurred at a dose of 375 mg/m^2.

Two multicenter phase II studies have evaluated 2 dose levels of Abraxane (300 mg/m^2, n = 63, and 175 mg/m^2, n = 43) in patients with metastatic breast cancer [10]. The overall response rates in these 2 phase II trials were 40% (95% CI 25-54%) for the 175 mg/m^2 dose, and 48% (95% CI 35-60%) for the 300 mg/m^2 dose. Of 39 patients receiving 300 mg/m^2 as first-line therapy for metastatic breast cancer, 64% (95% CI 49-79%) responded. This was contrasted with a 45% response rate in similar patients at the lower dose level. Grade 4 neutropenia was noted in 24% of patients at the higher dose level, occurred primarily during the first cycle and resolved rapidly.

A Phase III trial in patients with metastatic breast cancer compared Abraxane 260 mg/m^2 (n = 229) to Taxol 175 mg/m^2 (n = 225) given Q3W [11]. Efficacy analyses were based on the ITT population. The ORR was significantly greater for Abraxane than for Taxol for all patients (33% *v* 19%, respectively; *P* = 0.001), patients who received first-line therapy (42% *v* 27%, respectively; *P* = 0.029), patients who received second-line or greater therapy (27% *v* 13%, respectively; *P* = 0.006), and patients who had received prior anthracycline therapy in either the adjuvant/metastatic setting (34% *v* 18%, respectively; *P* = 0.002) or the metastatic setting only (27% *v* 14%, respectively; *P* = 0.010). Tumor response rate was also significantly higher for Abraxane than for Taxol in patients with visceral dominant lesions (34% *v* 19%, respectively; *P* = 0.002) and in patients aged younger than 65 years (34% *v* 19%, respectively; *P* < 0.001). ORR also was greater for Abraxane compared with standard paclitaxel in patients with nonvisceral dominant lesions (34% *v* 19%, respectively) and in patients ≥ 65 years old (27% *v* 19%, respectively), but the results did not reach statistical significance because of the small number of patients in these subsets.

Median time to progression was significantly longer with Abraxane than with Taxol for all patients (23.0 *v* 16.9 weeks, respectively; hazard ratio [HR] = 0.75; *P* = 0.006).

There was a trend for greater median survival for all patients treated with Abraxane than with Taxol (65.0 *v* 55.7 weeks, respectively; *P* = 0.374). Although no difference in survival was observed in first-line patients, the difference was statistically significant in patients who received Abraxane, compared to Taxol, as second-line or greater therapy (56.4 *v* 46.7 weeks, respectively; HR = 0.73; *P* = .024) [11].

The incidence of hypersensitivity reactions (any grade) was low for both arms (1% for Abraxane and 2% for Taxol). No severe (grade 3 or 4) treatment-related hypersensitivity reactions occurred in any of the patients in the Abraxane group despite the absence of premedication. In contrast, grade 3 hypersensitivity reactions occurred in the Taxol

group despite standard premedication (chest pain, two patients; allergic reaction, three patients). Per protocol, corticosteroids and antihistamines were not administered routinely to patients in the Abraxane group; however, premedication was administered for emesis, myalgia/arthralgia, or anorexia in 18 patients (8%) in the Abraxane group in 2% of the treatment cycles, whereas 224 patients (> 99%) in the Taxol group received premedication in 95% of the cycles.

Although the patients in the Abraxane group received an average paclitaxel dose-intensity 49% greater than that received by patients in the Taxol group, the incidence of treatment-related **grade 4 neutropenia** was significantly lower in the Abraxane group than in the Taxol group (9% *v* 22%, respectively; $P < 0.001$), with a higher mean neutrophil nadir (1.67 *v* 1.31 x 10^9/L, respectively; $P = 0.046$), suggesting that polyethylated castor oil may have contributed to this toxicity in patients who received standard (solvent-based) paclitaxel.

As expected with a higher dose of paclitaxel, treatment-related **grade 3 sensory neuropathy** occurred more frequently in the Abraxane arm than in the Taxol arm (10% *v* 2%, respectively; $P < 0.001$); however, these episodes improved with interruption of treatment to grade 2 or 1 in a median 22 days and were easily managed with treatment interruption and dose reduction. By day 28 after its first occurrence, the number of patients with persistent grade 3 sensory neuropathy was the same (n = 4) in both study arms. No episodes of motor neuropathy or grade 4 sensory neuropathy were reported in either group.

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

Subgroup analyses revealed that the safety profiles of Abraxane (n = 97) and Taxol (n = 30) in patients who received the drugs as first-line therapy were similar to those in the overall study population. In subgroup analyses by age, the reported AEs were similar in patients less than 65 years old and patients ≥ 65 years old in both groups. Of the patients ≥ 65 years old, the incidences of the following AEs were notably lower in the Abraxane group (n = 30) than in the Taxol group (n = 32): neutropenia (23% *v* 59%, respectively), leukopenia (10% *v* 31%, respectively), nausea (20% *v* 38%, respectively), hyperglycemia (0% *v* 19%, respectively), and flushing (0% *v* 16%, respectively). These data indicate no additional safety concerns for elderly patients, and stimulated the development of combinations for NSCLC including stratification for age <70 and ≥70 years (see below).

Weekly (QW) Schedule with Carboplatin in advanced Non-small cell Lung (NSCLC) Cancer

A combination of Abraxane at 100mg/m^2 on days 1, 8 and 15 of a 21 day cycle in combination with carboplatin AUC 6 every 21 days was studied in NSCLC, and led to the FDA approval of the combination for this particular indication. Overall response

rates (ORR) for the Abraxane combination were statistically significantly increased over the Taxol/carboplatin arm (33% vs 25% *P* = 0.005, with the secondary endpoint of progression free survival favoring the Abraxane combination. Treatment Emergent AEs (TEAEs) in the Abraxane combination were alopecia, neutropenia, anemia, and thrombocytopenia; peripheral sensory neuropathy, arthralgia and myalgia were significantly more often TEAEs in the Taxol combination; TEAEs frequency and distribution did not differ by the age stratification (see **Table 2**, section 4.0). *However, the incidence of TEAEs resulting in taxane delay/dose not given was higher for the Abraxane combination (71%) as opposed to the Taxol combination (41%).* On the other hand, the improvement in ORR for Abraxane/carboplatin was achieved without significant increase in Serious AEs (SAEs) over Taxol/carboplatin (18% vs 15%). The toxicity experience in the 1052 patients (521 receiving Abraxane) enrolled in this trial provides the major rationale for dropping the day 15 dose of Abraxane in this feasibility/toxicity reduction feasibility study.

1.4 Rationale Behind Abraxane + Carboplatin in Endometrial Cancer

A major impetus behind our clinical trial is verifying the activity of a more optimal and potentially less toxic taxane schedule and formulation than GOG 209. While in ovarian cancer trialists have switched to weekly regimens (based on results from Phase III Japanese GOG and experience with divided dose Taxol for recurrences and metastatic breast cancer), results obtained by the GOG every-3-week carboplatin + Taxol doublet regimen are the only available Phase III clinical data for endometrial cancer. Accordingly, a regimen of carboplatin and divided dose (D1 and D8) Abraxane is worthy of a study in patients with high-risk histologic subtypes, advanced stage (III and IV) or recurrent endometrial cancer. Once feasibility across 6 cycles is established, a phase III trial versus the standard Taxol/carboplatin every 3 weeks is justified – not only because of toxicity reduction but also the possibility of improved efficacy from the divided dose taxane schedule. Thus, we propose a phase II feasibility design for Abraxane 100 mg/m^2 on days 1 and 8 + carboplatin AUC 6 every 3 weeks given for 6 cycles in previously untreated patients with endometrial cancer who meet eligibility criteria. *This day 1, 8 dosing seeks toxicity reduction (and a reduction of dose delays and doses not given that were seen in 71% in the day 1, 8, 15 dosing in the NSCLC trial) for endometrial cancer patients who are generally older with a high percentage of comorbidities, and also pretreated with pelvic and/or vaginal radiation*. In summary, the better hematologic tolerance of Abraxane vis-à-vis paclitaxel when given together with carboplatin, and the omission of day 15 dosing in our regimen (as opposed to the NSCLC study summarized in 1.3) support the feasibility testing of this regimen in advanced and/or recurrent endometrial cancer. If declared feasible, it would be an alternative doublet to Taxol/carboplatin every 3 weeks in a phase III study.

Table 1: Summary of GOG studies in advanced stage and recurrent endometrial cancers

Trial and reference	Years of accrual	Regimen	N^	% RR (CR)	Median PFS (m)	Median OS (m)
GOG 48[16]	1979-1985	**Doxorubicin**	132	22(5)	3.2	6.7
		Doxorubicin/cyclophosphamide	144	30(13)	3.9	7.3
GOG 107[17]	12/1988-12/1991	**Doxorubicin**	150	25(8)	3.8	9.2
		Doxorubicin/cisplatin	131	42(19)	5.7 HR = 0.736*	9.0
GOG 139[18]	3/1993-8/1996	**Doxorubicin/cisplatin**	173	49(15)	5.9	13.2
		Doxorubicin/circadian cisplatin	169	46(17)	6.5	11.2
GOG 163[19]	8/1996-11/1998	**Doxorubicin/cisplatin**	157	40(NR)	7.2	12.6
		Doxorubicin/paclitaxel/G-CSF	160	43(NR)	6.0	13.6
GOG 177[20]	12/1998-8/2000	**Doxorubicin/cisplatin**	129	34(7)	5.3	12.3
		Doxorubicin/cisplatin/paclitaxel/ G-CSF (i.e., 'TAP' regimen)	134	57(22)	8.3 HR = 0.60*	15.3 HR = 0.75*
GOG 209[21]	8/2003-4/2009	Carboplatin/paclitaxel	663	NR	14	32
		Doxorubicin/cisplatin/paclitaxel/G-CSF (TAP)	642	NR	14	38

2.0 Objectives

This is a feasibility study of a day 1, 8 dose-schedule of Abraxane given in combination with carboplatin every 3 weeks in patients with newly diagnosed or recurrent endometrial cancer.

2.1 Primary Endpoint

The primary endpoint is the percent completion of 6 cycles of therapy on this protocol. Completion is defined as completing 6 cycles of the doublet (including pre-specified up to two dose level reductions).

2.2 Secondary Endpoints

1. To determine percent progression free survival at 6, 12,18, 24 months from onset of study treatment with carboplatin and Abraxane in patients with high-risk histologic subtypes, advanced, or recurrent endometrial cancer.

2. To determine objective response rates by RECIST 1.1 (in patients with measurable disease) at the above time points.

3. To evaluate the safety of treatment with carboplatin and Abraxane in this patient population and determine the nature and degree of toxicities following treatment.

3.0 Study Design

3.1-3.2 Description and Rationale for Study Design

The single stage open label Phase II feasibility study is designed to estimate the proportion of patients who can tolerate the proposed regimen for 6 cycles with no more than two dose level reductions.

3.3 Outcome Measures

3.3.1 Primary Outcome Measures

The tolerability of the regimen is the primary outcome. Tolerability for an individual patient will be defined as remaining on the study for 6 cycles with two or fewer dose reductions.

3.3.2 Secondary Outcome Measures

The percent of patients without disease progression or death at 6, 12, 18, 24 months since start of treatment will be determined by CT scans at baseline compared to at the above specified time points (+/- 2 weeks). Responses at those time intervals will be assessed by the RECIST 1.1 criteria in those patients with measurable disease at baseline (but will not require objective responses to be confirmed by subsequent imaging). Patients who enroll following complete cytoreduction for advanced disease will not be evaluable for response, but will be evaluated for progression-free survival data.

3.3.3 Safety Outcome Measures

Toxicity will be assessed with each dosing visit while on protocol and at the 30 day post-treatment visit. Signs and symptoms will be characterized into grade as per the CTCAE protocol. Treatment limiting toxicities will include grade 3 and 4 non-hematologic toxicities lasting more than 1 week (excluding fatigue, alopecia or aggravation of pre-existing problems) as well as grade 4 thrombocytopenia and febrile neutropenia as defined by the NCI-CTCAE.

4.0 Safety Plan

Dosing Abraxane on days 1 and 8 without day 15 should be able to circumvent many of the hematologic toxicities observed in the NSCLC trial cited at the end of section 1.3 and summarized in **Table 2.** During post marketing surveillance, rare cases of severe hypersensitivity reactions have occurred [23]. The overall rate of grade 3 and 4 toxicities were low and comparable to that of solvent based Taxol with the exception of significantly less grade ≥ 3 neuropathy, neutropenia, arthralgia and myalgias in the Abraxane arm. On the other hand an increase in grade 3 and 4 thrombocytopenia and anemia was associated with use of Abraxane versus paclitaxel at 175 mg/m^2. The omission of day 15 dosing makes it likely that this Abraxane/carboplatin doublet will prove feasible within the statistical framework established in this protocol.

Table 2. Toxicity of Weekly Abraxane + Carboplatin in NSCLC Trial

Most Common Treatment-Related Grade ≥ 3 AEs According to NCI-CTCAE

AE	*nab*-PC (%) (n = 514)		sb-PC (%) (n = 524)		*P*
	Grade 3	Grade 4	Grade 3	Grade 4	
Hematologic AEs					
Neutropenia	33	14	32	26	< .001*
Thrombocytopenia	13	5	7	2	< .001†
Anemia	22	5	6	< 1	< .001†
Febrile neutropenia	< 1	< 1	1	< 1	N/S
Nonhematologic AEs					
Fatigue	4	< 1	6	< 1	N/S
Sensory neuropathy	3	0	11	< 1	< .001*
Anorexia	2	0	< 1	0	N/S
Nausea	< 1	0	< 1	0	N/S
Myalgia	< 1	0	2	0	.011*
Arthralgia	0	0	2	0	.008*

- Abbreviations: AE, adverse event; *nab*-PC, 130-nm albumin-bound paclitaxel + carboplatin (PC); NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events;
- N/S, not significant; ↵ * *P* < .05 in favor of *nab*-PC.
- † *P* < .05 in favor of sb-PC.

Treatment limiting toxicities for this protocol will be grade 3-4 non-hematologic toxicities lasting more than one week (with exception of alopecia, fatigue or aggravation of pre-existing problems) as well as grade 4 thrombocytopenia and febrile neutropenia. Patients experiencing a treatment limiting toxicity will be dose reduced according to the protocol treatment schema described below

4.1 Plan to manage safety

A number of measures will be taken to ensure the safety of patients participating in this trial. These measures will be addressed through exclusion criteria (see Section 5.3) and routine monitoring as follows.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements. Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study. Patients discontinued from the treatment phase of the study for any reason will be evaluated ~30 days (28–42 days) after the decision to discontinue treatment (see Section 7.1.3).

Specific monitoring procedures are as follows:

- **Hematologic toxicity**: a complete blood count with differential will be obtained at the start of each treatment cycle. Any hematologic toxicity will be noted and followed closely. If a grade 4 toxicity is identified, the treatment will be held until the laboratory value reaches the parameters for treatment and the dose will be adjusted according to the protocol stated below. If a patient requires two dose reductions over the duration of the trial and still incurs a treatment limiting toxicity, the patient will be discontinued from the study and counted as unable to complete the prescribed dose.
- **Non-hematologic toxicity**: this will likely be identified in the pre-treatment interview, physical examination and/ or other laboratory tests obtained prior to each cycle of chemotherapy (complete metabolic panel). Again, any toxicity will be noted and followed closely. If a grade 3 or above toxicity is identified, treatment will be held and restarted once the toxicity has recovered to a grade 1 or lower. When the treatment is restarted, the dose will be reduced as specified below:

Dose Reduction Levels

Initial Treatment Dose	Dose Level -1	Dose Level -2
Abraxane 100mg/m^2 IV D1, 8	Abraxane 75mg/m^2 IV D1, 8	Abraxane 60/m^2 IV D1, 8
Carboplatin AUC 6 IV D1	Carboplatin AUC 5 IV D1	Carboplatin AUC 4 IV D1

Dose Reduction Levels for Patients with Prior Whole Pelvic Radiation

Initial Treatment Dose	Dose Level -1	Dose Level -2
Abraxane 75mg/m^2 IV D1, 8	Abraxane 60mg/m^2 IV D1, 8	Abraxane 50/m^2 IV D1, 8
Carboplatin AUC 5 IV D1	Carboplatin AUC 4 IV D1	Carboplatin AUC 3 IV D1

Again, if a patient requires two dose reductions over the duration of the trial and still incurs a treatment limiting toxicity, the patient will be discontinued from the study and counted as unable to complete the prescribed dose.

5.0 Study Subjects

5.1 Subject Selection

General Guidelines
Patients will be recruited from the offices of gynecologic oncologists and medical oncologists at the NYU Perlmutter Clinical Cancer Center as per selection criteria below. The patients will be identified by the treating physician and referred to the research nurse for trial eligibility. Physicians and/or Co-investigators will explain the informed consent document to the patient. Any questions or concerns will be addressed by doctors and or study staff. Once all questions are addressed, the patient will sign the consent form. At the start of trial an H&P, basic vital signs and GOG performance status will be noted on the patient's medical record.

Registration Process
Patients must sign an informed consent prior to any screening procedures. Registration is done centrally by the NYU Perlmutter Cancer Institute's Clinical Trial Office (CTO). Documents required upon registration include last page of signed informed consent, eligibility checklist form (signed by PI or sub-investigator) and documentation confirming eligibility (including labs, history, availability of tissue specimen).

5.2 Inclusion Criteria

1 Female patients must have high risk resected stage I or 2 disease (papillary serous, clear cell, carcinosarcoma histology or Grade 3), advanced stage (III or IV, all histologies) or recurrent endometrial cancer (all histologies). Patients do not need measurable disease and can enroll following surgery.

2 Patients may not have received prior cytotoxic chemotherapy. However, nonplatinum/non-taxane chemotherapy used for radiation sensitization is allowed. Patients may have received prior radiation therapy (including whole pelvic or vaginal brachytherapy), hormonal therapy, or therapy with biologic agents, but such therapy must be discontinued at least 2 weeks prior to entry on this study.

3 If patients underwent surgery, and chemotherapy is indicated after surgery either as adjuvant or to treat residual disease, study treatment should be initiated within 8 weeks of surgery.

4 In patients who have received prior radiation, at least 4 weeks should have elapsed since the completion of radiation therapy involving the whole pelvis or over 50% of the spine. If vaginal brachytherapy is planned with chemotherapy, it should be done before or after completion of chemotherapy treatment.

5 Poorly differentiated histology, uterine papillary serous carcinoma, clear cell carcinoma or carcinosarcoma is acceptable as long as the predominant metastatic component is epithelial (versus sarcomatous).

6 Patients may have synchronous endometrial and ovarian cancer primaries.

7 Patients must have a GOG performance status of 0, 1, or 2

8 Patients must be at least 18 years of age.

9 Patients must understand and willingly sign an approved informed consent, and authorization permitting release of personal health information.

10 Patients must have adequate liver function: AST and ALT ≤ 2.5 X upper limit of normal (ULN), and bilirubin ≤ 1.5mg/dL.

11 Patients must have adequate bone marrow function: platelets ≥ 100,000 cells/mm^3 (transfusion independent, defined as not receiving platelet transfusions within 7 days prior to laboratory sample), hemoglobin > 9.0g/dl and ANC ≥ 1,500 cells/mm^3.

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

13 Patients must have < grade 2 pre-existing peripheral neuropathy (per CTCAE).

5.3 Exclusion Criteria

1. Other prior malignancies within 3 years, except non-melanoma skin cancers and synchronous ovarian primaries.

2. Eligibility to a higher priority trial for first line or recurrent endometrial cancer (unless patient is unwilling to participate in such a trial).

3. Patients with concomitant medical illness such as serious uncontrolled infection, or uncontrolled angina, which in the opinion of the treating physician, make the treatments prescribed on this study unreasonably hazardous for the patient.

4. Patients who are pregnant or breastfeeding.

5. Patients with third degree or complete heart block are not eligible unless a pacemaker is in place. Patients on medications, which alter cardiac conduction, such as digitalis, beta-blockers, or calcium channel blockers, or who have other conduction abnormalities or cardiac dysfunction could be entered at the discretion of the investigators.

6. Patients with history of myocardial infarct within 6 months before enrollment, New York Heart Association (NYHA) class II or greater heart failure or symptoms suspicious for congestive heart failure are not eligible unless a LVEF in the past 6 months is documented to be 50% or greater. Patients who have had a LVEF (performed for any reason) that is less than 50% in the past 6 months are ineligible.

6.0 Study Design

6.1 Treatment Plan

In a phase II open-label tolerability study, women with high-risk histologic subtypes, advanced or recurrent endometrial cancer will be treated with Abraxane 100mg/m^2 IV and carboplatin AUC 6 on day 1 and Abraxane 100mg/m^2 IV on day 8 of a 21 day cycle for 6 cycles. Subjects will undergo pre-treatment evaluation within 4 weeks of enrolling into the study (as described in section 8.1). Clinical and laboratory evaluation will be performed as described is section 8.2. Imaging studies will be performed within 4 weeks of enrollment and at the 6, 12, 18, 24 month after start of treatment while on study. Dose reductions and modifications for toxicity are described below.

Subjects who received whole pelvic radiation therapy or greater than 50% spine, will start at a reduced dose. (see section 4.1). Subjects must wait at least 4 weeks after completion of whole pelvic or >50% spine radiation prior to starting chemotherapy. If vaginal brachytherapy is planned with chemotherapy, it may be performed before starting or after completion of chemotherapy at the discretion of the treating physician. Subjects DO NOT need to start at a reduced dose if they received only vaginal brachytherapy. Vaginal brachytherapy may not be performed in the middle of chemotherapy treatment.

For subjects who underwent surgery and for whom chemotherapy is indicated after surgery, either as to treat adjuvantly or to treat residual disease, the study treatment should be administered within 8 weeks of surgery. For subjects who have recurrent disease and have had prior surgery, study treatment does not need to be initiated within 8 weeks of surgery.

7.0 Study Medications

7.1 Abraxane Dosage and Formulation

ABRAXANE for Injectable Suspension (also known as ABI-007, nab-paclitaxel, paclitaxel protein-bound particles for injectable suspension) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a non-crystalline, amorphous state. ABRAXANE is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel and approximately 900mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5mg paclitaxel. ABRAXANE is free of solvents. The active agent in ABRAXANE is paclitaxel.

ABRAXANE is a biologically interactive albumin-bound paclitaxel combining a protein with a chemotherapeutic agent in the particle form. This composition provides a novel approach of increasing intra-tumoral concentrations of the drug by a receptor-mediated transport process allowing transcytosis across the endothelial cell. This albumin-specific receptor mediated process involves the binding of albumin to a specific receptor (gp60) on the intralumminal endothelial cell membrane, resulting in activation of a protein (caveolin-1), which initiates an internalization process in the endothelial cell through the formation of caveolae, with transport of the intact albumin-bound chemotherapeutic complex via these caveolae to the underlying tumor interstitium [18] A protein specifically secreted by the tumor (SPARC) binds albumin, allowing release of the hydrophobic drug to the tumor cell membrane [19]. ABRAXANE is the first biologically interactive nanoparticle product leveraging this gp-60/caveolin-1/caveolae/SPARC pathway to increase intra-tumoral concentration of the drug and reducing toxic effects in normal tissue.

Preclinical studies comparing ABRAXANE to Taxol® (paclitaxel Cremophor® EL solvent-based, BMS) demonstrated lower toxicities, with an MTD approximately 50% higher for ABRAXANE compared to Taxol. At equal doses there was less myelosuppression and improved efficacy in a xenograft tumor model of human mammary adenocarcinoma. At equitoxic doses of paclitaxel, ABRAXANE treated groups showed more complete regressions, longer time to recurrence, longer doubling time, and prolonged survival. At equal dose, tumor paclitaxel area under the curve was 33% higher for ABRAXANE versus solvent based paclitaxel, indicating more effective intratumoral accumulation of ABRAXANE[18].

The dose used in this protocol is extrapolated from the phase III clinical trial of the combination of carboplatin and Abraxane for non-small lung cancer. In that study, the Abraxane was dosed weekly (days 1, 8, 15 of a 21 day cycle), however, in this study we will use a divided dose of Abraxane (days 1 and 8) and no treatment will be administered on day 15 in preparation for the initiation of the following cycle on day 1/ 21. As in the NSCLC trial, the recommended dose of Abraxane is 100mg/m^2

administered as an intravenous infusion over 30 minutes on days 1 and 8 of a 21 day cycle. Standardizing the order of Abraxane and Carboplatin administration has no effect on patient toxicity; however, administration of Abraxane before Carboplatin is preferred but not required.

7.1.2 Abraxane Storage and Administration

Use caution when handling cytotoxic drugs. Closely monitor the infusion site for extravasation and infiltration.

Packaging, Labeling, and Storage of Study Drug

Availability

ABRAXANE will be supplied by Celgene Corporation. Each single-use vial contains 100mg of paclitaxel and approximately 900mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5mg paclitaxel.

Storage and Stability

Storage: Store the vials in original cartons at 20ºC to 25ºC (68º F to 77ºF). Retain in the original package to protect from bright light.

Stability: Unopened vials of ABRAXANE are stable until the date indicated on the package when stored between 20ºC to 25ºC (68ºF to 77ºF), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

Stability of Reconstituted Suspension in the Vial

Reconstituted ABRAXANE should be used immediately, but may be refrigerated at 2ºC to 8ºC (36ºF to 46ºF) for a maximum of 24 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

Stability of Reconstituted Suspension in the Infusion Bag

The suspension for infusion when prepared as recommended in an infusion bag should be used immediately, but may be refrigerated at 2°C to 8°C (36°F to 46°F) and protected from bright light for a maximum of 24 hours.

The total combined refrigerated storage time of reconstituted ABRAXANE in the vial and in the infusion bag is 24 hours. This may be followed by storage in the infusion bag at ambient temperature (approximately 25°C) and lighting conditions for a maximum of 4 hours. Discard any unused portion.

Study Medication Administration

ABRAXANE is injected into a vein [intravenous (IV) infusion] over 30 minutes. The use of an in-line filter is not recommended.

Following administration, the intravenous line should be flushed with Sodium Chloride 9mg/ml (0.9%) solution for injection to ensure complete administration of the complete dose, according to local practice.

Reconstitution and use of ABRAXANE

1. Calculate the patient's body surface area at the beginning of the study and if the weight changes by >10% by using the formula provided in the study manual.
2. Calculate the total dose (in mg) to be administered by:

$$Total\ Dose\ (mg) = BSA(m^2)\ \times Study\ Dose\ \left(\frac{mg}{m^2}\right)$$

3. Calculate the total number of vials required by:

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

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

4. Using sterile technique, prepare the vials for reconstitution.
5. Swab the rubber stoppers with alcohol.
6. Aseptically, reconstitute each ABRAXANE vial by injecting 20mL of 0.9% Sodium Chloride Injection, USP.
   - **Slowly** inject the 20mL of 0.9% Sodium Chloride Injection, USP, over a minimum of **1 minute**, using the sterile syringe directing the solution flow onto the **inside wall** of the vial.
   - **DO NOT INJECT** the 0.9% Sodium Chloride Injection, USP solution directly onto the lyophilized cake as this will result in foaming.
   - Once the injection is complete, allow the vial to sit for a **minimum of 5 (five) minutes** to ensure proper wetting of the lyophilized cake/powder.
   - **Gently** swirl and/or invert the vial **slowly** for at least **2 minutes** until complete dissolution of any cake/powder occurs. Avoid generation of foam. Rapid agitation or shaking will result in foaming.
   - If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.
   - Each ml of reconstituted product will contain 5 mg of paclitaxel.
7. Calculate the exact total dosing volume of 5 mg/ml suspension required for the subject:

$$Dosing\ Volume\ (ml) = \frac{Total\ dose\ (mg)}{5\ \left(\frac{mg}{ml}\right)}$$

8. The reconstituted suspension should be milky and homogeneous without visible particulates. If particulates or settling are visible, the vial should be **gently** inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed.

9. Once the exact volume of reconstituted ABRAXANE has been withdrawn from the vials, discard any excess solution left over in accordance with standard operating procedures.
10. Further dilution is not necessary. Inject the calculated dosing volume of reconstituted ABRAXANE suspension into an empty sterile, standard PVC IV bag using an injection port. Inject perpendicularly into the center of the injection port to avoid dislodging plastic material into the IV bag.
11. Administer the calculated dosing volume of reconstituted ABRAXANE suspension by IV infusion over 30 minutes. The use of in-line filters is not recommended because the reconstituted solution may clog the filter.

Drug Distribution and Destruction

a. Supplier

Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

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

b. Drug Distribution

ABRAXANE® will be distributed by Celgene Corporation. No supplies will be shipped to any site until regulatory approval has been obtained. Investigational sites will be supplied with ABRAXANE® upon identification and screening of a potential trial subject.
Upon identification of a potential subject, sites must fax a completed Drug Request Form to Celgene Corporation. Allow at least 5 working days for drug shipment. There are no shipments on Fridays or holidays.
For re-supply of drug, please complete and fax the Drug Request Form to Celgene Corporation at 908-673-2779.

c. Drug Return and Destruction

If the investigational site does not have a policy, procedure or SOP detailing the process to follow for study drug destruction, the study drug must then be returned to Celgene using the Drug Return Form provided in the package containing the study drug. The following information must be recorded on the site's pharmacy drug

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

7.1.3 Abraxane Dose Modification and Toxicity Management

Hematologic toxicity
Initial protocol treatment will only occur if ANC ≥ 1500 cells/mm^3 and platelet count is ≥ 100,000 cells/mm^3 on day 1. Subsequent cycles of therapy (i.e. Day 1 treatment) will not begin until the ANC is ≥ 1000 cells/mm^3 and the platelet count is ≥ 100,000/mm^3. Therapy will be delayed for a maximum of three weeks until these values are achieved. Subjects who fail to recover adequate counts within a three-week delay will be removed from study. For day 8, ANC must be ≥ 500 cells/mm^3 and the platelet count must be ≥ 75,000/mm^3. If day 8 dosing criteria are not met, the dose will be held until the following cycle, if toxicity has resolved and start the next cycle at one dose level reduction.

- For subjects with ≥ grade 3 neutropenia or thrombocytopenia, treatment will be withheld until counts recover to ANC ≥ 1000 cells/mm^3 and platelet count is ≥ 100,000 cells/mm^3 on day 1 or ANC ≥ 500 cells/mm^3 and platelet count is ≥ 75,000 cells/mm^3 on day 8 of the cycle.
- If treatment is withheld, upon resumption of dosing, Abraxane and carboplatin dosing will be permanently reduced as per the following guidelines:

1. Dose Reduction of one dose level
   - Febrile neutropenia
   - Nadir ANC < 500 cells/mm^3 persistent for more than one week
   - Nadir platelet count < 50,000 cells/mm^3
   - Delay of next cycle (D1 treatment) by more than 7 days for nadir ANC < 1000 cells/mm^3
   - If unable to give D8 treatment
   - Dose is held for neutropenia or thrombocytopenia

2. Dose Reduction of two dose levels
   - If any of the above listed conditions re-occurs following first dose reduction, except for thrombocytopenia see note below*

If the conditions listed above reoccur following reduction of two dose levels, the treatment will NOT be further reduced, but instead will be discontinued.

*IMPORTANT: Thrombocytopenia – if nadir platelet levels drop below 50,000 cells/mm^3, the treatment will be withheld until the levels recover to 100,000 cells/mm^3 for day 1 or 50,000 cells/mm^3 on day 8 and the dose will be reduced one dose level. If the levels are noted to drop below 50,000 cells/mm^3 again, the treatment will not be further reduced and instead will be discontinued.

Non-hematologic toxicity

1. Neuropathy

   Grade 2 (or greater) peripheral neuropathy requires reduction of one dose level and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1. If recurrent neuropathy to ≥ grade 2 occurs after 1 dose reduction, treatment will be held until resolution of symptoms to ≤ grade 1, and treatment will be reinitiated at a second dose reduction.

2. Renal

   Grade 2 (or greater) renal toxicity requires reduction of one dose level and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1.

3. Hepatic
   - Subjects with bilirubin levels above the ULN will be excluded from this clinical trial.
   - For subjects with moderate hepatic impairment (AST < 10 x ULN and bilirubin > 1.5 to ≤ 3 x ULN): the Abraxane dose will be reduced one dose level (see section 4.1), and subsequent therapy delayed for a maximum of 3 weeks until recovered to grade 1.
   - For severe hepatic impairment (AST < 10 x ULN and bilirubin > 3 - ≤ 5 x ULN): the Abraxane dose will be reduced to two dose levels, and subsequent therapy delayed for a maximum of 3 weeks until recovered to grade 1.
   - Any subjects with very severe hepatic impairment (AST > 10 x ULN OR bilirubin > 5 x ULN) will be taken off trial.

4. Alopecia

   There will be no dose modifications for alopecia.

5. GI

   It is expected that subjects with nausea, emesis, diarrhea, or constipation will receive appropriate medical management without dose modification. However, subjects with persistent (greater than 24 hours) ≥ grade 3 toxicity in spite of

optimal medical management require reduction of one dose level and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1.

6. Other

   Non-hematologic toxicities with an impact on organ function of ≥ grade 2 require reduction of one dose level and delay in subsequent therapy for a maximum of 2 weeks until recovered to grade 1, or pre-therapy baseline.

7. Hypersensitivity

   Routine premedication to prevent hypersensitivity, nausea, or vomiting is not required. However, Abraxane contains paclitaxel, and hypersensitivity reactions have been observed in some patients treated to date. Mild hypersensitivity reaction (Grade 1 or 2 such as flushing, pain, urticaria, drug fever, and asymptomatic bronchospasm) can often be successfully treated with slowing or interrupting the infusion of Abraxane and administering antihistamines and antipyretics (such as diphenhydramine, promethazine, acetaminophen). Frequently, per investigator discretion, the infusion can be restarted and completed after the symptoms have abated. Injectable steroids and epinephrine should be immediately available to provide prompt treatment of any severe hypersensitivity reactions that may occur during or following study treatment. Subjects with grade 3 hypersensitivity reactions can be retreated after standard paclitaxel premedication at the discretion of the investigator. Pre-medicated subjects with grade 3 hypersensitivity reaction and all subjects with grade 4 hypersensitivity reaction should not be retreated.

Important – Abraxane contains albumin, a derivative of human blood and should not be administered to subjects who object to receiving blood products.

Overdose

Overdose, as defined for this protocol, refers to ABRAXANE® alone or in combination dosing only.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of ABRAXANE® assigned to a given subject, regardless of any associated adverse events or sequelae.

PO any amount over the protocol-specified dose

IV 10% over the protocol-specified dose

SC 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. For nab-paclitaxel, an infusion completed in less than 25 minutes may

increase Cmax by approximately 20%, therefore a nab-paclitaxel infusion completed in less than 25 minutes will meet the infusion rate criterion for an overdose.

Important: We will conduct strict education with all co-investigators and infusion nurses to ensure infusion should not be completed in less than 25 minutes.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

Concomitant Medications
Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the Investigator. Concurrent treatment with bisphosphonates is allowed. Erythropoietin and G-CSF may be administered at the discretion of the investigator, consistent with institutional guidelines.

7.2 Carboplatin Dosage and Formulation (Paraplatin® - NSC #241240)

Carboplatin is supplied as a sterile, pyrogen-free, 10mg/mL aqueous solution in multi-dose vials containing 50mg/5mL, 150mg/15mL,450mg/45mL, or 600g/60mL of carboplatin. Commercially available both from Bristol-Myers Squibb Oncology as well as generic manufacturers. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information. Carboplatin is given per standard of care, FDA-approved dosing.

7.2.1 Administration

Carboplatin aqueous solution can be further diluted to concentrations as low as 0.5mg/mL with 5% Dextrose in Water or 0.9% Sodium Chloride for Injection, USP. When prepared as directed, carboplatin aqueous solutions are stable for 8 hours at room temperature (25°C / 77°F). Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded 8 hours after dilution. Institutional pharmacy policy may allow refrigeration and longer storage. NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must NOT be used for the preparation or administration of carboplatin.

7.2.2 Storage

Unopened vials of carboplatin are stable to the date indicated on the package when stored at 25°C (77°F). Excursions from 15 to 30°C (59 to 86°F) are permitted. Protect from light. Carboplatin multi dose vials maintain microbial, chemical, and physical stability for up to 14 days at 25°C following multiple needle entries.

7.2.3 Carboplatin dose modifications and toxicity management:

Dose Calculations
Carboplatin is dosed by AUC calculated as per the GOG calculator on www.gog.org. For subject safety GOG clinical research studies limit GFR values to less than or equal to 125ml/min. For GFR greater than 125, 125 is used to calculate the carboplatin dose. Therefore for GOG studies, the maximum dose is capped at 450mg for AUC 3, 600mg for AUC 4, 750mg for AUC 5 and 900mg for AUC 6. Calvert Formula: Carboplatin dose (mg) = (Target AUC) x (GFR + 25). For the purposes of this calculation, the GFR will be considered to be equivalent to the estimated creatinine clearance (Ccr). The estimated creatinine clearance is calculated by the method of Cockcroft-Gault. The Cockcroft-Gault formula for calculating the estimated creatinine clearance for women is:

$$Ccr\ \left(\frac{ml}{min}\right) = \frac{\left(140 - Age(years)\right) \times Weight(kg)}{72 \times Serum\ Creatinine\ \left(\frac{mg}{dl}\right)} \times 0.85$$

For this study carboplatin will be dosed at AUC 6 IV (or AUC 5 if prior radiation therapy).

Dose modifications will occur as follows:

Dose level -1: Carboplatin IV AUC 5 (with Abraxane at 75mg/m^2 IV)
Dose level -2: Carboplatin IV AUC 4 (with Abraxane at 60mg/m^2 IV)

If the subject had prior whole pelvic radiation therapy, dose modifications will occur as follows:

Dose level -1: Carboplatin IV AUC 4 (with Abraxane at 60mg/m^2 IV)
Dose level -2: Carboplatin IV AUC 3 (with Abraxane at 50mg/m^2 IV)

There will be no third dose reduction level for carboplatin, instead treatment will be discontinued.

There will be no treatment modifications for grade 1 or grade 2 non-hematologic toxicities or grade 1 or 2 hematologic toxicities. For grade ≥ 3 non-hematologic toxicities, the treatment will be withheld until the toxicity has improved to ≤ grade 1 and restarted at dose level -1 (as specified above). For recurrent toxicity, the treatment will once again be held until the toxicity has improved to ≤ grade 1 at which point it will be restarted at dose level -2 (as specified above).

Hepatic, neurologic and hematologic toxicities are treatment limiting in this study, please see description above (under Abraxane) for instructions on dose reductions for specific scenarios. When a dose reduction is undertaken, both the abraxane and carboplatin will be dose reduced.

Important: severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions have been reported. Subjects who experience a severe hypersensitivity to carboplatin should not be rechallenged with the drug.

7.3 Concomitant medications:

No premedications are necessary with Abraxane administration. For cycle day 1 we suggest decadron 10mg IV once prior to carboplatin administration. Carboplatin is an emetogenic chemotherapy. Support with antiemetics is encouraged.

Caution should be exercised when administering ABRAXANE concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4.

8.0 Clinical and Laboratory Evaluations

All treatments performed throughout the study are considered standard of care, with the exception of Abraxane, which will be provided by the manufacturer. Administration of drugs (both Carboplatin and Abraxane) will be considered standard of care.

8.1 Pre-Treatment evaluations:

- Vital signs, including blood pressure, height, weight, and performance status (within 14 days)
- History and physical examination (within 14 days)
- CT-scan of chest, abdomen and pelvis should be performed (within 30 days). The imaging study performed during pre-treatment evaluation will be repeated at 6 months.
- Complete blood count, basic metabolic panel (including magnesium), liver function test, CA-125 (within 14 days); approximately 9mL of blood will be collected.

8.2 In-Treatment Evaluations

Every 3 weeks:

- Vital signs, including blood pressure, performance status, blood pressure, and weight (within 4 days of treatment)
- History and physical examination (within 4 days)
- Complete blood count, basic metabolic panel, liver function test (within 4 days). CA-125 level is optional and will be drawn at the discretion of the provider. Approximately 9mL of blood will be collected.

†

Interval imaging (CT scans) will not be routinely performed during treatment. However, if done for medical reasons in order to assess signs and symptoms that have arisen during treatment warranting evaluation, such scan may be used to determine early progression during treatment.

8.3 Post-Treatment Evaluations

8.3.1 Imaging Follow-Up:

Evaluations by CT will take place at 6, 12, 18, 24 months (+/- 2 weeks) after initiation of protocol treatment or until disease progression:

- At 6, 12, 18, 24 months (+/- 2 weeks), imaging (CT scan) will be performed. Imaging may be performed earlier than set intervals for medical reasons in order to assess signs and symptoms that have arisen during treatment warranting evaluation. If at any time point progressive disease is noted, the subject will be followed up to the 24 month landmark only for survival. All samples collected during the study will be destroyed at the end of the study. No samples will be stored for future research.

8.3.2 Clinical Evaluation Follow-Up:

Evaluations will take place at 3, 6, 9, 12, 15, 18, 21, 24 months (± 2 weeks) after End of Treatment visit or until disease progression:

- History and physical examination, assessment of performance, survival status
- Complete blood count, basic metabolic panel (without magnesium)
- CA-125 (approximately 3mL of blood)
- Toxicity assessment

9.0 Risks of Participation

Taking Abraxane may cause the subject to have one or more of the side effects listed below. The FDA considers the use of Abraxane to be investigational for treating endometrial cancer. Because this is a research study about Abraxane not all side effects are known. There may be rare and unknown side effects. Some of these side effects may be severe enough to cause death.

Below is a list of the most common side effects of Abraxane:

- Hair loss
- Numbness, tingling, pain, or weakness in the hands or feet
- Abnormal heart beat
- Tiredness
- Joint and muscle pain
- Changes in your liver function tests, which may indicate liver problems
- Rash
- Low red blood cell count (anemia) which can cause fatigue and shortness of breath
- Nausea and vomiting
- Infections
- Diarrhea

- Loss of body fluid (dehydration)
- Swelling in the hands or feet

Below is a list of potential serious side effects of Abraxane:
- Decreased blood counts. Abraxane can cause a severe decrease in neutrophils
- Numbness, tingling, pain, or weakness in the heads or feet (neuropathy)
- Severe infection (sepsis)

Below is a list of other potential side effects of Abraxane:
- Treatment with Abraxane can make liver problems worse. If you have liver problems, your starting dose of Abraxane should be lowered or withheld.
- Abraxane contains albumin (human), a product of human blood

As with any drug, an allergic reaction can occur. Allergic reactions can be mild or more serious and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat or trouble breathing.

It is also important to note the potential side effects when using Carboplatin, as these reactions are unknown when using Carboplatin and Abraxane together to treat endometrial cancer. The following is a list of potential side effects with Carboplatin:

Likely side effects while using Carboplatin:
- Low white blood cell counts
- Low platelet count
- Low red blood cell count
- Tiredness
- Loss of appetite and weight loss
- Diarrhea, constipation, nausea and vomiting, and abdominal pain
- Complete hair loss
- Skin rash
- Changes in taste
- Changes in electrolytes (salts) in the blood such as magnesium and potassium

Less Likely, but serious:
- Numbness or tingling in fingers or toes
- Ringing in the ears and hearing loss
- Allergic reactions
- Chills and fever with aches and pains
- Decrease in kidney or liver function
- Sores in mouth and throat (that can lead to difficulty swallowing and dehydration)
- Altered vision

Rare, but serious:
- Seizures
- Secondary cancers such as acute leukemia
- Kidney failure requiring dialysis

- Deafness
- Death

Risk of taking other medication with study drug:
It is not known whether Abraxane interacts with other drugs, so all medications the subject is taking will be recorded and reviewed while they participate in this study.

10.0 Potential Benefits of Treatment:

Potential benefits can include a decrease in disease progression, or even potentially improvement in health. It is also a benefit in studying potential new treatments for subjects with endometrial cancer based on the information gathered in this study.

11.0 Subject discontinuation from treatment

Subjects who meet the following criteria should be discontinued from study treatment:

- Recurrent treatment limiting toxicity status post reduction to dose level -2 (see section 4.1)
- Unwillingness or inability of subject to comply with study requirements
- Withdrawal of consent
- Determination by the investigator that it is no longer safe for the subject to continue therapy
- Hypersensitivity to Abraxane
- Disease progression during treatment

12.0 Study discontinuation

- Death from any cause
- Loss to follow-up
- Receipt of other anticancer therapy

If a subject is thought to be lost to follow-up, discontinues study treatment, or discontinues the study, attempts should be made to contact the subject to determine the reason for discontinuation. For subjects who are thought to be lost to follow-up, at least 3 documented attempts, including 1 via certified mail, should be made to contact the subject before the subject is deemed lost to follow-up.

13.0 Statistical Methods

The proportion of subjects who can remain on study for 6 cycles with 2 or fewer dose reductions will be estimated with exact 95% confidence intervals. All subjects who receive any drug will be included in this intent to treat (ITT) analysis.

Characteristics of subjects at baseline will be summarized using descriptive statistics and graphical displays. Responses evaluated by RECIST 1.1 criteria will be summarized using frequency distributions. Survival and percent progression free survival will be displayed using Kaplan-Meier curves and progression free survival rates, respectively.

13.1 Determination of sample size

Based on a single stage design, we can test the null hypothesis that the proportion of subjects completing 6 cycles as defined above is ≤ 0.5 versus the alternative that the proportion completing 6 cycles is ≥ 0.75 with an alpha of 0.05 (actual 0.047) and power of 80% with 23 subjects. If we observe 16 or more regimen completions in the 23 subjects, we reject the null hypothesis. Calculations from PASS, NCSS 2008. J Hintze, Kaysville, Ut.

14.0 Safety Reporting Of Adverse Events

14.1 Adverse Events Reporting and Definitions

Toxicity will be scored using CTCAE version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP homepage –see also Appendix 8. (http://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40). All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the onset date, duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

All AEs will be collected and recorded in the for each patient from the day of signed informed consent until 30 days after the last dose of study treatment or until the patient begins participation in a new clinical trial or initiates a new chemotherapy regimen.

In general, CTCAE (v 4.03) severity grades are:

> Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
>
> Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). (Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc)
>
> Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-

care ADL. (Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.)

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details on attribution to study treatment (i.e., unrelated, possibly, probably, definitely related and on any actions taken with respect to the test drug and about the patient's outcome.

In deciding on causality/attribution to treatment, one the following categories should be selected:

Related: A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration, and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment should be clinically plausible.

Possibly related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other drugs or chemicals.

Unlikely related: A clinical event, including laboratory test abnormality, with a temporal relationship to treatment administration which makes a causal relationship improbable, or in which other drugs, chemicals or underlying disease provide likely explanations.

Unrelated: A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. Typically explained by extraneous factors (eg, concomitant disease, environmental factors, or other drugs or chemicals).

14.2 NYU Data Safety Monitoring Committee.

According to the NCI approved DSMB plan. The Data Safety Monitoring Committee (DSMC) of the NYU Cancer Center will monitor this study upon approval by its Protocol Research Monitoring Committee (PRMC). The DSMC operates based on the 2014 National Cancer Institute approved Charter. The DSMC is responsible for monitoring safety, conduct and compliance with protocol data and safety monitoring plans for cancer clinical trials that are not monitored by any other institution or agency.

This study will be monitored according to the monitoring plan detailed below. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit. A risk-based, data-driven monitoring approach will also

include a centralized review of data for quality, trends, consistency and general safety review.

During scheduled monitoring visits, the investigator and the investigational site staff must be available to meet with the quality assurance specialist in order to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor. In addition to on-site monitoring visits, the Sponsor and/or representatives will also be routinely reviewing data. Inquiries related to study conduct, which require further information or action will be discussed within the study team for appropriate and documented escalation plans. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database.

In accordance with HIPAA and associated privacy regulations, a patient's authorization to use personal identifiable health information may be required from each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

At the NYU Perlmutter Cancer Center, all investigator-initiated protocols are subject to a standardized data and safety monitoring, which includes scientific peer review, IRB review and DSMC review as well as internal auditing.

The review of AEs and trial conduct for this trial occurs at several levels:

(1) Principal Investigator: Adverse events are evaluated monthly by the principal investigator in conjunction with the research team.

(2) DSMC, twice annually

(3) Institutional Review Board (IRB): An annual report to the IRB is submitted by the trial PI for continuation of the protocol. It includes a summary of all AEs, total enrollment with demographics, protocol violations, and status of subjects as well as available research data.

(4) In addition, the quality assurance unit will monitor this trial every 6-8 weeks, to verify adherence to the protocol; the completeness, accuracy and consistency of the data; and adherence to ICH Good Clinical Practice guidelines.

In the event of an adverse event, the first concern will be for the safety of the subject. Investigators are required to report to Celgene ANY serious treatment emergent adverse event (STEAE) within 24 hours of being aware of the event.

A STEAE is any sign, symptom or medical condition that emerges during treatment or during a post-treatment follow-up period that (1) was not present at the start of treatment and is not a chronic condition that is part of the patient's medical history, OR (2) was present at the start of treatment or as part of the patient's medical history but worsened in severity and/or frequency during therapy, AND that meets any of the following regulatory serious criteria:

- Results in death
- Is life-threatening
- Requires or prolongs inpatient hospitalization
- Is disabling
- Is a congenital anomaly/birth defect
- Is medically significant or requires medical or surgical intervention

14.3 Celgene Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management
86 Morris Avenue
Summit, NJ 07901
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com
Telephone: 1-908-673-9667
Toll Free: 1-800-640-7854

14.4 Safety Reporting Requirements

Expedited Reporting by Investigator to Celgene

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (AX-CL-OTHER-PI-005275) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the

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

Report of Adverse Events to the Institutional Review Board
The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

Investigator Reporting to the FDA
Serious adverse events (SAEs) that are **unlisted/unexpected, and at least possibly associated to the drug,** and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) by telephone or by fax. Fatal or life threatening SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 7 calendar days after awareness of the event. All other SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 15 calendar days after awareness of the event. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.
If this is a multicenter trial, suggest including language indicating that participating study sites should NOT report SAEs to the FDA. Rather, participating sites should report SAEs to Celgene and the primary study site, and the primary site will be responsible for reporting to FDA.
Adverse event updates/IND safety reports
Celgene shall notify the Investigator via an IND Safety Report of the following information:

- *Any AE associated with the use of drug in this study or in other studies that is both serious and unexpected.*
- *Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.*

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all AE information, including correspondence with Celgene and the IRB/EC, on file.

15.0 Retention of Records

All documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for at least 2 years after the investigation is completed.

15.1 Confidentiality

The research team will maintain clinical and laboratory data in a manner that ensures patient confidentiality. All study personnel have passed human subject protection

courses. Systems used for electronic data capture are compliant with HIPAA and applicable local regulatory agency guidelines. All documents are kept in strictly confidential files and are only made accessible for specific study personnel, CTO quality assurance specialists, and authorized representatives of regulatory agencies as described in the informed consent document.

15.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documentation refers to original records of observations, clinical findings, and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into Velos. Relevant source documentation to be reviewed by the DSMC throughout the study includes:

1. Baseline measures to assess pre-protocol status
2. Concurrent medications
3. Treatment records
4. Adverse events

15.3 Data and Source Documentation

Velos, an electronic database capture system will be created to record the data for this trial. Research coordinators will input clinical trial data into the database. This database is password protected and only the PI, assigned research coordinator, and CTO quality assurance specialists will have access to the database. Velos is the primary data collection instrument for the study. All data requested in Velos must be reported. All missing data must be explained. The quality assurance specialists will monitor this trial every 6-8 weeks for data entry accuracy.

DATA MANAGEMENT

A clinical research associate (CRA) will be assigned to the study and his/her responsibilities will include protocol compliance, data collection, abstraction and data entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of activities of the protocol study team.

16.0 Costs Incurred to Patients on Study

Standard of care procedures will be billed to the patient's insurance company. If the patient does not have insurance costs will be billed directly to them. The following procedures are considered standard of care:

- Vital Signs (blood pressure, pulse, temperature)
- Physical Examination
- Blood Samples
- CT Scans
- Administration costs for carboplatin and abraxane
- Carboplatin (the drug)

Since Abraxane is not FDA approved for the treatment of endometrial cancer, the drug will be provided to the patients free-of-charge from the Sponsor, Celgene INC. Administration procedures for Abraxane, however, will be billed to insurance (or the patient in the event the patient does not have insurance).

Subjects will not be paid for their participation in this study.

17.0 References:

1. American *Cancer Society, Facts and Figures, 2016* https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2016/estimated-number-of-new-cancer-cases-and-deaths-by-sex-us-2016.pdf

2. Goldfinger, M., Diaz, I , Muggia F. *Systemic treatment of endometrial cancer: what is doxorubicin's role?* J Clin Oncol. 2014 32(20):2181-2.

3. Randall ME, Filiaci VL, Muss H, et al: Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol 24:36-44, 2006

4. Cancer Genome Atlas Research Network KC, Schultz N, Cherniack AD, et al: *Integrated genomic characterization of endometrial carcinoma*. Nature 2:67-73, 2013

5. Muggia FM*. Introduction: why a supplement on taxanes? A*nticancer Drugs. 2014 May;25(5):481.

6. Katsumata N, Yasuda M, Isonishi S, et al. *Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomized, controlled, open-label trial*. Lancet Oncology 2013;14:10:1020-6

7. Vandenput I, Vergote I, et al. Leuven dose-dense paclitaxel/carboplatin regimen in patients with primary advanced or recurrent endometrial carcinoma. Int J Gynec Cancer 2009 106 (2):1147-51

8. Brochure, I.s., *ABRAXANE® (Paclitaxel Albumin Nanoparticle for Injectable Suspension) (ABI-007). American BioScience, Inc.*

9. Ibrahim, N.K., et al., *Phase I and pharmacokinetic study of ABI-007, a Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel.* Clin Cancer Res, 2002. **8**(5): p. 1038-44.

10. Ibrahim, N.K., et al., *Multicenter phase II trial of ABI-007, an albumin-bound paclitaxel, in women with metastatic breast cancer.* J Clin Oncol, 2005. **23**(25): p. 6019-26.

11. Gradishar, W.J., et al., *Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer.* J Clin Oncol, 2005. **23**(31): p. 7794-803.

12. Nyman, D.W., et al., *Phase I and pharmacokinetics trial of ABI-007, a novel nanoparticle formulation of paclitaxel in patients with advanced nonhematologic malignancies.* J Clin Oncol, 2005. **23**(31): p. 7785-93.
13. Blum, J.L., et al., *Phase II study of weekly albumin-bound paclitaxel for patients with metastatic breast cancer heavily pretreated with taxanes.* Clin Breast Cancer, 2007. **7**(11): p. 850-6.

14. Gradishar, W.J., et al., *Significantly longer progression-free survival with nab-paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer.* J Clin Oncol, 2009. **27**(22): p. 3611-9.

15. Robidoux, A., et al., *A phase II neoadjuvant trial of sequential nanoparticle albumin-bound paclitaxel followed by 5-fluorouracil/epirubicin/cyclophosphamide in locally advanced breast cancer.* Clin Breast Cancer, 2010. **10**(1): p. 81-6.

16, Thigpen, J.T., et al., *A randomized comparison of doxorubicin alone versus doxorubicin plus cyclophosphamide in the management of advanced or recurrent endometrial carcinoma: A Gynecologic Oncology Group study.* J Clin Oncol, 1994. **12**(7): p. 1408-14.

17. Thigpen, J.T., et al., *Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: a gynecologic oncology group study.* J Clin Oncol, 2004. **22**(19): p. 3902-8.

18. Gallion, H.H., et al., *Randomized phase III trial of standard timed doxorubicin plus cisplatin versus circadian timed doxorubicin plus cisplatin in stage III and IV or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study.* J Clin Oncol, 2003. **21**(20): p. 3808-13.

19. Fleming, G.F., et al., *Phase III randomized trial of doxorubicin + cisplatin versus doxorubicin + 24-h paclitaxel + filgrastim in endometrial carcinoma: a Gynecologic Oncology Group study.* Ann Oncol, 2004. **15**(8): p. 1173-8.

20. Fleming, G.F., et al., *Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study.* J Clin Oncol, 2004. **22**(11): p. 2159-66.

21. Miller, D., Fillaci V et al., *Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: a Gynecologic Oncology Group study*, in *GynecolOncol*. 2012. p. 771-3.

22. Tiersten, A.D., et al., *A phase I trial of dose-dense (biweekly) carboplatin combined with paclitaxel and pegfilgrastim: a feasibility study in patients with untreated Stage III and IV ovarian, tubal or primary peritoneal cancer: a Gynecologic Oncology Group study.* Gynecol Oncol, 2010. **118**(3): p. 303-7.

23. Socinski, M.A., et al., *Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial.* J Clin Oncol, 2012. **30**(17): p. 2055-62.

24. Desai, N., et al., *Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel.* Clin Cancer Res, 2006. **12**(4): p. 1317-24.

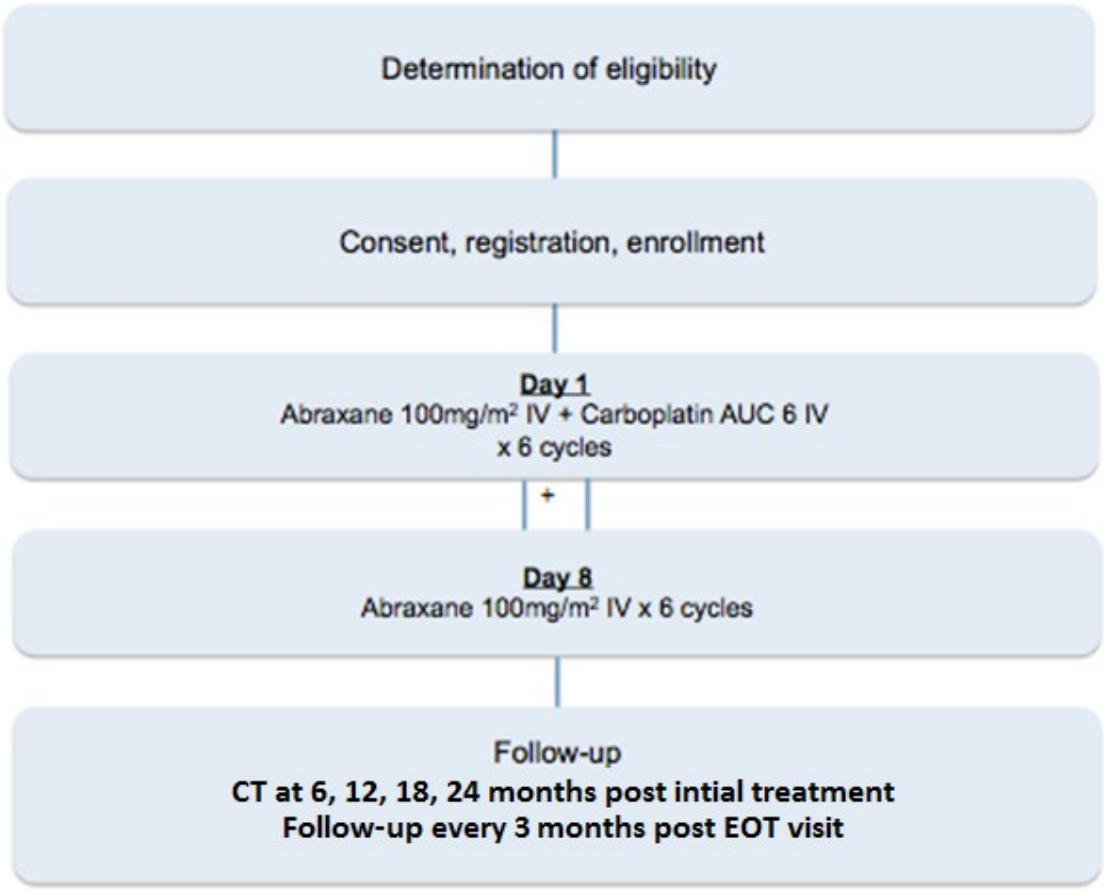
25. Desai, N.P., et al., *Improved effectiveness of nanoparticle albumin-bound (nab) paclitaxel versus polysorbate-based docetaxel in multiple xenografts as a function of HER2 and SPARC status.* Anticancer Drugs, 2008. **19**(9): p. 899-909.

Appendix 1: Study Schema

Test/Procedures	Pre-Study	Cycle 1 Day 1	Cycle 1 Day 8	Cycles 2-6 days 1	Cycles 2-6 days 8	End of Treatment Follow-up (aprx 30 days after treatment)	Follow Up every 3 mo for 2 years unless specified
H&P, Vitals	X	X	X	X		X	X
Weight, Performance Status	X	X	X	X		X	X
CT Scan of chest, abdomen, and pelvis	X						X[a] (6, 12, 18, 24 mo (± 2 weeks) after start
CA 125[b]	X						X
Toxicity Notation[c]	X	X	X	X		X	X[d]
Medication Review	X	X	X	X		X	X
CBC with diff	X	X	X	X	X	X	X
Basic Metabolic Panel	X[e]	X	X	X	X	X	X
LFTs	X	X	X	X		X	X

[a]. Scans will take place at 6, 12, 18, 24 months (± 2 weeks) after onset of treatment, as per standard of care, unless medically indicated to obtain imaging sooner. Scans will not be a part of the clinical follow-up every 3 months.
[b]. Measurement routinely used to follow treatment but not mandatory in this trial
[c]. Monitoring for toxicity is mandatory prior to each cycle; any intervening side effect will also be recorded before the next cycle
[d]. After treatment, monitoring primarily for any non-hematologic persistent treatment-related adverse events for 30 days after treatment discontinuation.
[e] Basic metabolic panel with magnesium

Appendix 2: Treatment Schema



Appendix 3: Common NCI Toxicity Criteria

Common NCI Toxicity Criteria: CTCAE version 4

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Appendix 4: FDA Medwatch

FDA Medwatch 3500a Form

http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

Appendix 5: NYHA Guidelines

NYHA Grading	Functional Capacity
Class I	No limitations. Ordinary physical activity does not cause undue fatigue, dyspnoea or palpitations (asymptomatic LV dysfunction)
Class II	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina pectoris (mild CHF).
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (moderate CHF).
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of CHF present at rest (severe CHF).

Appendix 6: Dose Reduction Levels

Dose Reduction Levels

Initial Treatment Dose	Dose Level -1	Dose Level -2
Abraxane 100mg/m^2 IV D1, 8	Abraxane 75mg/m^2 IV D1, 8	Abraxane 60mg/m^2 IV D1, 8
Carboplatin AUC 6 IV D1	Carboplatin AUC 5 IV D1	Carboplatin AUC 4 IV D1

Dose Reduction Levels for Patients with Prior Whole Pelvic Radiation

Initial Treatment Dose	Dose Level -1	Dose Level -2
Abraxane 75mg/m^2 IV D1, 8	Abraxane 60mg/m^2 IV D1, 8	Abraxane 50mg/m^2 IV D1, 8
Carboplatin AUC 5 IV D1	Carboplatin AUC 4 IV D1	Carboplatin AUC 3 IV D1