STUDY NUMBER: CASE 13815

Clinicaltrials.gov: NCT02756013

Protocol Date: March 8, 2016

STUDY TITLE: A phase II trial of weight-based dosing for dense weekly paclitaxel and carboplatin in overweight patients with a BSA > 2.0.

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SPONSOR: None

SUPPORT/FUNDING: None

STUDY AGENT**:** Paclitaxel and Carboplatin both commercially available

STUDY SCHEMA:

Paclitaxel 80 mg/m2 IV over 1 hour Days 1, 8, and 15 plus
Carboplatin (AUC=6) IV Day 1
Every 21 days x 6 - 9cycles

PROTOCOL SUMMARY

Protocol Number/Title	Case 13815 A phase II trial of weight-based dosing for dense weekly paclitaxel and carboplatin in overweight patients with a BSA (Body Surface Area) of 2.0.
Study Phase	II
Brief Background/Rationale	The percentage of patients who are overweight or obese (BMI > 30) in the United States is increasing yearly.[1] Overweight and obese patients are at increased risk of certain cancers.[2] Gynecologic cancers that are increased in obese patients include endometrial, cervical and ovarian cancer. Cancer patients who are overweight or obese have poorer survival across many tumor types. Suboptimal chemotherapy dose delivery is a potential contributing factor in this poorer survival outcome. Retrospective studies in breast cancer demonstrate the relative dose intensity (RDI) of chemotherapy decreases with increasing body mass index.[3] In breast cancer, survival is decreased as the RDI falls below 85% of prescribed dose.[4] In 2012 the American Society of Clinical Oncology (ASCO) issued practice guidelines for chemotherapy dosing in the obese.[5] These guidelines recommended weight-based dosing for all but a few agents (i.e. carboplatin and bleomycin). Unfortunately there is a dearth of prospective studies supporting this approach. This is in part due to the fact that the Gynecologic Oncology Group has always capped the maximum body surface area (BSA) at 2.0. Despite the ASCO guidelines weight-based dosing remains controversial.[6] Clinicians often avoid weight-based chemotherapy dosing because of concerns of increased toxicity with these very large doses.
Primary Objective	The primary objective is to prospectively evaluate the Relative Dose Intensity (RDI) and toxicity of weight-based dose dense weekly paclitaxel and carboplatin in overweight patients with a BSA > 2.0 compared to the Japanese Gynecologic Oncology Group trial (JGOG 2016) during 6 – 9 cycles of chemotherapy.
Secondary Objective(s)	The secondary objective is to evaluate progression-free survival in this patient population.
Sample Size	28-34 females age 18 and over
Disease sites/Conditions	158.8 (C48.1), 180.9 (C53.9), 182.0(C54.1), 183.0 (C56.9), 183.2 (C57.00)
Interventions	Paclitaxel 80mg/m2 IV days 1,8, and 15 every 21 days x 6-9 cycles
	Carboplatin AUC 6 IV day 1 every 21 days x 6-9 cycles

ABBREVIATIONS

ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AUC	Area Under the Curve
BMI	Body Mass Index
BSA	Body Surface Area
CCCC	Case Comprehensive Cancer Center
CCF	Cleveland Clinic Foundation
CI	Confidence Interval
CRF	Case Report Form
c-TC	Conventional taxol and carboplatin
CTCAE	Common Terminology Criteria for Adverse Events
dd-TC	Dose dense taxol and carboplatin
DEHP	Diethylhexyl phthalate
DLT	Dose Limiting Toxicity
DSTC	Data Safety and Toxicity Committee
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
ICF	Informed Consent Form
IRB	Institutional Review Board
JGOG	Japanese Gynecologic Oncology Group
NCI	National Cancer Institute
NYHA	New York Heart Association
OS	Overall Survival
PFS	Progression Free Survival
PRMC	Protocol Review and Monitoring Committee
PVC	Polyvinyl Chloride
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	Standard of Care
WBC	White Blood Count

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1.0 Introduction

1.1 Background and Rationale of Study Disease

The percentage of patients who are overweight or obese (BMI > 30) in the United States is increasing yearly.[1] Overweight and obese patients are at increased risk of certain cancers.[2] Gynecologic cancers that are increased in obese patients include endometrial, cervical and ovarian cancer. Cancer patients who are overweight or obese have poorer survival across many tumor types. Suboptimal chemotherapy dose delivery is a potential contributing factor in this poorer survival outcome. Retrospective studies in breast cancer demonstrate the relative dose intensity (RDI) of chemotherapy decreases with increasing body mass index.[3] In breast cancer, survival is decreased as the RDI falls below 85% of prescribed dose.[4] In 2012 the American Society of Clinical Oncology (ASCO) issued practice guidelines for chemotherapy dosing in the obese.[5] These guidelines recommended weight-based dosing for all but a few agents (i.e. carboplatin and bleomycin). Unfortunately there is a dearth of prospective studies supporting this approach. This is in part due to the fact that the Gynecologic Oncology Group has always capped the maximum body surface area (BSA) at 2.0. Despite the ASCO guidelines weight-based dosing remains controversial.[6] Clinicians often avoid weight-based chemotherapy dosing because of concerns of increased toxicity with these very large doses.

In gynecologic oncology only one prospective trial evaluated the impact of BMI on progression-free survival (PFS) and overall survival (OS).[7] This trial used weight-based chemotherapy, and no difference in carboplatin or paclitaxel doses were noted based on BMI. No difference on PFS or OS based on BMI was observed. This trial was conducted in Scotland and BMIs >30, >40 and >50 were infrequent. Retrospective studies in gynecologic oncology patients receiving weight-based chemotherapy have not demonstrated increased toxicity.[8,9] Counter-intuitively, in one study patients with a BSA >2.0 receiving weight-based chemotherapy dosing had less toxicity than patients with a BSA >2.0 receiving capped BSA chemotherapy dosing.[9]

Based on the practice of dose capping in the Gynecologic Oncology Group there is limited prospective data regarding the use of weight-based dosing in gynecologic cancers.

Dose dense weekly paclitaxel has improved progression-free and survival compared to every three week paclitaxel in breast and ovarian cancer. The dose dense administration schedule of chemotherapy administers smaller more frequent doses of chemotherapy. The Japanese Gynecologic Oncology Group performed a randomized phase III trial of conventional paclitaxel and carboplatin (c-TC) versus dose dense weekly paclitaxel and carboplatin (dd-TC) in women with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer.[10] The patients were randomly assigned to receive carboplatin (AUC=6) with either paclitaxel at 180 mg/m2 on day 1 (c-TC) or paclitaxel at 80 mg/m2 on days 1, 8, and 15 (dd-TC). The treatments were repeated every 3 weeks for six cycles. Of 637 patients, the median duration of PFS in the c-TC group and dd-TC group was 17.1 and 27.9 months, respectively (p=0.0014), and overall survival at 2 years was 77.7% and 83.6%, respectively (p=0.05). Grade 3 and 4 anemia was reported more

frequently in the dd-TC group, and other toxicities were similar in both groups. These authors concluded that dose dense weekly TC improves PFS as compared with c-TC in patients with advanced epithelial ovarian cancer. A potential advantage of weekly versus every 3 week chemotherapy in weight based dosing is the ability to hold or reduce weekly chemotherapy doses in patients who demonstrate hematologic and non-hematologic toxicities.

The European Organization for Research and Treatment of Cancer randomized patients to primary debulking surgery followed by platinum-based chemotherapy versus neoadjuvant platinum-based chemotherapy followed by debulking surgery.[11] Of 670 patients, the hazard ratio for death in the group assigned to neoadjuvant chemotherapy followed by interval debulking, as compared with the group assigned to primary debulking surgery followed by chemotherapy, was 0.98 (90% confidence interval [CI], 0.84 to 1.13; P = 0.01 for noninferiority), and the hazard ratio for progressive disease was 1.01 (90% CI, 0.89 to 1.15). These investigators concluded that neoadjuvant chemotherapy followed by interval debulking surgery was not inferior to primary debulking surgery followed by chemotherapy as a treatment option for patients with bulky stage IIIC or IV ovarian carcinoma. Although it is not the intent of this current study to compare neoadjuvant chemotherapy followed by interval debulking vs. primary surgery with adjuvant chemotherapy, it is important to include this subset of patients in this clinical trial to afford them the greatest potential benefit of dose dense and weight based chemotherapy dosing.

The purpose of the current study is to prospectively evaluate the toxicity and efficacy of weight-based dose dense weekly paclitaxel and carboplatin in overweight patients with a BSA > 2.0.

2.0 Objectives

2.1 Primary Objective

The primary objective is to prospectively evaluate the Relative Dose Intensity (RDI) and toxicity of weight-based dose dense weekly paclitaxel and carboplatin in overweight patients with a BSA > 2.0 compared to the Japanese Gynecologic Oncology Group trial (JGOG 2016) during 6 – 9 cycles of chemotherapy.

2.2 Secondary Objective(s)

The secondary objective is to evaluate progression-free survival in this patient population.

3.0 Study Design

This is a descriptive study to determine what the relative dose intensity of patients who are overweight with a BSA of greater than 2.0 can achieve.

3.1 Number of Subjects

Approximately 28- 34 subjects will be enrolled in this trial.

3.2 Expected Duration of Treatment and Subject Participation

Patients will receive carboplatin and weekly taxane therapy every 21 days for six – nine cycles, unless disease progression, or adverse events require discontinuing protocol treatment.

4.0 Subject Selection

Each of the criteria in the sections that follow must be met in order for a subject to be considered eligible for this study.

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment:

4.11 Patients with a histologically confirmed or presumed diagnosis of gynecologic malignancy for whom chemotherapy with paclitaxel and carboplatin is planned.

4.12 Body Surface area >2.0

4.13 Patients must have adequate:

4.131Renal function: Creatinine <1.5 x Institutional upper limits of normal (ULN)

4.132 Bone marrow function:

4.1321 Absolute neutrophil count (ANC) $\geq$ 1,500/mcl. This ANC cannot have been induced or supported by granulocyte colony stimulating factors.

4.1322 Platelets $\geq$ 100,000/mcl.

4.133 Hepatic function:

4.1331 Bilirubin $\leq$ 1.5 x ULN.

4.1332 AST (SGOT) $\leq$ 2.5 x ULN.

4.1333 Alkaline phosphatase $\leq$ to 2.5 x ULN.

4.134 Neurologic function:

4.1341 Neuropathy (sensory and motor) $\leq$ CTCAE Grade 1.

4.14 Patients must have a Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2. (Appendix I)

4.15 Patients must be entered within 12 weeks of diagnosis.

4.16 Age >18 years. Patients under the age of 18 are best treated by pediatric oncology.

4.17 Subjects must have the ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

The presence of any of the following will exclude a subject from study enrollment.

4.21 Patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis. Prior radiation for localized cancer of the breast, head and neck, or skin is permitted, provided that it was completed more than three years prior to registration, and the patient remains free of recurrent or metastatic disease.

4.22 Patients who have received prior chemotherapy.

4.23 Patients with acute hepatitis or active infection that requires parenteral antibiotics.

4.24 Patients with clinically significant cardiovascular disease. This includes:

4.241 Myocardial infarction or unstable angina < 6 months prior to registration.

4.242 New York Heart Association (NYHA) Grade II or greater congestive heart failure (Appendix II).

4.243 Serious cardiac arrhythmia requiring medication. This does not include asymptomatic, atrial fibrillation with controlled ventricular rate.

4.25 Patients who are pregnant or nursing. Pregnant or breastfeeding women are excluded from this study because here are no adequate and well controlled studies using paclitaxel or carboplatin in pregnant women. Animals studies have revealed evidence of embryotoxicity and teratogenicity.

4.26 Patients under the age of 18.

4.27 Patients with medical history or conditions not otherwise previously specified which in the opinion of the investigator should exclude participation in this study.

4.28 Patients with known allergy to cremophor or polysorbate 80.

4.3 Inclusion of Women and Minorities

Women of all races and ethnic groups are eligible for this trial.

5.0 Registration

All subjects who have been consented will be registered in the OnCore™ Database. For those subjects who are consented, but not enrolled, the reason for exclusion will be recorded.

6.0 Treatment Plan

Each investigator must be CITI (Collaborative Institutional Training Initiative) certified to participate in clinical research at the Cleveland Clinic Health System.

6.1 Treatment Regimen Overview: Chemotherapy administration

All patients will receive Paclitaxel 80 mg/m2 IV over 1 hour on days 1, 8, and 15 plus Carboplatin (AUC 6) IV day 1 every 21 days x 6 – 9 cycles.

One cycle = 21 days.

Paclitaxel dosing only will be based on actual BSA. There will be no capping of doses for Paclitaxel. BSA will be recalculated for a 10% weight change.

Carboplatin will be recalculated each cycle. (See Appendix III for Carboplatin Dose Calculations)

Intravenous paclitaxel will be infused over one hour. Due to the risk of immediate hypersensitivity reaction, paclitaxel should always be the first drug to be infused during any combination. Carboplatin will be administered as a 30 minute infusion, following paclitaxel administration.

6.2 Premedications:

The following premedication is suggested prior to chemotherapy infusion on **all days**.

Ondansetron 8-16 mg IV or PO 30 minutes prior to administration of chemotherapy. (On Day 1 of each cycle palonosetron 0.25mg IV can be given instead of ondansetron per physician discretion).
Dexamethasone 20 mg PO 12 and 6 hours prior to paclitaxel or
10-20 mg IV just prior to IV therapy.
Diphenhydramine 25- 50 mg IV 30 minutes prior to paclitaxel.
Famotidine 20mg IV 30 minutes prior to chemotherapy.

Because the number of dexamethasone doses for a weekly paclitaxel regimen may be problematic for some patients, investigators can consider tapering the dexamethasone dose down in subsequent weeks for those patients who have no evidence of hypersensitivity reactions.

Appropriate dose modifications for paclitaxel and carboplatin are described in Section 7.0.

6.3 General Concomitant Medications and Supportive Care Guidelines

Subjects should receive full supportive care, including transfusions of blood and blood products, cytokines, antibiotics, antiemetics, etc when appropriate.

6.4 Criteria for Removal from Study

In the absence of treatment delays due to adverse events, treatment may continue for 6 – 9 cycles or until one of the following criteria applies:

• Disease progression,

• Intercurrent illness that prevents further administration of treatment,

• The investigator considers it, for safety reasons, to be in the best interest of the subject.

• Unacceptable adverse event(s)

6.5 Duration of Follow Up

Subjects will be followed for progression free survival after discontinuation from study treatment as follows: every 3 months for 2 years, then every 6 months for 3 years, then annually until disease progression.

7.0 Dose Delays/Dose Modifications

General Guidelines for Hematologic Toxicity:
In order to maintain dose-intensity and cumulative dose-delivery on this study, reasonable efforts will be made to minimize dose reduction and treatment delays as specified. Any patient whose treatment is delayed must be evaluated on a weekly basis until adequate hematologic and non-hematologic parameters have been met. No dose escalation is planned for this study. Treatment decisions will be based on the absolute neutrophil count (ANC) rather than the total white cell count (WBC).

Day 1 of a subsequent cycle of cytotoxic chemotherapy will not be administered until the ANC is ≥ 1000 cells/mcl and a platelet count of 75,000/mcl.

Day 8 and 15 paclitaxel dose will not be given unless the ANC is at least 500 cells/mcl and the platelet count is at least 50,000/mcl. If not given, these doses are omitted and not made up.

All treatment will be delayed for a maximum of three weeks until these values are achieved. Patients who fail to recover adequate counts within a three-week delay will no longer receive protocol-directed cytotoxic therapy.

7.1 Use of Hematopoietic Cytokines and Protective Agents
Hematopoietic growth factors should not be used to avoid initial chemotherapy dose modifications as stipulated in the protocol. However, subjects may also receive growth factors for the management of neutropenic complications in accordance with institutional treatment guidelines.

7.11 Patients will NOT receive prophylactic thrombopoietic agents.

7.12 Patients may NOT receive amifostine or other protective reagents.

7.2 Modifications for Hematologic Toxicity
Neutropenia and thrombocytopenia events defined below will be handled according to Table A.

7.21 Neutropenia defined as the occurrence of febrile neutropenia, prolonged Grade 4 neutropenia persisting ≥ 7 days, delay of treatment for more than 7 days because of neutropenia, ANC<1000cells/mcl on day 1, or omission of day 8 or day 15 paclitaxel because of neutropenia.

7.211 Febrile neutropenia is defined within the CTCAE as a disorder characterized by an ANC <1000/mcl and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour.

7.22 Thrombocytopenia defined as any occurrence of Grade 4 thrombocytopenia (<25,000/mcl) or bleeding associated with Grade 3 thrombocytopenia (25,000 to <50,000/mcl), delay of treatment on day 1 of a cycle by more than 7 days because of thrombocytopenia, platelet count of <75,000/mcl on day 1, or inability to give day 8 or day 15 paclitaxel due to thrombocytopenia.

7.221 There will be no modifications for uncomplicated Grade 3 thrombocytopenia except as above.

Table A

Neutropenia as described above	Thrombocytopenia as described above	First Occurrence	Second Occurrence	Third Occurrence
YES	**NO**	Reduce paclitaxel to 70 mg/m²	Reduce paclitaxel to 60 mg/m²	Omit day 15 paclitaxel and administer G-CSF starting after day 8 paclitaxel
YES	**YES**	Reduce carboplatin to an AUC of 5 and paclitaxel to 70 mg/m²	Reduce carboplatin to an AUC of 4 and paclitaxel to 60 mg/m²	Reduce carboplatin to an AUC of 4, Omit day 15 paclitaxel and administer G-CSF starting after day 8 paclitaxel
NO	**YES**	Reduce carboplatin to an AUC of 5	Reduce carboplatin to an AUC of 4	Reduce carboplatin to an AUC of 4, Omit day 15 paclitaxel

7.23 There will be no dose modifications made for anemia. Patients my receive red blood cell transfusions per institutional guidelines.

7.3 Guidelines for Non-hematologic Toxicity

7.31 Peripheral Neuropathy grade 2 or higher requires treatment delay until recovery to grade 1 and dose reduction according to table B.

7.32 Hepatic Toxicity. For a grade 3 or higher elevation in SGOT, SGPT, alkaline phosphatase or bilirubin delay treatment until recovery to grade 1 and follow table B.

7.33 Hypersensitivity Reaction
Patients who experience hypersensitivity reactions to either drug may need to repeat the premedication and to be rechallenged with a dilute solution and slow infusion per institutional guidelines. Severe hypersensitivity reactions to paclitaxel do not have to proceed with a rechallenge. Removal from study should be considered.

7.34 Other grade 3 or grade 4 treatment related toxicities (except alopecia, nausea/vomiting, constipation, diarrhea, hypokalemia, hypocalcemia, hypophosphatemia, hyponatremia, or hypomagnesemia) delay treatment until recovery to grade 1 and dose reduce according to table B.

Table B

Toxicity	First Occurrence	Second Occurrence	Third Occurrence
Neuropathy grade 2 or higher	Decrease paclitaxel to 70 mg/m2.	Decrease paclitaxel to 60 mg/m2.	Contact PI. Consider study removal.
Hepatic grade 3 or higher	Decrease paclitaxel to 70 mg/m2.	Decrease paclitaxel to 60 mg/m2.	Contact PI. Consider study removal.
Other grade 3 or 4 treatment related	Decrease one dose level of drug presumed responsible (Paclitaxel 70mg/m2 or carboplatin AUC 5)	Decrease one dose level of drug presumed responsible (Paclitaxel 60mg/m2 or carboplatin AUC 4)	Contact PI. Consider study removal.

For any toxicity not recovering to a grade 1 or better following a 3 week delay despite dose reductions discuss with study PI and consider removal from study.

8.0 Adverse Events and Potential Risks

8.1 Paclitaxel

The most common (> 10%) adverse events associated with paclitaxel are:

- Low white blood cell counts – this may make you more open to infection
- Low platelet count – this may make you bruise more easily and bleed longer if injured
- Low red blood cell count which may cause tiredness, shortness of breath and may cause the need for a blood transfusion
- Bleeding
- Mild to severe allergic reaction which may be life-threatening with hives, wheezing and a change in blood pressure (low or high)
- Changes in the nerves that can cause numbness, tingling, or pain in the hands and feet. This may lead to difficulty walking, buttoning clothes, etc.
- Nausea and/or vomiting
- Sores in the mouth or throat (that can lead to difficulty swallowing and dehydration)
- Local swelling, redness, or skin tissue damage if some of the drug leaks from the vein while it is being given
- Diarrhea
- Hair loss
- Muscle and joint aches
- Low blood pressure that may cause lightheadedness

Please refer to the package insert(s) for the comprehensive list of adverse events.

8.2 Carboplatin

The most common (> 10%) adverse events associated with carboplatin are:

- Low white blood cell counts - this may make you more open to infection
- Low platelet count - this may make you bruise more easily and bleed longer if injured
- Low red blood cell count which may cause tiredness, shortness of breath or fatigue and may cause the need for a blood transfusion.
- 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 and minerals in the blood such as magnesium, potassium, sodium, and calcium

Please refer to the package insert(s) for the comprehensive list of adverse events.

8.3 Definitions

8.31 Adverse Event

An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

8.32 Serious Adverse Events

A **serious adverse event** (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Results in **death.**
- Is a **life-threatening** adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.

- Requires **inpatient hospitalization or prolongation of existing hospitalization**. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:
  - The admission results in a hospital stay of less than 24 hours OR
  - The admission is pre-planned (e.g., elective or scheduled surgery arranged prior to the start of the study) OR
  - The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

  However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependant on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.
- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. The development of a new cancer is always considered an important medical event.

8.33 Adverse Event Evaluation

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) criteria version 4.0 will be used to classify toxicities observed during treatment. The severity of each toxicity will be assessed according to the NCI CTCAE 4.0 grading system. Patients will be tabulated according to their maximum severity for each organ system or preferred term.

Safety endpoints will be summarized with descriptive statistics for the patients in the safety analysis dataset. The safety analysis dataset will include all patients enrolled to the study who receive any study treatment Patients who do not receive any study treatment will not be included in these analyses.

In addition to toxicity an important measure of tolerance of dose dense therapy is the ability to receive chemotherapy at the planned dose and schedule. Comparison of the study patient adherence to planned dose and schedule will be computed utilizing relative dose intensity (RDI). The RDI of the study population will be compared to

the RDI reported by Katsumata and the RDI of a CCF (Cleveland Clinic Foundation) cohort of patients with a BSA <2.0.

9.0 Pharmaceutical Information

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section #8.

9.1 Commercial Agents

9.11 Name of Agent: **paclitaxel** (NSC #673089)
Other Names: Taxol

Product description:

Paclitaxel is supplied as a 6mg/mL non-aqueous solution in multi dose vials containing 30mg/5mL, 100mg/16.7mL, or 300mg/50mL of paclitaxel. In addition to 6mg of paclitaxel, each mL of sterile non-pyrogenic solution contains 527mg of purified Cremophor® EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

Solution preparation:

Paclitaxel must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride for Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C / 77°F) and room lighting conditions.
NOTE: In order to minimize patient exposure to the plasticizer DEHP, which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should be stored in bottles (glass, polypropylene) or plastic (polypropylene, polyolefin) bags and administered through polyethylene-lined administration sets.
Paclitaxel should be administered through an inline filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® or IVEX-HP®, which incorporate short inlet and outlet PVC-coated tubing, has not resulted in significant leaching of DEHP.

All patients should be premedicated with corticosteroids, diphenhydramine, and H2 antagonists prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Patients who experience severe hypersensitivity reactions to drug may need to repeat the premedication and to be rechallenged with a dilute solution and slow infusion. Severe hypersensitivity reactions to paclitaxel do not have to proceed with a rechallenge.

Storage requirements:

Unopened vials of paclitaxel are stable to the date indicated on the package when stored between 20 to 25°C (68 to 77°F). Protect from light.

Supplier: 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.

9.12 Name of Agent: **paraplatin**
Other Names: Carboplatin

Product description: Carboplatin is supplied as a sterile, pyrogen-free, 10mg/mL aqueous solution in multi-dose vials containing 50mg/5mL, 150mg/15mL, 450mg/45mL, or 600mg/60mL of carboplatin.

Solution preparation: Preparation: 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.

Storage requirements: 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.

Supplier: 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.

10.0 Study Parameters and Calendar

10.1Study Parameters

10.11 Screening Evaluation

Within 28 days prior to initiating protocol therapy the following are required: history and physical examination and a CA-125 blood test.
An initial CT scan or MRI of at least the abdomen/ pelvis and Chest CT or X-ray is required to establish post-surgical baseline for the extent of residual disease within 4 weeks before beginning treatment.

Within 14 days prior to initiating protocol therapy: Toxicity assessment, CBCD, CMP, phosphorus, Magnesium and serum pregnancy test (for those of childbearing potential).

10.12 Treatment Period

During chemotherapy a weekly CBCD within 2 days of retreatment is required.

Prior to each course of therapy: History and physical, toxicity assessment and a CA-125 is required. In addition within 2 days of retreatment: CBCD, CMP, Magnesium, and phosphorus.

Radiographic disease assessment (the same as baseline assessment) is required prior to every 3 cycles.

10.13 Follow up Period

History and physical, and CA-125 is required every 3 months for 2 years, every 6 months for 3 years, then annually until disease progression.
CBCD, CMP, Magnesium, and phosphorus to be performed as clinically indicated. Radiographic disease assessment (same as baseline) to be performed as clinically indicated or at least yearly.

10.2 Study Calendar

	Pre-Treatment	**During Cytotoxic Chemotherapy**			**Post-Treatment**
Observations and Tests	Prior to Initial Study Treatment	Weekly	Prior to Each Course	Prior to every other course	Every 3 months for 2 years, every 6 months for 3 years, then annually until disease progression
History & Physical	1		X		X
Toxicity Assessment	2		X		
CBC/Differential/Platelets	2	3	3		5
Serum Creatinine	2		3		5
Bilirubin, SGOT, Alkaline Phosphatase	2		3		5

Ca/PO4/Mg	2		3		5
Serum Pregnancy test (if childbearing potential exists)	2				
Radiographic disease assessment	4			prior to every 3 cycles	5 - at least yearly
Chest X-Ray (or CT chest)	4			prior to every 3 cycles	5 - at least yearly
Serum CA-125 level	1		X		X

1. Must be obtained within 28 days prior to initiating protocol therapy.
2. Must be obtained within 14 days prior to initiating protocol therapy.
3. Must be obtained within 2 days of re-treatment with protocol therapy.
4. An initial CT scan or MRI of at least the abdomen/ pelvis and Chest CT or X-ray is required to establish post-surgical baseline for the extent of residual disease within 4 weeks before beginning treatment.
5. When clinically indicated

11.0 Measurement of Effect

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.0 Data Reporting / Regulatory

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

The OnCore™ Database will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. OnCore™ is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. OnCore™. Access to data through OnCore™ is restricted by user accounts and assigned roles. Once logged into the OnCore™ system with a user ID and password, OnCore™ defines roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore™ Administrator at OnCore-registration@case.edu.

OnCore™ is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. This study will utilize electronic

Case Report Form completion in the OnCore™ database. A calendar of events and required forms are available in OnCore™.

12.2 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

12.3 Written Informed Consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and be allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject. Additionally, documentation of the consenting process should be located in the research chart.

12.4 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

12.5 Retention of records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with local, national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

12.6 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

13.0 Statistical Considerations

The purpose of the study is to evaluate the relative dose intensity that can be achieved in the obese patient population. Previous studies have demonstrated that the relative dose intensity of less than 85% is suboptimal and associated with a poorer survival in breast cancer. In ovarian cancer, Kutsamata et al was able to deliver a relative dose intensity of paclitaxel of 79% and the relative dose intensity of carboplatin of 77%. Therefore, this is a descriptive study to determine what the relative dose intensity of patients who are obese with a BSA of greater than 2.0 can achieve.

Sample size calculations were performed on the primary objective of the study, evaluating whether RDI can be increased from 0.77 to 0.90. We believe that the standard deviation of RDI will be similar in magnitude of those in Japanese GOG article. Thus, we base our sample size calculations on these estimates. Calculations assumed the use of a one-sided T-test with a 0.05 significance level and a standard deviation of 0.18, as suggested by previous research, Japanese GOG article. Under these assumptions, there will be 80% power to show an increase from 0.77 to 0.90 of RDI with a total of 50 subjects.

Table 1: Sample size

Null RDI	Proposed RDI	Standard Deviation	Power	N
0.77	0.90	0.18	0.8	50

The total population accrued will be evaluated to evaluate their relative dose intensity relative to the previous achieved results by Kutsamata et al. Analysis of subgroups of patients with BMIs between 30 and <40, 40 and <50, 50 and <60, and >60 will be planned.

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APPENDIX I

ECOG Performance Status

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

APPENDIX II

NEW YORK HEART ASSOCIATION (NYHA) CARDIAC CLASSIFICATION
http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classesof-Heart-Failure_UCM_306328_Article.jsp
Please refer to link for most current and up to date information on heart failure Classification.

APPENDIX III

Carboplatin Calculations

Dosing of Carboplatin:
1. The carboplatin dose will be calculated to reach a target area under the curve (AUC) according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Cockcroft-Gault formula.

2. The dose of carboplatin must be calculated using GFR and **recalculated each cycle.**

3. Carboplatin doses are required to be recalculated if the subject has a weight change of greater than or equal to 10%. Subjects are permitted to have chemotherapy doses recalculated for < 10% weight changes.

4. At the time of dose modification, if the subject's age had changed (the subject has had a birthday), the site can use the current age.

5. In subjects with an abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using a minimum value of 0.7 mg/dl. For trials where subjects enter and are treated within less than or equal to 12 weeks of surgery: If a more appropriate (higher) baseline creatinine value is available from the pre-operative period (within 4 weeks of surgery that value may also be used for the initial estimation of GFR.

CALVERT FORMULA:

Carboplatin dose (mg) = target AUC × (GFR + 25)
NOTE: the GFR used in the Calvert formula should not exceed 125 ml/min. **Maximum** carboplatin dose (mg) = target AUC (mg/min) × 150 ml/min. **The maximum allowed doses of carboplatin are:**
- **AUC 6 = 900 mg**
- **AUC 5 = 750 mg**
- **AUC 4 = 600 mg**

For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance.

The estimated creatinine clearance (ml/min) is calculated by the method of Cockcroft-Gault using the following formula:

$$\textbf{Creatinine Clearance (mL/min)} = \frac{\textbf{[140-Age (years)]} \times \textbf{Weight (kg)} \times \textbf{0.85}}{\textbf{72} \times \textbf{serum creatinine (mg/dl)}}$$

Notes:
1. Weight in kilograms (kg)
a. Body Mass Index (BMI) should be calculated for each patient. A BMI calculator is available at the following link: http://www.nhlbisupport.com/bmi/

b. Actual weight should be used for estimation of GFR for patients with BMI of less than 25
c. **Adjusted** weight should be used for estimation of GFR for patients with **BMI of greater than or equal to 25**
d. Adjusted weight calculation:

- Ideal weight (kg) = (((Height (cm)/2.54) – 60) × 2.3) + 45.5

- **Adjusted weight (kg) = (Actual weight – Ideal weight) × 0.40) + Ideal weight**

2. The Cockcroft-Gault formula above is specifically for women (it includes the 0.85 factor).

At the time of a dose modification for toxicity:
If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.

Appendix IV

RECIST 1.1
Response Evaluation Criteria in Solid Tumors (RECIST)
Quick Reference:
ctep.cancer.gov/protocolDevelopment/docs/quickrcst.doc

Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

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

  Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

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

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

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

Methods of Measurement –

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous

reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

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

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

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

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

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

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

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

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

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

- All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions

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

Evaluation of non-target lesions

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

(1) Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail.

Evaluation of best overall response

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

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

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

Confirmation

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

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

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

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first

date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

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

- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Reporting of results

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

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

- All conclusions should be based on all eligible patients.

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

- The 95% confidence intervals should be provided.

Appendix V

General Chemotherapy Guidelines

● A subject will be permitted to have a new cycle of chemotherapy delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.

● It will be acceptable for individual chemotherapy doses to be delivered within a 24-hour window before and after the protocol-defined date for "Day 1" treatment. If the treatment due date is a Friday, and the subject cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through the Monday (Day 3 past due).

● For weekly regimens, it will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window," for example; "Day 8 chemotherapy" can be delivered on Day 7, Day 8, or Day 9 and "Day 15 chemotherapy" can be given on Day 14, Day 15, or Day 16.

● Chemotherapy doses can be "rounded" according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately ± 5% of the calculated dose).

● Chemotherapy doses are required to be recalculated if the subject has a weight change of greater than or equal to 10%. Subjects are permitted to have chemotherapy doses recalculated for < 10% weight changes.