Title: Feasibility and safety of avoiding granulocyte colony-stimulating factor prophylaxis during the Paclitaxel portion of dose dense Doxorubicin-Cyclophosphamide and Paclitaxel regimen

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TITLE: Feasibility and safety of avoiding granulocyte colony-stimulating factor prophylaxis during the Paclitaxel portion of dose dense Doxorubicin-Cyclophosphamide and Paclitaxel regimen

Coordinating Center: *Dana –Farber Cancer Institute*

***Principal Investigator (PI):**

Other Investigators:

[redacted]

Statisticians:

[redacted]

Agent(s): Paclitaxel [Commercial], Neulasta™ (pegfilgrastim)[Commercial]

SCHEMA

ENROLLMENT AND REGISTRATION

Stage I-III Breast Cancer

Planned treatment with dose dense (neo) Adjuvant Doxorubicin Cyclophosphamide (AC)-Paclitaxel

TREATMENT

4 Cycles of Paclitaxel

*1 Cycle= 2 weeks

S*implification of Paclitaxel pre-medication aimed to reduce the risk of hypersensitivity reactions (HRS)*

Granulocyte-colony stimulating factor (Neulasta™**- Pegfilgrastim) support as defined by protocol.**

Pre-specified safety rules will be verified every cycle.

OFF STUDY

4 weeks post treatment with Taxol

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1. OBJECTIVES

1.1 Study design

This is an open label phase II, non-randomized study at Dana-Farber/Harvard Cancer Center (DF/HCC), to evaluate the safety and feasibility of omitting granulocyte-colony stimulating factor (G-CSF), using pre-specified safety rules, during the Paclitaxel portion of dose- dense Doxorubicin and Cyclophosphamide (AC) and Paclitaxel (T) for patients with Stage I-III breast cancer. The planned sample size is 125 patients, Patients that have been deemed appropriate for adjuvant or neoadjuvant dose dense AC-T chemotherapy by their treating physician will be enrolled in the study at the beginning of Paclitaxel. We will examine the feasibility and safety of this strategy, and its impact on treatment schedule and costs. A Simon optimal two-stage design will be used to monitor the number of patients who are able to complete 4 cycles of Paclitaxel within 7 weeks from day 1 (D1) of cycle 1 of Paclitaxel to D1 of cycle 4 of Paclitaxel. The accrual will be halted if an excessive number of patients are not able to complete treatment within 7 weeks.

1.2 Primary Objectives

1.2.1 *To evaluate the rate of Paclitaxel treatment completion omitting Neulasta™ (Pegfilgrastim) using pre-specified safety rules within 7 weeks (from D1 of cycle 1 of Paclitaxel to D1 of cycle 4 of Paclitaxel).*

1.3 Secondary Objectives

1.3.1 *Omission of Neulasta™ (Pegfilgrastim) during Paclitaxel portion of dose dense ACT*

- To characterize the utilization of Neulasta™ (Pegfilgrastim) using pre-specified safety rules in patients receiving dose dense Paclitaxel.

- To evaluate safety of omitting Neulasta™ (Pegfilgrastim) support using pre-specified safety rules in patients receiving dose dense Paclitaxel (according to the Cancer therapy evaluation program (CTEP) active version of the National cancer institute (NCI) common terminology criteria for adverse events (CTCAE), version 4, Appendix A)
    a. To estimate the rate of hematological toxicity, including the incidence of grade 3-5 neutropenia and febrile neutropenia among the 4 cycles of Paclitaxel
    b. To estimate the rate of other toxicities grade 3-4 among the 4 cycles of Paclitaxel

- To evaluate the schedule impact of omitting *Neulasta™* (Pegfilgrastim) support using pre-specified safety rules in patients receiving dose dense Paclitaxel:
    a. To estimate the percentage of patients who receive all planned cycles of chemotherapy
    b. To characterize reasons for treatment delays (defined as schedule/preference, absolute neutrophil count (ANC) < 1,000/mm^3, hypersensitivity, neurotoxicity, transaminitis, other).

1.3.2 Simplification of the pre-medication used for the Paclitaxel portion of dose dense ACT

- To estimate the safety of simplifying the pre-medication regimen used for the Paclitaxel portion of the regimen (withholding premedication after 2 cycles without evidence of allergic reactions).
    a. To evaluate the rate of hypersensitivity reactions on cycles 3-4 of Paclitaxel, when steroid is avoided.

Exploratory Objectives:

- To estimate the impact on costs of omitting *Neulasta*™ (Pegfilgrastim) support using pre-specified safety rules in patients receiving dose-dense Paclitaxel
    a. To calculate the costs of omitting Neulasta™ (Pegfilgrastim) using the planned treatment algorithm

2. BACKGROUND

2.1 Adjuvant chemotherapy for breast cancer

Multiple randomized clinical trials, supported by meta-analyses, have demonstrated that adjuvant chemotherapy significantly reduces the risk of recurrence in women with early breast cancer. The Early Breast Cancer Trialists' Collaborative Group estimated a relative risk reduction of 20-30% and overall survival (OS) improvement for women with early breast cancer.[1] In addition, this same group also suggested that adding taxanes to anthracylines is associated with disease-free and overall survival gains.[1]

2.1.1 Dose dense chemotherapy for breast cancer

Over a decade ago a large cooperative group trial [CALGB 9741] which compared sequential Doxorubicin (A), Paclitaxel (T), and Cyclophosphamide (C) versus combination AC followed by Paclitaxel, all given on either an every 3 week or every 2 week schedule as postoperative treatment of node-positive breast cancer demonstrated improvements in survival outcomes [Disease-free survival (DFS) and OS] for breast cancer patients treated with "dose dense" schedules in the adjuvant setting. At 4 years, dose dense was associated with a risk ratio of 0.74; P = .010 for DFS and of 0.69; P = .013 for OS when compared with non- "dose dense regimens".[2] More recently, these findings were corroborated by a meta-analysis of 10 randomized controlled trials comparing standard vs. "dose dense" chemotherapy regimens, in which, patients who received dose dense chemotherapy had better survival outcomes,[3] and by another large cooperative group study comparing a novel continuous schedule of AC vs. six cycles of AC once every two-weeks followed either by weekly Paclitaxel or by six cycles of Paclitaxel once every two weeks which, showed the highest OS in the arm using once-every-2-weeks treatment for both AC and Paclitaxel.[4]

2.2 G-CSF support in dose dense regimens

2.2.1 Use of Neulasta™support in dose dense regimens

Historically, neutrophil recovery was the limiting factor in crafting chemotherapy schedules. The emergence of Neulasta™allowed the design and subsequent sucess of dose dense regimens. In the studies that tested dose dense ACT, no difference in the number of treatment delays and grade 3 and 4 adverse events, particularly in the hematologic adverse events was found between the dose dense with Neulasta™support and conventional treatment arms.[2] In a prospective study that used Neulasta™ in D2 of every cycle of dose dense ACT, there were less than 2% of treatment delays due to hematologic toxicity; 88.6% of patients who started Paclitaxel completed the 4 cycles, with a mean cycle duration of 14 days and >85% of patients received planned chemotherapy dose on time.[5]

2.2.2 Omitting Neulasta™in Paclitaxel portion of dose dense ACT

Although G-CSFs are well-tolerated, they are not completely devoid of adverse reactions, the most common one being medullar bone pain, reported in ~ 25% of subjects. In addition, other adverse reactions such as leukocytosis, transient thrombocytopenia, increased risk of secondary myelodisplastic syndromes and acute myeloid leukemia, rare case of splenic ruptures, adult respiratory distress syndrome (ARDS), allergic type reactions, and severe sickle cell crisis have been reported in patients receiving G-CSF.[6,7] Moreover, the use of Neulasta™ adds considerable expenses and represents the major driver of the variation in costs among treatments used for early breast cancer. A recent analysis described a 20-fold increase in costs for dose dense ACT regimen, primarily due to the need of growth factor.[8]

Recently, it has been questioned whether the support of G-CSF is needed during all the cycles of a dose dense chemotherapy schedule. AC and Paclitaxel have different toxicity profiles, and it is well known that Paclitaxel is associated with a less myelosuppressive profile, in the CALGB 40101 trial, the incidence of any grade 3 or higher hematologic toxicity was considerably higher in the AC arms compared with the Paclitaxel arms.[9] In a prospective experience from the Dana-Farber Cancer Center, the absolute neutrophil count during the AC portion of dose dense ACT was 5,000/μL and during the Paclitaxel portion was 10,000/μL.[5]

To our knowledge, only one prospective trial has been conducted without G-CSF support in dose dense Paclitaxel. The primary endpoint of the trial was feasibility and tolerability of Paclitaxel every 2 weeks without G-CSF support defined as the absence of neutropenic fever and neutropenia on the day of planned treatment. Patients were considered eligible for the study if they had an absolute neutrophil count of 1,500/mm^3. The granulocyte count was repeated on the day of each planned treatment and if the count was less than 1,000/ mm^3 the patient would be considered an "attempt to treat failure" and would drop out study. No pre-specified safety rules were applied. Fifty-four patients were initially enrolled in the trial, which was terminated when the sixth patient could not be treated on time because of neutropenia. At the time of study termination, 15 patients were evaluable, only 9 of whom completed the entire course of chemotherapy without treatment delays.[10]

In contrast to this negative experience, two recent retrospective experiences suggest that there may be a role of omitting G-CSF in selected patients.

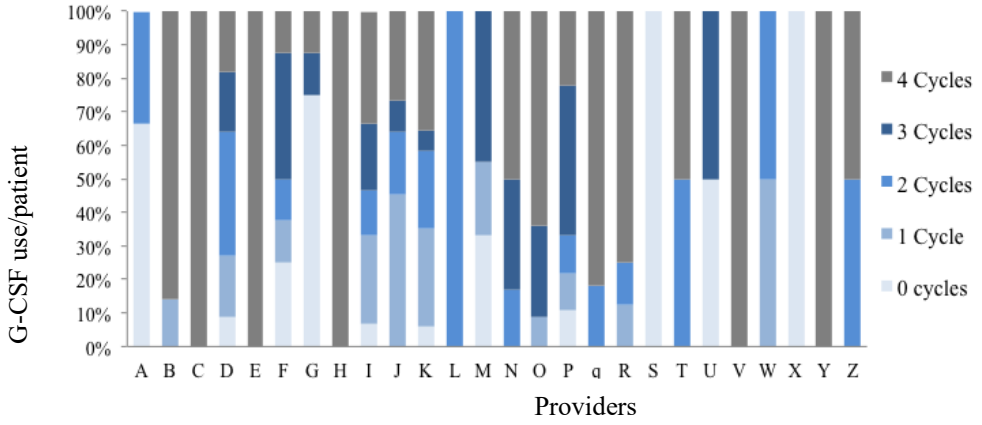
In the retrospective study from SUNY Upstate Medical University, Syracuse, of 115 patients, 109 received no G-CSF support during the Paclitaxel portion. 88 patients completed all the 4 planned cycles of Paclitaxel and only 5 patients had dose delays, with only a small minority developing neutropenic complications.[11] In a retrospective experience of our institution, of 155 patients treated with dose dense ACT 13.6% did not receive any G-CSF support during the Paclitaxel portion of the regimen. Among those, who did not receive G-CSF, there were no treatment delays nor neutropenia, and 90.4% completed the 4 cycles of Paclitaxel treatment on time (Table 1). The median absolute neutrophil count among these patients ranged 2,820-3,612/mm^3, minimum ranged from 1,480-1,670/mm^3 and maximum ranged from 5,960-19,260/mm^3. [12]

Table 1. Chemotherapy Cycles Administered.

Patients who did not receive any G-CSF					**Patients who received G-CSF in at least one cycle**				
	Treatment completion	**Delays**	**Duration of cycle length (weeks)**		**Use of G-CSF**	**Treatment completion**	**Delays**	**Duration of cycle length (weeks)**	
Cycle	**N (%)**	**N (%)**	**Median**	**Range**	**N (%)**	**N (%)**	**N (%)**	**Median**	**Range**
5	21 (100%)	NA	2	2-2	130 (97%)	134 (100%)	NA	2	2-5
6	19 (90%)	0 (%)	2	2-2	102 (77%)	131 (98%)	6 (5%)	2	2-4
7	19 (90%)	0 (%)	2	2-2	100 (78%)	127 (95%)	2 (2%)	2	2-3
8	19 (90%)	0 (%)	NA	NA	74 (58%)	127 (95%)	1 (1%)	NA	NA

In addition, in this study there was important variation in the use of G-CSF among providers (Figure 1), which by itself reveals the uncertainty on the need to use G-CSF in the Paclitaxel portion of dose dense ACT.[12]

Figure 1. Use of G-CSF by providers/patient



The G-CSF could be more cost-effectively and cautiously applied to patients with identified risk factors and to those who are more likely not to manage to complete all the scheduled cycles of Paclitaxel without myeloid growth factor support.

2.2.3 Risk of *myelosuppression*

In a prospective cohort study, Lyman et al. validated a model to identify patients at greater risk for severe neutropenia or febrile neutropenia as the result of cancer chemotherapy in the community setting. Several factors were significantly associated with cycle 1 severe or febrile neutropenia in the final model and included: a history of previous chemotherapy, patients on other immunosuppressive medications, patients with elevated aspartate aminotransferase (AST), alkaline phosphatase or bilirubin, or reduced white blood count or reduced estimated glomerular filtration rate. Neutropenic events occurred in cycle 1 in 34% of patients classified as high risk compared with only 4% of those classified as low risk (using these variables as classifiers).[13]
We plan to use this information to identify patients for whom we can safely omit G-CSF during cycles of dose dense Paclitaxel.

2.3 Rationale

Dose-dense chemotherapy has been proven to offer a survival advantage in the adjuvant treatment of breast cancer. Growth factor support is thought to be required in order to allow bone marrow recovery and facilitate the administration of chemotherapy in an every two week schedule. Nevertheless, G-CSF is not devoid of adverse effects, and adds significant costs to treatment. The different drugs employed in a dose-dense ACT regimen have different toxicity profiles, with Paclitaxel being the less myelotoxic drug than the AC combination. The uncertainty regarding the safety of omitting Neulasta™ (Pegfilgrastin) in the Paclitaxel portion of dose dense ACT leads to significant variability in its use. In this study, we aim to define if, by using pre-specified safety rules, a subset of patients can undergo the Paclitaxel portion of dose-dense ACT without growth factor support, and complete all cycles of planned treatment timely fashion.

2.4 Secondary studies background

2.4.1 *Pre-medication for dose dense Paclitaxel*

In early trials, hypersensitivity reactions to Paclitaxel occurred in up to 30 percent of patients receiving Paclitaxel, and some, were life-threatening and regimen-limiting. After the introduction of premedication with antihistamines and glucocorticoids and after prolonging infusion time the rate of severe reactions was reduced to 2 to 4 percent.[14,15]

For Paclitaxel, conventional practice is to administer 12-20 mg of dexamethasone orally prior to drug administration, with H1- and H2- receptor antagonists administered IV 30 minutes prior to drug infusion and with this approach the rate of severe infusion reactions is around 1-2%.[16]

The vast majority of the reactions occur in the first 2 cycles. In a study of 450 patients pre-treated with this regimen, 44 (approximately 9% of the patient population) experienced a total of 71 episodes of clinically relevant Paclitaxel-associated hypersensitivity reactions. 48% of the total reactions occurred during the initial course of Paclitaxel, with 23%, 13%, 8%, and 4% reactions developing during cycles 2, 3, 4, and 5, respectively. Seventy-seven percent of the 44 patients who developed a Paclitaxel-associated hypersensitivity reaction experienced their first episode during their initial treatment with the agent, whereas 18% had their first reaction during cycle 2. Only 5% experienced an initial reaction to Paclitaxel after the second course of treatment with the drug.[17]

Given this experience, for patients who did not have reactions within the first two cycles, our group began using a simplified schema to reduce glucocorticoid exposure. In this schema we omit the steroids received at 12 hours prior treatment. In this sub-study we aim to validate the safety of this approach.

3. PARTICIPANT SELECTION

Participants must meet the following criteria on screening examination to be eligible for the study. All laboratory tests required for eligibility must be completed within 14 days prior to study entry. Other non-laboratory tests must be performed within 3 months of study entry.

3.1 Inclusion Criteria

3.1.1 Patients must have histologically or cytologically confirmed Stage I-III breast cancer (as defined by the revised, AJCC 7th edition criteria) and be at sufficient risk for tumor recurrence. Staging studies to exclude metastatic disease are not required in asymptomatic patients. However, patients with findings considered suspicious for metastatic disease on any staging studies that are obtained need to be evaluated to exclude stage IV breast cancer.

3.1.2 Patients must be deemed by their treating oncologist as candidates for (neo) adjuvant chemotherapy with dose dense ACT.

3.1.3 Age ≥ 18 years and < 65 at the time of informed consent.

3.1.4 ECOG performance status (PS) ≤ 1 (Appendix B).

3.1.5 Any grade 3 or clinically significant grade 2 treatment-related non-hematological toxicity must be resolved to grade 1 before retreatment with chemotherapy (with exception of alopecia)

3.1.6 Laboratory Evaluations:

- Adequate blood marrow function defined as:
  - Absolute neutrophil count (ANC) ≥1500 μL,
  - Hemoglobin ≥9.0 g/dl
  - Platelets ≥100,000/mm3
- Adequate hepatic function defined as:
  - Total bilirubin ≤ 1.2 institutional upper limit of normal (ULN)
  - AST(SGOT), ALT(SGPT), alkaline phosphatase ≤ 1.5 X ULN
- Adequate renal function defined as:
  - Serum creatinine ≤ 1.5 X ULN
- Premenopausal women (including women who have had a tubal ligation and for women less than 12 months after the onset of menopause) must have a negative serum pregnancy test.

3.1.7 Patients with risk factors for Hepatitis B or C should be tested (anti-HCV antibody, HBsAg or anti-HBc). If infection is suspected, HBV DNA and *HCV* RNA should be requested as appropriate.

Note: Patients with positive Hepatitis B or C serologies without known active disease must meet the eligibility requirements for ALT, AST, total bilirubin, and alkaline phosphatase and must have a normal INR on at least two consecutive occasions, separated by at least 1 week, within the 30 day screening period.

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

3.2 Exclusion Criteria

3.2.1 Patients who have received previous cytotoxic chemotherapy including an AC-T regimen or previous therapeutic radiation therapy for any reason in the last 5 years. Because of possible limitations in bone marrow reserve, patients with such prior treatments are not appropriate candidates for this trial. Patients who have had prior hormonal therapy (for instance, tamoxifen for prevention of breast cancer) are eligible. Patients who have participated in a window study (treatment with an investigational agent prior to surgery for ≤2 weeks) are eligible but must have discontinued the investigational agent at least 14 days before enrollment.

3.2.2 Participants who are receiving any other investigational agents

3.2.3 Have had at least one prior episode of fever and neutropenia (ANC< 500/mm3 or expected to fall below < 500/mm3) during AC.

3.2.4 Patients taking lithium.

3.2.5 Patients receiving chronic treatment with oral steroids or another immunosuppressive agent (excluding steroids as part of the chemotherapy pre-medication or emetic medication).

3.2.6 Known HIV-positive individuals or with any immunodeficiency status.

3.2.7 Patients with history of hematologic disease, including myelodisplasia or bone marrow malignancies.

3.2.8 History of allergic reaction attributed to compounds of similar chemical or biologic composition to Paclitaxel, which cannot be managed by premedication.

3.2.9 Currently pregnant or breast-feeding.

3.2.10 Uncontrolled intercurrent illness including, not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements or other significant diseases or disorders that, in the investigator's opinion, would exclude the subject from participating in the study.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the QACT protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Notify the QACT Registrar of registration cancellations as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin protocol therapy during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

- Obtain written informed consent from the participant prior to the performance of any protocol specific procedures or assessments.

- Complete the QACT protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. **To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.**

  Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for a treatment protocol. Registration to both treatment and ancillary protocols will not be completed if eligibility requirements are not met for all studies.

- Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.

- The QACT Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol.

- An email confirmation of the registration will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration and/or randomization.

5. TREATMENT PLAN

5.1 Treatment regimen: Chemotherapy administration, Neulasta™ (Pegfilgrastim) and Supportive Measures

Treatment will be administered on an outpatient basis. Pre-treatment criteria are described in

Section 5.2. Reported adverse events and potential risks are described in Section 7. Appropriate treatment and dose modifications for adjuvant chemotherapy are described in Section 6.

Patients may receive treatment as adjuvant therapy after breast surgery, or as part of a neoadjuvant treatment program (see Section 5.3.2).

5.1.1 Paclitaxel

Following completion of 4 cycles of dose dense AC, patients will start protocol therapy and receive dose dense Paclitaxel, consisting of:

Paclitaxel 175 mg/m^2 IV as an approximately 3 hour infusion once every 2 weeks x 4 cycles (total of 4 doses). The day of treatment is day 1. The chemotherapy dose is determined by actual body weight on the day of treatment for cycle 1. If there is a ≥5% weight modification the dose will be modified accordingly.

Paclitaxel therapy will begin two weeks after the last dose of AC chemotherapy.

Prior to receiving the first and second dose of Paclitaxel, patients should be pre-medicated with the following to reduce the risk of hypersensitivity reactions:

- **Dexamethasone 12 mg PO taken approximately 2-6 hours prior to infusion;**
- **Diphenydramine 25 or 50 mg PO/IV approximately 30-60 minutes prior to infusion;**
- **Any histamine H2 blocker (ranitidine 150 mg PO or 50 mg IV; famotidine 20mg; or equivalent) approximately 30-60 minutes prior to infusion.**

If after completion of the first 2 cycles no hypersensitivity reaction has occurred, the Dexametasone will be withdrawn, otherwise the regimen will be maintained.

Suggested management of Paclitaxel hypersensitivity reactions is as follows. Investigators may use clinical judgment for diverge from guidelines below as clinically indicated.

Mild symptoms: localized cutaneous reactions such as mild pruritus, flushing, or rash:
- Consider decreasing the rate of infusion until recovery from symptoms, stay at bedside and monitor patient. Assess vital signs. If symptoms resolve or do not progress, complete Paclitaxel infusion at the initial planned rate.

Moderate symptoms: any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, or dyspnea, hypotension with systolic BP 80 mmHg:
- Interrupt Paclitaxel infusion
- Assess vital signs, including oxygen saturation
- Give dyphenydramide 50 mg IV with or without dexamethasone 10 mg IV
- Monitor patient until resolution of symptoms
- Resume Paclitaxel infusion after recovery of symptoms; depending o the physician's assessment of the patient, the Paclitaxel can be resumed at a slower infusion rate, and then

increased incrementally to the planned rate of infusion
- Depending on the intensity of the observed reaction, additional oral or intravenous premedication should also be given prior to the next cycle of treatment, and the rate of infusion should be decreased initially and the increased back to the recommended rate.

Severe symptoms: any reaction such as bronchospasm, generalized urticaria, hypotension with systolic BP < 80 mmHg, angioedema:
- Discontinue Paclitaxel infusion
- Assess vital signs, including oxygen saturation
- Alert treating physician
- Give diphenydramine 50 mg IV with or without dexamethasone 10 mg IV with or without epinephrine 0.1 cc 1:1000 solution SC
- Consider supplemental oxygen therapy and intravenous fluid therapy
- Monitor patient until symptoms resolve
- Re-treat as per recommendations under moderate symptoms

Anaphylaxis (toxicity grade 4):
- Treat patient as for severe symptoms
- Patient taken off study

Patients may use analgesics to control symptoms of mylagias/arthralgias related to Paclitaxel use.

*5.1.2 Neulasta™ (*Pegfilgrastim)

If required by the protocol algorithm (section 5.2.2), Neulasta™ (pegfilgastrim) with be used for growth factor support.

Neulasta™ (pegfilgastrim) will be administered as follows:
- Neulasta™ (pegfilgastrim) 6 mg SQ x1 is administered on day 2 of each treatment cycle, approximately 24 hours after the chemotherapy treatment.

5.2 Pre-Treatment Criteria

5.2.1 Chemotherapy pre-treatment criteria

In order to initiate each cycle of chemotherapy (Paclitaxel) the following is needed:
- ANC≥ 1000/mm^3
- Platelets ≥100.000/mm^3

If these criteria are not met, treatment must be delayed until counts return to ANC≥ 1000/mm^3 and Platelets ≥100.000/mm^3. It is recommended that these values be checked 3 days after the scheduled day. Refer to Section 6.0 for dose modification guidelines.

5.2.2 Use of Neulasta™ (Pegfilgrastim) during treatment with Paclitaxel chemotherapy

Neulasta™ (Pegfilgastrim) **will be administered during treatment with Paclitaxel, if: The**

patient experiences a prior episode of fever and neutropenia.

Neulasta™ (Pegfilgastrim) will be administered at the discretion of the treating investigator during treatment with Paclitaxel, if:

- **If the patient has an active infection this decision will be at provider discretion.**
- **Treatment delays of > 1 week**

If Neulasta™(Pegfilgrastim) is administered in any Paclitaxel cycle for a given patient, it will be then administered for all future cycles. Administration of Neulasta™(Pegfilgrastim) will be as outlined in section 5.1.2.

5.3 Duration and sequencing of therapy

5.3.1 *Duration of treatment*

In the absence of treatment delays due to adverse event(s), treatment may continue for up to a maximum of 4 cycles of Paclitaxel, or until one the following criteria applies*:*

1. Disease progression;
2. Intercurrent illness that prevents further administration of treatment;
3. Unacceptable adverse event(s) per provider discretion;
4. Patient decides to withdraw from the study;
5. General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.3.2 *Sequencing of treatment*

This protocol is generally intended as a trial of adjuvant therapy, with the administration of therapy following definitive breast surgery. However, patients may receive neoadjuvant chemotherapy treatment at the same doses and schedules as outlined above. In such instances, patients may receive 4 cycles of dose dense Paclitaxel as preoperative therapy.

5.4 Duration of Follow up

Participants will be followed for 4 weeks after the last cycle of Paclitaxel or until stabilization of adverse events. It is recommended that a 4-8 week post-taxol visit take place with a provider, subsequent visits can occur with clinical staff by phone. If the 4-week post-taxol visit creates significant burden for the patient, it is acceptable to do this visit by phone.

5.5 Criteria for Taking a Participant Off Study

Participants will come off study once they have completed the duration of follow-up required or if they choose to end their participation. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF).

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator, [redacted]

5.6 General Concomitant Medication and Supportive Care Guidelines

5.6.1 Antibiotics

The use of prophylactic antibiotics such as cyprofloxacin (or equivalent) is prohibited in the study.

5.6.2 Anticoagulants

The use of systemic anticoagulation is not a contraindication to participation in the trial. Patients requiring such therapy should be appropriately monitored to ensure that they are not excessively anticoagulated.

5.6.3 Red blood cell (RBC) Transfusion

The optimal Hgb for initiation of RBC transfusion is not well characterized. In general, ASCO guidelines and DF/HCC clinical guidelines suggest that Hgb be less than 10 g/dl before consideration of transfusion. Thus, RBC transfusion is left to the discretion of the treating clinician, but should not be initiated in patients with Hgb ≥ 10 g/dl.

5.6.4 Other supportive care

The intent of this protocol is to evaluate the safety and feasibility of omitting Pegfilgrastim support in the Paclitaxel portion of dose dense ACT. Any and all appropriate supportive measures not related to neutrophil recovery/function should be given as warranted to patients, using standard clinical judgment.

5.6.5 Concurrent Therapy

Patients may receive other appropriate medical treatments while undergoing dose dense adjuvant treatment, with the following exceptions:

- Patients may not receive concurrent radiation therapy
- Consistent with current clinical practice, patients should receive adjuvant hormonal therapy at the conclusion of chemotherapy treatment, and not while on study. However, use of adjuvant hormonal treatment is permitted if deemed medical necessary. Patients may for example be on ovarian suppression prior concurrently with chemotherapy.

- Patients may not receive other concurrent experimental therapy or be participating in other clinical trials that are designed as anti-neoplastic therapy. Patients may participate in supportive care studies, including use of biphosphonates, that do not affect utilization of growth factors or chemotherapy treatments

5.6.6 Iron and nutritional supplements

Patients who, during the course of the treatment, have evidence of iron or metabolite deficiency (e.g. folate or B12 deficiency) should receive appropriate repletion therapy.

6. DOSING DELAYS/DOSE MODIFICATIONS

ACT dose-dense is a standard regimen used for early breast cancer.

Dose delays and modifications will be made using the following recommendations and per treating physician discretion. Toxicity assessments will be done using the CTEP Active Version of the NCI CTCAE which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be implemented per treating physician discretion.

Grade 3-4 AEs experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit.

6.1 Chemotherapy

6.1.1 Hematological toxicity

Chemotherapy treatment with AC or Paclitaxel should be held if the ANC < 1000 µl or PLT < 100,000 µl on the scheduled day of treatment. Chemotherapy should be administered as soon as reasonably possible once the ANC or PLT have recovered to allow treatment. If grade 3 or 4 thrombocytopenia, treatment should be resumed, with a recommended 20% dose reduction in taxol dose. If grade 3 or 4 neutropenia without fever occurred for ≤ 7 days in the absence of growth factors, taxol dose should be maintained. In this situation, the use of prophylactic Pegfilgrastim is not manadatory per protocol, but it can be administered at the discretion of the treating investigator. If grade 3 or 4 neutropenia occurred in the presence of growth factor support, taxol dose should be reduced by 20%. If treatment delay of more than one week is required, taxol dose should be maintained and growth factor should be instituted when the cycle resumes (i.e. day 2 of the following cycle and subsequent cycles). If a delay ≥ 21 days is required it is recommended that the patient discontinue AC or Paclitaxel, but this decision will be per physician discretion

6.1.2 Febrile neutropenia

A 20% dose reduction in taxol dose was recommended in patients following episodes of febrile

neutropenia while receiving dose dense adjuvant chemotherapy in CALGB 9471. For patients not treated with prophilatic Pegfilgrastim, Pegfilgrastim should be instituted.

6.1.3 Gastrointestinal toxicity

Patients who develop gastrointestinal toxicity (mucositis, dysphagia, nausea, vomiting, diarrhea, constipation) in excess of grade 3 should have chemotherapy held until symptoms have resolved to grade 0 or 1. Chemotherapy dose is not reduced for grade 2 or 3 gastrointestinal toxicity. Patients with grade 4 gastrointestinal toxicity should have chemotherapy dose(s) reduced by 20% at the time of treatment.

6.1.4 Hepatic toxicity

Patients should have bilirubin ≤ 1.2 ULN at the time of each chemotherapy treatment. Contact the principal investigators if treatment delay in excess of one week is required.

6.1.5 Neurotoxicity

Paclitaxel will be discontinued for neurotoxicity of grade 3 or greater. For clinically significant grade 2 neurotoxicity, chemotherapy should be held until symptoms resolve to grade 1 or below. If symptoms resolve to grade 1 or below within 1 week, Taxol dose reduction is not required, but a 20% dose reduction may be considered at the discretion of the treating provider. If symptoms resolve after more than 1 week but less than 21 days, Taxol should be administered at a 20% dose reduction. If a delay ≥ 21 days is required it is recommended that the patient discontinue Taxol, but this decision will be per physician discretion

6.1.6 Myalgias/arthralgias

Chemotherapy dose or schedule is not affected. It is suggested that patients receive appropriate symptom control with analgesics and/or corticosteroids as required.

6.1.7 Extravasation/phlebitis

Skin damage or phlebitis from chemotherapy may occur. Extravasation should be treated urgently according to nursing and institutional practice. Chemical irritation on phlebitis are not reasons for discontinuing therapy, however, and chemotherapy can continue to be administered through appropriate intravenous access sites.

6.1.8 Genitourinary Toxicity

At the discretion of the treating physician, patients may receive mesna if they experience gross hematuria or symptomatic cystitis related to chemotherapy

6.1.9 Other toxicity

Other grade 3 or clinically significant grade 2 treatment-related non-hematological toxicity should resolve to grade 1 before retreatment with chemotherapy and reduce Taxol by 20%. (with exception of alopecia).

6.2 Neulasta™ (Pegfilgrastim)

There is no dose or schedule modification to Neulasta™ (Pegfilgrastim). Patients with bone pain related to administration of Neulasta™ (Pegfilgrastim) should be treated with appropriate analgesics.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Chemotherapy

While widely studied and used, Paclitaxel chemotherapy carries many potential side effects, some of which may be life-threatening of even fatal. Toxic side effects include bone marrow suppression (neutropenia, anemia, and thrombocytopenia, with risks of infection, sepsis, bleeding, fatigue, and the requirement for transfusion of blood products): hair loss: nausea: vomiting< diarrhea, mucositis, anorexia, liver function tests abnormalities, myalgias, arthralgias, flu-like symptoms, seizures, pharyngitis, and skin reactions. Local infiltration of Paclitaxel may cause erythema and discomfort that usually resolves in one week.

Paclitaxel administration can be associated with acute anaphylactic reactions, including flushing, fever, urticaria, dyspnea, hypotension, and anaphylactic shock. Paclitaxel administration may cause transient bradycardia, chest pain, and myocardial infarction. See section 5.2.2 for
Paclitaxel can cause peripheral neuropathy, which can be painful. Paclitaxel chemotherapy can cause ovarian failure, with cessation of menses and other symptoms of menopause such and hot flashes, weight gain, and vaginal dryness.

In the recent CALGB 40101, the rate of selected grade 3 and 4 adverse events during the protocol therapy by treatment were as follows for 4 cycles of Paclitaxel (which was administered every 2)[9]:

Table 3. Selected grade 3 and 4 adverse events during 4 cycles of Paclitaxel

Adverse events	**% of events for 4 cycles of Paclitaxel**	
	Grade 3	**Grade 4**
Hemoglobin	<1	0
Neutropenia	2	1
Febrile neutropenia	<1	0
Thrombocytopenia	<1	0
Neuropathy	5	<1
Diarrhea	1	0
Vomiting	<1	<1
Fatigue	1	<1
Arthralgia	2	0

Toxicity analyses with dose dense sequential ACT have noted that grade 4 neutropenia was less common in patients receiving dose dense ACT with G-CSF support than with standard chemotherapy scheduling where G-CSF was not routinely employed, though more lymphopenia

and anemia were noted. There was no apparent difference in the risk of secondary cancers, including leukemia, with dose dense therapy compared to standard dose scheduling, nor of cardiotoxicity. The risk of leukemia in CALGB 9741 was approximately 0.2% through 3 years of follow-up. One percent of patients receiving dose dense ACT had grade 3 or 4 cardiotoxicity, compared to 2.3% receiving the standard treatment schedule. There was a small increase in neurotoxicity with dose dense therapy; among such patients, 4.5% had grade 3 or 4 neurotoxicity compared to 3.9% with standard dose scheduling.

7.1.2 Neulasta™ (Pegfilgastrim)

The most common adverse event attributed to Neulasta™ (pegfilgrastim) in clinical trials was medullar bone pain, reported in 26% of subjects, which was comparable to the incidence in Filgrastim-treated patients and it is generally reversible with non-narcotic agents. This bone pain was generally reported to be mild-to-moderate severity. Approximately 12% of all subjects utilized non-narcotic analgesics and less than 6% utilized narcotic analgesics. No patients withdrew from the study due to bone pain. Reversible elevations in LDH, alkaline phosphatase and uric acid have been observed in clinical trials. Neulasta™ (Pegfilgrastim) has also been associated with leukocytosis and transient thrombocytopenia.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. (Refer to appendix A)
- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 *Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.*

7.3.2 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC and DF/PCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

7.4 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.5 Routine Adverse Event Reporting

All grade 3-4 Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

8. PHARMACEUTIC INFORMATON

8.1 Chemotherapy

Paclitaxel (Taxol) is a commercially available chemotherapeutic agent. The drug should be stored, reconstituted, prepared for administration, and administered according to manufacturer's guidelines in the package insert, and in accordance with standard institutional practices.

8.2 Neulasta™ (Pegfilgastrim)

8.2.1 *Availability*

Neulasta™ (pegfilgastrim) is commercially available from Amgen.

8.2.2 *Packaging and formulation*

Neulasta™ (pegfilgrastim) is a covalent conjugate of recombinant methionyl human G-CSF (filgrastim) and monomethoxypolyethylene glycol. Filgrastim is a water-soluble 175 amino acid protein with a molecular weight of approximately 19 kilodaltons (kD). Filgrastim is obtained from the bacterial fermentation of a strain of E coli transformed with a genetically engineered plasmid containing the human G-CSF gene. To produce Neulasta™ (pegfilgrastim), a 20 kD monomethoxypolyethylene glycol molecule is covalently bound to the N-terminal methionyl residue of filgrastim. The average molecular weight of Neulasta™ (pegfilgrastim) is approximately 39 kD.

Neulasta™ (pegfilgrastim) is supplied in 0.6 mL prefilled syringes for subcutaneous injection. Each syringe contains 6 mg pegfilgrastim (based on protein weight) in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), polysorbate 20 (0.02 mg), sodium (0.02 mg), and sorbitol (30 mg) in Water for Injection, USP.

8.2.3 *Storage conditions and stability*

Neulasta™ is supplied in a prefilled single use syringe containing 6 mg pegfilgrastim, supplied with a 27-gauge, 1/2-inch needle with an UltraSafe® Needle Guard. The needle cover of the prefilled syringe contains dry natural rubber (a derivative of latex). Neulasta™ is provided in a dispensing pack containing one syringe (NDC 55513-190-01).

Neulasta™ must be stored refrigerated between 2° to 8°C (36° to 46°F) in the carton to protect from light, and might not be shaken. Syringes stored at room temperature for more than 48 hours must be discarded. Avoid freezing; if frozen, Neulasta ™ should be allowed to thaw in the refrigerator before administration. Syringes frozen more than once should be discarded.

8.2.4 *Preparation and administration*

No preparation is required for administration of Neulasta™ (pegfilgrastim). Each subject will receive a fixed dose of 6 mg of pegfilgrastim. The entire contents of the 0.6 mL prefilled syringe should be administered irrespective of the subject's actual weight.

8.2.5 *Overdosage*

The maximum amount of Neulasta™ (pegfilgrastim) that can be safely administered in single or multiple doses has not been determined. Single subcutaneous doses of 300 mcg/kg have been administered to 8 healthy volunteers and 3 patients with non-small cell lung cancer without serious adverse effects. These patients experienced a mean maximum absolute neutrophil count (ANC) of 55 x 109/L, with a corresponding mean maximum WBC of 67 x 109/L. The absolute maximum ANC observed was 96 x 109/L with a corresponding absolute maximum WBC observed of 120 x 109/L. The duration of leukocytosis ranged from 6 to 13 days. The effectiveness of leukapheresis in the management of symptomatic individuals with Neulasta™ -induced leukocytosis has not been studied.

8.2.6 *Toxicity/Warnings*

Neulasta™ (pegfilgrastim) is contraindicated in patients with known hypersensitivity to E coli-derived proteins, pegfilgrastim, filgrastim, or any other component of the product. In addition, the following events have also been reported: Splenic rupture, including fatal cases, can occur following the administration of Neulasta™. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving Neulasta™.

- Acute Respiratory Distress Syndrome Acute respiratory distress syndrome (ARDS) can occur in patients receiving Neulasta™. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Neulasta™, for ARDS. Discontinue Neulasta™ in patients with ARDS.

- Serious Allergic Reactions Serious allergic reactions, including anaphylaxis, can occur in patients receiving Neulasta™. The majority of reported events occurred upon initial exposure. Allergic reactions, including anaphylaxis, can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue Neulast™ a in patients with serious allergic reactions. Do not administer Neulasta™ to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim.

- Use in Patients with Sickle Cell Disorders Severe sickle cell crises can occur in patients with sickle cell disorders receiving Neulasta™. Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim, the parent compound of pegfilgrastim.

- Potential for tumor growth stimulatory effects on malignant cells. The G-CSF receptor through which pegfilgrastim and filgrastim act has been found on tumor cell lines. The possibility that pegfilgrastim acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim is not approved, cannot be excluded.

8.2.7 Pregnancy and Lactation

There are no adequate and well-controlled studies in pregnant women¸ neither it is known whether pegfilgrastim is secreted in human milk. Therefore, pregnant or nursing mothers may not take part in this study.

8.2.8 Drug interactions

No formal drug interaction studies between Neulasta™ and other drugs have been performed. Increased hematopoietic activity of the bone marrow in response to growth factor therapy may result in transiently positive bone-imaging changes. Consider these findings when interpreting bone-imaging results.

Drugs such as lithium may potentiate the release of neutrophils; patients receiving lithium are ineligible for the study.

8.2.9 Preparation and administration

No preparation is required for administration of (Neulasta™). Each subject will receive a fixed dose of 6 mg of Neulasta™. The entire contents of the 0.6 mL prefilled syringe should be administered irrespective of the subject's actual weight.

9. STUDY CALENDAR

9.1 Study tests, procedures and treatment schedule

Table 2 presents the Schedule of Visits and Procedures. During the treatment period, visits should occur within +/- 3 days of the scheduled day. If a subject fails to appear for a scheduled study visit, the investigator will make every attempt to contact the subject and determine the reason(s) for the missed visit as completely and accurately as possible. Subjects will only be judged as lost to follow-up if they cannot be reached after three documented attempts (1 week apart) by the site to contact them. For the post-treatment visits, visits should occur within +/- 2 months of the scheduled day.

		TREATMENT PERIOD				
Tests, procedures and treatments	**Pre-Study** [a]	**Cycle 1 Day 1** (week 1)	**Cycle 2 Day 1** (week 3)	**Cycle 3 Day 1** (week 5)	**Cycle 4 Day 1** (week 7)	**Off –Study Visit** [h] (4-8 weeks post Taxol)
Informed consent	X					
Complete medical history	X					
Physical exam	X	X	X	X	X	X[g]
ECOG PS	X					
Vital signs, weight, height (height at baseline only)	X	X	X	X	X	
CBC w/diff, platelets	X	X	X	X	X	
Serum chemistry [b]	X	X	X	X	X	
Hepatitis B/C[c]	X					
Adverse event evaluation	X	X	X	X	X	X
Pregnancy test [d]	X					
PT/INR[e]	X	X				
Concomitant Medications	X	X	X	X	X	
CHEMOTHERAPY						
Paclitaxel [f]		X	X	X	X	
Neulasta™ (pegfilgrastim) [g]						

Table 4. Study calendar

a: Laboratory tests required for eligibility must be completed within 14 days prior to study entry. Informed consent to be completed within 30 days prior to registration. Patients are able to undergo screening during treatment with AC and should be registered to the trial within 14 days of begining treatment with paclitaxel.

b: Sodium, potassium, chloride, bicarbonate, BUN, creatinine, total protein, albumin, total bilirubin, SGOT(AST), SGPT(ALT), Alkaline Phosphatase. At baseline, patients with high risk factors for Hepatitis B or C should be tested (anti-HCV antibody, HBsAg and anti-HBc-positive). In case of suggestion of infection a HBV DNA or HCV RNA-positive should be requested as appropriate. Patients with positive Hepatitis B or C serologies should have an ALT, AST, total bilirubin, alkaline phosphatase, INR, sample collected on at least two consecutive occasions, separated by at least 1 week, within the 30 day screening period. INR testing is not required for any other patients.

c: Patients with risk high factors for Hepatitis B or C should be tested (anti-HCV antibody, HBsAg or anti-HBc-positive). In case of suggestion of infection a HBV DNA and HCV RNA-positive should be requested as appropriate. Note: Patients with positive Hepatitis B or C serologies without known active disease must meet the eligibility requirements for ALT, AST, total

bilirubin, alkaline phosphatase and INR on at least two consecutive occasions, separated by at least 1 week, within the 30 day screening period.
d: Serum pregnancy test (women of childbearing potential).
e: For patients deemed to be at risk for Hepatitis B and C.
f: In order to initiate each cycle of chemotherapy (Paclitaxel) the following is needed: ANC≥ 1000/mm3; Platelets ≥100.000/mm3.If these criteria are not met, treatment must be delayed until counts return to ANC≥ 1000/mm^3 and Platelets ≥100.000/$mm^{3.}$ It is recommended that these values be checked 3 days after the scheduled day. Refer to Section 6.0 for dose modification guidelines.
g: During Paclitaxel growth factor will be administered if: the patient experiences a prior episode of fever and neutropenia, the patient has an active infection, it is at provider discretion the use of Neulasta™. If Neulasta™ is administered in any Paclitaxel cycle for a given patient, it will be then administered for all future cycles.
h: If the 4-week post-taxol visit creates significant burden for the patient, it is acceptable to do this visit by phone.
Patients with ongoing grade 3-4 AE will be followed until stabilization or resolution of AE.

10. MEASUREMENT OF EFFECT

Effect will be measured as defined in Section 13.

11. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

11.1 Data Reporting

11.1.1 Method

The QACT will collect, manage, and perform quality checks on the data for this study.

11.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the QACT according to the schedule set by the QACT.

11.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12. REGULATORY CONSIDERATIONS

12.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall PI (or Protocol Chair) will disseminate protocol amendment information to all participating investigators. All decisions of the IRB concerning the conduct of the study must be made in writing.

12.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

12.3 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

12.4 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13. STATISTICAL CONSIDERATIONS

13.1 Study design/ endpoints

This is a DF/HCC single-arm phase II study designated to evaluate the rate of Paclitaxel treatment completion omitting Neulasta™ (pegfilgrastim) using pre-specified safety rules within 7weeks (from D1of cycle 1 of Paclitaxel to D1 of cycle 4 of Paclitaxel). If there is strong evidence of lack of feasibility/safety, accrual will terminate early. A Simon Optimal design was selected with an overall one-side type I error of 10% and 90% power to detect the difference between unacceptable Paclitaxel treatment completion rate (75%) and desirable completion rate (85%).

Primary endpoint

- Paclitaxel treatment completion omitting Neulasta™(pegfilgrastim) using pre-specified safety rules within 7 weeks (from D1of cycle 1 of Paclitaxel to D1 of cycle 4 of Paclitaxel)

This study will enroll up to 125 patients eligible for the primary analysis. (We estimated that 5% of patients who started AC will not proceed to Paclitaxel).[2]

The secondary endpoints include:

- Utilization of Neulasta™ (pegfilgrastim) using pre-specified safety rules in patients receiving dose dense Paclitaxel,
- Safety of omitting Neulasta™ (pegfilgrastim) support using pre-specified safety rules in patients receiving dose dense Paclitaxel,
- Impact on schedule of omitting Neulasta™ (pegfilgrastim) support using pre-specified safety rules in patients receiving dose dense Paclitaxel
- Impact on costs of omitting Neulasta™ (pegfilgrastim) support using pre-specified safety rules in patients receiving dose dense Paclitaxel,
- Safety of simplify the pre-medication used for the Paclitaxel portion of the regimen,

13.2 Sample Size/Accrual Rate

If 85% patients completed Paclitaxel treatment within 7 weeks, the Neulasta™ (pegfilgrastim) intervention would be considered worthy of further study. A true rate of 75% or less would not be of clinical interest. The sample size was chosen to have high power (90%) with a Type I error no more than 10%.

In the first stage, 51 evaluable patients will be enrolled. If during the first stage, at any point, a total of 12 or more patients do not complete treatment within 7 weeks the trial will be closed permanently. Among the 51 patients enrolled after the first stage, if at least 40 patients completing treatment without dose delay, accrual will continue to the third stage where an additional 74 evaluable patients will be enrolled. If there are at least 100 among the 125 evaluable patients completing treatment without dose delay, the regimen will be considered

worthy of further study. If during the second stage, at any point, a total of 26 patients do not complete treatment within 7 weeks the trial will be closed permanently and the study intervention would not be of clinical interest.

In addition, observation of 3 FN will trigger the DSMC to make a decision whether the trial should be closed to further treatment and enrollment of patients.

If the true response rate is 75%, the chance the regimen is declared ineffective is 91% (exact alpha = 0.094) and if the true response rate is 85% the chance that the regimen is falsely declared ineffective is 10% (exact power = 0.899).

Based on historical rates of treatment at the DF/HCC, accrual is estimated to be 6-8 per month and will be completed between 16-21 months.

Throughout the course of the trial, two patients were registered, but did not move forward with participating in the trial. Since the study endpoint is powered to assess feasibility of completion of paclitaxel without neulasta, there is statistical justification to replace these two patients so that we have 125 evaluable participants for the primary endpoint. As such, we will raise the overall accrual to 127.

13.3 Data analysis and Primary Objective

For this phase II trial, the analysis population is all patients who initiate Paclitaxel. All patients who receive at least one dose of Paclitaxel will be evaluable for duration of treatment from the time of their first treatment. The primary analysis will evaluate the percent of patients who complete Paclitaxel treatment within 7 weeks using a pre-specified algorithm and the decision rules give in 13.2. We will estimate this percentage and a corresponding 95% confidence interval (CIs) will be calculated.

13.4 Statistical considerations for Secondary objectives

13.4.1 Utilization of Neulasta™ (pegfilgrastim) using pre-specified safety rules in patients receiving dose dense Paclitaxel

The proportion and corresponding 95% CI of Neulasta™ (pegfilgrastim) utilization per cycle will be tabulated. If the primary endpoint is met, this study will be considered successful if, in addition a substantial of savings is achieved (omission of 25% Neulasta™ (pegfilgrastim) without additional expenses, or the equivalent; we will calculate total costs and compare them with costs of an historical matched cohort of patients treated with Neulasta™ (pegfilgrastim)).

13.4.2 Safety of omitting Neulasta™ (pegfilgrastim) support using pre-specified safety rules in patients receiving dose dense Paclitaxel

Safety data that will be evaluated include AEs, clinical laboratory results and vital signs. Abnormal laboratory values will be flagged. Treatment-emergent AEs (TEAEs) will be analyzed. AEs will be regarded as TEAEs if they started on or after the date and time of administration of

the first dose of study treatment or if they were present before the administration of the first dose of study treatment and increased in severity during the study. AEs that are not treatment emergent will be listed.

AEs will be graded using CTCAE v 4.0 (Appendix A). Investigators will collect all CTCAE grades for all AEs (to assess both increasing and decreasing severity). AEs will be coded from verbatim terms using Medical Dictionary for Regulatory Activities (MedDRA) version 10.0 or above and grouped by system organ class (SOC) and preferred term (PT). Events will be summarized by frequency and percentage.

The incidence of TEAEs will be summarized by SOC, PT, CTCAE grade, and relatedness to study treatment. Although a MedDRA term may be reported more than once for a subject, that subject will be counted only one time in the incidence count for that MedDRA term by the highest CTCAE grade (in the summary by CTCAE grade) and by the closest causal relationship to study treatment (in the summary by relatedness to study treatment).

13.4.3 *Impact on schedule of omitting Neulasta™ (pegfilgrastim) support using pre-specified safety rules in patients receiving dose dense Paclitaxel*

Results will be tabulated appropriately, including the median chemotherapy cycle length, the rate of chemotherapy dose reductions, the percentage of patients who receive >85% of planned chemotherapy doses, the percentage of patients who receive all planned cycles of chemotherapy and reasons for treatment delays (defined as schedule/preference, absolute neutrophil count (ANC) < 1,000/mm^3, hypersensitivity, neurotoxicity, transaminitis, other).

13.4.4 *Impact on costs of omitting Neulasta™ (pegfilgrastim) support using pre-specified safety rules in patients receiving dose dense Paclitaxel*

We will compare charges/payments for study patients versus a matched set of non-study patients who were treated with dose-dense paclitaxel and also received peg-filgrastim at DFCI from 2012-present. [12] Peg-filgrastim patients will have had reimbursement for this agent, either as a facility administered medication or prescription, within the one-year observation window. Study and non-study patients will be matched based on their propensity to receive peg-filgrastim; the propensity score will be derived from a logistic regression model that includes age, race, co-morbidity and stage as covariates. Total charges/payments will be calculated during the year after diagnosis, adjusted for inflation, and expressed as 2016 $US. We will also assess charges/payments for specific services, including facility administered medications (i.e., chemotherapy), ED/inpatient hospitalizations, ambulatory clinic visits, and prescriptions.

13.4.5 *Safety of simplify of the pre-medication used for the Paclitaxel portion of the regimen*

We will estimate the rate of grade 3-4 HSR in cycle 3-4. As a safety stopping rule, we will evaluate the rate of grade 3-4 HSR after enrolling 51 patients. If the rate of grade 3-4 HSR in cycle 3-4 >10%, omitting steroid as pre-medicine for Paclitaxel in cycle 3-4 would be considered

too toxic. If 2 out of 51patients experienced a grade 3-4 HSR in cycle 3-4, the rate of grade 3-4 HSR is 4% (90% CI 1-12%). If 2 or more patients experienced a grade 3-4 HSR in cycle 3-4, the regimen would be considered too toxic, and this sub-study will be terminated due to safety concern. For the remaining study steroid standard regimen across the 4 cycles will be use.

14. PUBLICATION PLAN

14.1 Publication of Results

We plan to submit the results of this study within 12 months of the first analysis being available.

14.2 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the course of this study will be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study. These obligations of confidentiality and nonuse shall in no way diminish such obligations as set forth in the Confidentiality Agreement between the sponsor and the investigator. All persons assisting in the performance of this study must be bound by the obligations of confidentiality and nonuse set forth in the Confidentiality Agreement.

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16. APPENDICES

16.1 APPENDIX A: NATIONAL CANCER INSTITUTE COMMON TOXICITY CRITERIA

The National Cancer Institute's CTCAE v 4.0 published 28 May 2009 provides descriptive terminology to be used for AE reporting in clinical trials. A brief definition is provided to clarify the meaning of each AE term. To increase the accuracy of AE reporting, all AE terms in CTCAE version 4.0 have be correlated with single-concept, MedDRA® terms.

Grades in CTCAEs v 4.0 refer to the severity of the AE. Grades of 1 through 5, with unique clinical descriptions of severity for each AE, are based on this general guideline:

Grade	Status
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.*
3	Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL.**
4	Life-threatening consequences: urgent intervention indicated.
5	Death related to AE.

ADL = Activities of Daily Living
*: Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**: Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Cancer Therapy Evaluation Program, NCI CTCAE v 4.0. Available from http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev 4.pdf. **Error! Bookmark not defined.**

For further details regarding MedDRA, refer to the MedDRA website at:
http://www.meddramsso.com. CTCAE v 4.0 is available online at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev 4.pdf.

16.2 APPENDIX B: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.