Principal Investigator/Department:	Roisin E. O'Cearbhaill, MB BCh	Medicine/Gynecologic Medical Oncology
Co-Principal Investigator(s)/Department:	David Hyman, MD David R. Spriggs, MD	Medicine/Gynecologic Medical Oncology
Investigator(s)/Department:	Carol Aghajanian, MD Katherine M. Bell-McGuinn, MD, PhD Rachel Grisham, MD Martee L. Hensley, MD, MSc Jason A. Konner, MD Vicky Makker, MD Paul Sabbatini, MD William P. Tew, MD Jessica Gahres, PA-C Karen Cadoo, MB BCh Dmitriy Zamarin, MD, PhD Alexia Iasonos, PhD Elena Elkin, PhD	Medicine/Gynecologic Medical Oncology Epidemiology and Biostatistics Epidemiology and Biostatistics: Health Outcomes
Consenting Professional(s)/Department:	Carol Aghajanian, MD Katherine M. Bell-McGuinn, MD, PhD Rachel Grisham, MD Martee L. Hensley, MD, MSc David Hyman, MD Jason A. Konner, MD Vicky Makker, MD Roisin E. O'Cearbhaill, MB BCh Paul Sabbatini, MD David R. Spriggs, MD William P. Tew, MD Karen Cadoo, MB BCh Dmitriy Zamarin, MD, PhD	Medicine/Gynecologic Medical Oncology

Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Study Objective

- The primary objective of this study is to perform a randomized study to determine whether patients treated for relapsed ovary, fallopian and primary peritoneal with extended infusion carboplatin have lower rates of hypersensitivity reactions compared to those treated with standard infusion carboplatin.

Study Population

- Eligible patients (relapsed fallopian, ovary and primary peritoneal cancer), who will be re-treated with a carboplatin-containing regimen.

Number of Patients:

- Approximately 150 patients will be enrolled in order to obtain the 114 evaluable patients that are required to determine the primary endpoint of the study.

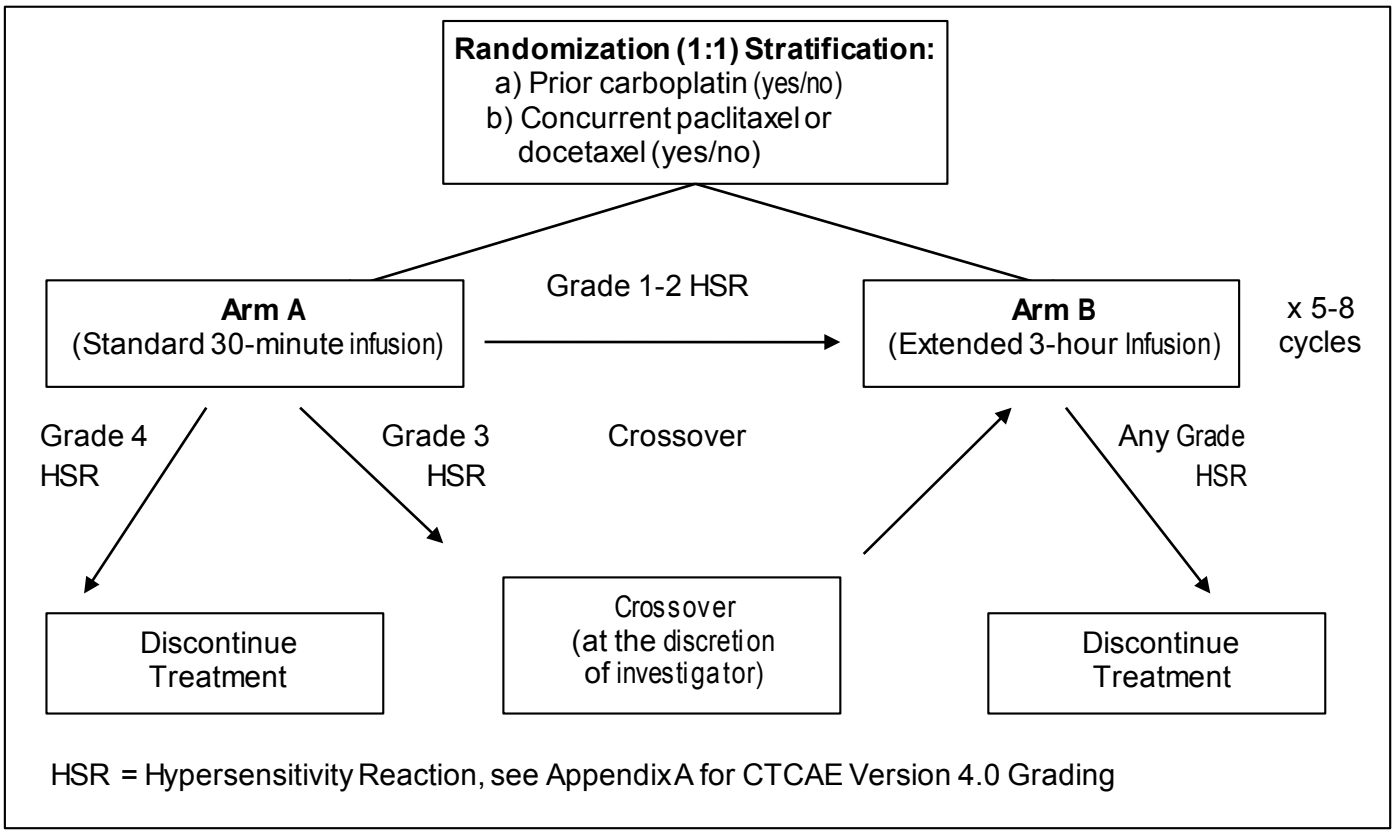
Study Design:

- This is a randomized, non-blinded trial, with a 1:1 randomized to the standard and experimental treatment arms.

Therapeutic Intervention:

- All patients receive standardized premedication with dexamethasone 20mg PO the night before and morning of treatment, montelukast 10mg PO once daily for the three days prior to carboplatin treatment, and ranitidine 50mg IV (or famotidine 20mg IV) and diphenhydramine 50mg IV prior to treatment to control for the contribution of premedication in preventing hypersensitivity reactions (see Section 5.6.3 for further details).
- Randomize between standard (30-minute) carboplatin infusion or an extended (3-hour carboplatin) infusion. Extended infusion carboplatin is given in three steps, 1% of total dose administered over the 1st hour, 9% of total dose administered over the 2nd hour, and the remaining 90% administered over the 3rd hour. Randomization is stratified by prior carboplatin (yes/no) and concurrent paclitaxel/docetaxel (yes/no).
- Dose of carboplatin (AUC) for each patient in each arm is determined by treating physician.
- Concomitant treatment with paclitaxel, docetaxel, pemetrexed, gemcitabine, liposomal doxorubicin and bevacizumab in both arms is determined by the treating physician.
- Cycles are repeated every 28 days if carboplatin is given in combination with liposomal doxorubicin. Carboplatin given alone or with gemcitabine, paclitaxel, docetaxel or pemetrexed may be administered on a 21 or 28 day cycle, at the discretion of the Investigator. Patients are treated for 5 to 8 cycles, at the discretion of their treating physician.

Schema:



2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Endpoint:

1. Determine the rate of hypersensitivity reaction in each group

Secondary Endpoints:

1. Determine the rate of successful planned treatment completion of carboplatin in each group
2. Perform a cost-identification analysis of extended infusion carboplatin to estimate the cost per hypersensitivity reaction prevented.
3. Perform exploratory analyses to correlate hypersensitivity rate to history of atopy, prior drug allergies, number of lifetime platinum cycles, duration since last platinum, and concomitant chemotherapy agent

3.0 BACKGROUND AND RATIONALE

Epithelial ovarian cancer is the second most common gynecologic malignancy and accounts for almost 22,000 incident cases and 16,000 deaths per year.[1] Early symptoms of ovarian cancer are often absent or non-specific and 75% of patients present with advanced (Stage III or IV) disease. These patients are offered maximal tumor debulking followed by intravenous or intraperitoneal platinum and taxane chemotherapy. Following this combination of

therapies, 50% of patients achieve a complete remission and an additional 30% a partial remission.[2] Of the patients in CR, 15% remain disease free for 5 years and are considered cured. The remaining patients will relapse and require further palliative chemotherapy.

Relapsed ovarian cancer is distinct from most solid tumors in that it often retains sensitivity to chemotherapy, specifically platinums, over multiple relapses. The most important prognostic factor in relapsed ovarian cancer is platinum sensitivity (defined as relapse ≥ 6 months since last platinum). Patients with recurrent platinum-sensitive ovarian cancer are usually retreated with carboplatin either alone or in combination with paclitaxel, docetaxel, pemetrexed, gemcitabine or liposomal doxorubicin. These patients can maintain platinum sensitivity over multiple recurrences spanning many years and be successfully retreated repeatedly with carboplatin-based chemotherapy. Unfortunately, patients can develop hypersensitivity reactions (HSRs) when they are retreated with carboplatin. These reactions present with significant heterogeneity. In some patients HSRs occur immediately upon initiation of the infusion while in others the reactions occur after at least half the treatment volume has been given. Delayed reactions (reactions that occur after carboplatin has been completed infused) are very rare. This diversity suggests multiple immunological and non-immunological mechanisms may be involved. The symptomatology of carboplatin HSRs is similarly heterogeneous. Some patients will develop mild manifestations including flushing, rash, diaphoresis, urticaria or hypertension. Other patients will present with severe symptoms including potentially life-threatening bronchospasm, chest pain, shortness of breath, hypotension or cardiac arrest.

Carboplatin HSRs rarely occur during the first course of therapy. Patients typically react early in their second course of therapy, most commonly during their 7th to 9th lifetime cycle of carboplatin.[3] Reactions, however, can occur at anytime. Estimates of the frequency of carboplatin HSRs are fairly consistent across multiple publications. Markman et al have report an incidence of 27%.[4] Polyzos et al report an incidence of 16%.[5] Morgan et al report an incidence of 44%.[6] The variation in these rates likely reflects the different treatment experience of each patient population as well as differences in the use of pre-medications. Carboplatin infusion rates may also play a role. Retrospective studies have suggested a number of risk factors for carboplatin HSR including a history of prior drug allergies, a lifetime platinum exposure of ≥8 prior cycles, and a treatment interval ≥12 months since last platinum.[7-8] None of these risk factors has been validated prospectively. The choice of chemotherapy agent administered in combination with carboplatin may also impact the likelihood of a HSR. For example, a recent randomized phase III trial demonstrated a HSR rate in patients retreated with concurrently paclitaxel or liposomal doxorubicin of 18% versus 5%, respectively.[9]

Several Investigators have developed desensitization regimens in order to re-challenge patients who have previously reacted to platinums. Like many antibiotic desensitization regimens, these strategies typically involve administering escalating aliquots of carboplatin slowly with premedication.[10-11] These procedures are labor-intensive and are typically performed over six or more hours under close observation in a monitored setting such as an intensive care unit. Many desensitization regimens utilize skin testing to risk stratify patients prior to re-challenge.[12] All these techniques require the expertise of allergists familiar with

managing chemotherapy HSRs and the chance of a second reaction is high. Castels et al have reported on their experience at a specialized chemotherapy desensitization unit at the Dana Farber Cancer Center. In their series 30-40% of patients will experience a second HSR upon re-challenge. Although these second reactions are generally mild, a small percentage will be severe and life threatening. Centers specialized in managing chemotherapy HSRs typically treat through repeated reactions. However, many women do not have access to these services. As a result, many patients will not successfully complete a planned course of carboplatin after developing an initial HSR and may have inferior clinical outcomes.[13] What is therefore most needed is an effective strategy to prevent patients who are continuing to benefit from platinum chemotherapy from developing HSRs in the first place.

The Gynecologic Medical Oncology (GMO) service at Memorial Sloan-Kettering Cancer Center (MSKCC) has developed 3-hour extended infusion carboplatin regimen that is a modification of the standard 12-step desensitization protocols used at several centers. Carboplatin is administered either a single agent or a carboplatin-containing combination treatment. Patients are premedicated with dexamethasone 20mg the night before and morning of chemotherapy, montelukast 10mg once daily for the three days preceding treatment, and ranitidine 50mg IV (or famotidine 20mg IV) and diphenhydramine 50mg IV prior to carboplatin. Carboplatin is given in the following manner: 1% of the total dose over the 1st hour, 9% of the total dose over the 2nd hour, and the remaining 90% over the 3rd hour. In contrast to the complex and lengthy desensitization protocols often used in post-HSR platinum re-challenge, this 3-hour extended infusion can be easily administered in the outpatient clinic setting. This extended infusion regimen is now the accepted standard of care at MSKCC to re-challenge patients who have developed a prior HSR to carboplatin.

Several physicians in the GMO have piloted using this regimen before women develop HSRs. A retrospective review of this experience has been published.[14] This review identified 707 patients who had received retreatment with second-line or greater carboplatin between January 1998 and December 2008. Of these a total of 174 patients (25%) received prophylactic extended infusion schedule. A total of 117 carboplatin HSRs were identified among the entire cohort of 707 patients. Only 6 patients (3.4%) who received the extended schedule versus 111 patients (21%) who received the standard schedule developed an HSR. Using the Fisher exact test, there was a significant relationship between the use of the extended regimen and a reduced incidence of HSRs ($P < 0.001$). Moreover, only 20% of patients who developed a HSR on standard infusion were re-challenged with extended infusion carboplatin and of these only 57% were able to complete treatment. The end result is that only 11.4% of patients who experienced a carboplatin HSR were able to successfully complete a planned course of therapy. This reinforces the importance of developing strategies to prevent platinum HSRs.

To date, no center has reported prospectively on the prophylactic use of extended infusion carboplatin regimen to reduce in incidence of HSRs. This will be the first prospective randomized clinical trial to compare standard to prophylactic extended infusion carboplatin in women with recurrent ovarian cancer. The results of this prospective trial, positive or negative, will define the best practice for retreating women with ovarian with platinum agents. The implications of this strategy are not limited to patients with ovarian cancer. Several other

cancer types can respond repeatedly to platinum-based chemotherapy including BRCA+ breast cancer and endometrial cancer. In addition, colon cancer patients are routinely given platinum-based chemotherapy in the adjuvant setting and are then retreated with platinum on recurrence and can develop HSRs. The results of this study may therefore inform the design of future clinical trials for these diseases.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a non-blinded randomized study comparing standard 30-minute infusion carboplatin to extended 3-hour infusion carboplatin in women with recurrent, ovary, fallopian tube, and primary peritoneal cancer who will be treated with a carboplatin-containing chemotherapy regimen.

4.2 Intervention

All patients will receive identical chemotherapy premedications including dexamethasone 20mg the night before and morning of infusion, montelukast 10mg once daily for three days prior to carboplatin infusion, and ranitidine 50mg IV (or famotidine 20mg IV) and diphenhydramine 50mg IV before carboplatin infusion. Patients who are intolerant to diphenhydramine 50mg IV can be dose reduced to 25mg IV or changed to hydroxyzine 25mg PO at the discretion of the Investigator. Patients will be randomized to receive standard infusion carboplatin or extended infusion carboplatin in a 1:1 manner. Patients will be stratified based on history of prior carboplatin exposure (yes/no) and concurrent paclitaxel or docetaxel treatment (yes/no). Patients may receive carboplatin alone or in combination with paclitaxel, docetaxel, pemetrexed, gemcitabine or liposomal doxorubicin at the discretion of the Investigator. Patients may also receive concurrent bevacizumab in addition to single-agent carboplatin or a carboplatin doublet, at the discretion of the Investigator. Carboplatin dose will be decided by the Investigator. Carboplatin will be administered on day 1 of each cycle. If carboplatin is administered alone or in combination with paclitaxel, docetaxel, pemetrexed or gemcitabine, each cycle will last 21 days. If carboplatin is given alone, with gemcitabine or with paclitaxel or docetaxel or pemetrexed, each cycle will last either 21 or 28 days, at the discretion of the Investigator. Patients will receive between 5 and 8 cycles, as is the standard of care, the exact number to be determined by their treating doctors.

The goal of this study is to accrue 57 patients to each arm for a total of 114 evaluable patients. With an anticipated accrual rate of 5-6 patients per month, this study should take 18-24 months to complete enrollment. Patients will be followed until they receive their last dose of carboplatin.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Carboplatin

Will be prepared as per MSKCC Guidelines. For complete details, see the package insert for further information.

Mechanism of action: Carboplatin binds to DNA and causes cross-linking with a non-cell cycle dependent tumor cell lysis. It inhibits DNA synthesis by altering the template via the formation of intra-strand cross-links.

Formulation: Carboplatin is available as a 10mg/ml solution.

Storage: Unopened vials are stable for the life indicated on the insert if protected from light.

Drug Administration: The total dose will be diluted in 250mls of D5W and infused over 30 minutes (standard MSKCC protocol) or by a 3-hour infusion (standard MSKCC desensitization protocol) in the following manner: 1% total dose 1st hour, 9% total dose 2nd hour, 90% of total dose 3rd hour (desensitization MSKCC protocol). Patients must have an absolute neutrophil count of ≥ 1000 cells/μL, platelet count ≥ 100,000 and creatinine ≤ 1.5 mg/dl. See section 9.1 for MSKCC/GMO guidelines for carboplatin dosing.

Toxicity: Myelosuppression, nausea, vomiting, alopecia, hyponatremia, hypomagnesemia, hypocalcemia, allergic reactions, fatigue, rare toxicities including ototoxicity (high doses), nephrotoxicity, edema, nervous system disorders (dizziness, blurred vision), hepatic dysfunction, fever, weight loss, interstitial pneumonitis, hemolytic uremic syndrome and uremia.

5.2 Paclitaxel

Will be prepared and administered as per MSKCC Guidelines. For complete details, see the package insert for further information

5.3 Gemcitabine

Will be prepared and administered as per MSKCC Guidelines. For complete details, see the package insert for further information

5.4 Liposomal Doxorubicin

Will be prepared and administered as per MSKCC Guidelines. For complete details, see the package insert for further information

5.5 Docetaxel

Will be prepared and administered as per MSKCC Guidelines. For complete details, see the package insert for further information

5.6 Pemetrexed

Will be prepared and administered as per MSKCC Guidelines. For complete details, see the package insert for further information

5.7 Bevacizumab

Will be prepared and administered as per MSKCC Guidelines. For complete details, see the package insert for further information

5.8 Concomitant Medications

5.6.1 Anticancer or experimental therapy

No other concurrent chemotherapy or anti-cancer therapy (other than those listed in Section 5.1-5.5) is permitted while the patient is enrolled and receiving treatment on study.

5.6.2 Hematopoietic Growth Factors

Colony-Stimulating Factor (G-CSF, pegylated G-CSF): Colony-stimulating factors may be used at the discretion of the treating physician but will not be used routinely.

Epoetin alfa (Procrit® or Aranesp®): Use of epoetin alfa is permitted at the discretion of the treating physician.

5.6.3 Antiemetics and Premedications

The premedications are required for all patients are as follows:

Premedications	
Day	**Drug**
Three days prior to carboplatin	Montelukast 10mg orally
Night before & morning of carboplatin	Dexamethasone 20mg orally
Prior to carboplatin	Diphenhydramine 50mg IV Ranitidine 50mg IV or Famotidine 20mg IV

Premedication Adjustments: If a patient is intolerant of 20mg of dexamethasone, the dose may be reduced to 12mg the night before and morning of carboplatin. If the patient is intolerant of 12mg of dexamethasone, they will be removed from study. If a patient is intolerant of 50mg of diphenhydramine the dose can be reduced to 25mg IV or changed to hydroxizine 25mg PO once.

Patients will be given a pill diary to document compliance with premedications (see Appendix B.1 & B.2). Patients who miss doses of premedications may begin their next cycle of chemotherapy at the discretion of the Investigator.

Suggested Antiemetics:
Per institutional guidelines for Carboplatin AUC ≥ 3

Day 1: Palonosetron 250mcg IVPB once, Aprepitant 125mg PO once

Day 2 to 3 after Carboplatin Infusion: Dexamethasone 12mg PO morning, Aprepitant 80mg PO morning, Ondansetron 8mg PO q8hr PRN and/or Metoclopramide 10 mg PO every 4 hr PRN and/or prochlorperazine 10mg q6hr PRN

This is only a suggested antiemetic regimen, modifications are permitted. If nausea and vomiting are not well controlled on this regimen or a patient has intolerance to once of these agents, substitutions and additions of alternate antiemetics such as lorazepam may be used at the discretion of the treating oncologist.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

Subjects must meet the following criteria to be eligible for this protocol.

6.1 Subject Inclusion Criteria

1. MSKCC histologically confirmed ovarian, fallopian tube or primary peritoneal carcinoma.
2. Patient has received at least one prior platinum-containing (cisplatin or carboplatin) regimen
3. Age ≥ 21 years old
4. Karnofsky Performance Status (KPS) ≥ 70%
5. Adequate hematologic, hepatic and renal function as defined below:
    a. Hemoglobin ≥ 7.0 g/dl
    b. Absolute neutrophil count ≥ 1,000/mm^3
    c. Platelet count ≥ 100,000/mm^3
    d. Serum creatinine ≤ 1.5 x the upper limit of normal or calculated creatinine clearance ≥ 60 mL/min

6.2 Subject Exclusion Criteria

1. Prior carboplatin or cisplatin hypersensitivity reaction
2. Uncontrolled intercurrent illness including infection, congestive heart failure, myocardial infarction, transient ischemic attack or stroke within 6 months. Any such conditions that have occurred in the last 6 months but are no longer active at the time of registration are not considered exclusionary.
3. Patients receiving other investigational agents
4. Patients with HIV disease will be permitted, only if they are on effective anti-retroviral therapy, have a CD4 count greater than 400, and have had no opportunistic infections within the past 6 months
5. Pregnant or lactating women
6. Life expectancy of less than 12 weeks

7.0 RECRUITMENT PLAN

Patients will be recruited through the outpatient gynecologic medical oncology clinics of the Memorial Sloan-Kettering Cancer Center. The gynecologic medical oncology service holds weekly meetings to review open clinical trials and identify appropriate patients. All patients will be under the care of attending medical oncologists of MSKCC. Members of all ethnic groups are eligible for this trial. All eligible patients (Section 6) will be offered enrollment on this study. The trial will be registered with the National Cancer Institute clinicaltrials.gov website.

The protocol will be included on the MSKCC website describing therapeutic protocols open at the institution.

8.0 PRETREATMENT EVALUATION

Part I: Initiation of Treatment
Screening Procedures within 28 Days Prior to Starting Treatment

The following screening procedures must be performed within 28 days of initiating study treatment:

- Medical history (including demographics, oncologic history, history of other active or resolved disease processes)
    - Directed medical history to obtain the following information:
        - History of drug allergies (the number of drug allergies will be recorded, counting multiple allergies within a specific drug class only once)
        - History of food allergies
        - History of environmental allergies, including seasonal
        - History of asthma
        - History of atopic dermatitis (eczema)
        - Number of documented allergies (including contrast dye and contact skin allergies, but not including food allergies)
- Assessment of baseline symptoms and complaints
- Karnofsky Performance Status (KPS)
- Height and weight
- Vital signs (temperature, blood pressure, heart rate, respiratory rate)
- Physical examination including examination of major body systems
- Review of concomitant medications/other treatments
- Complete Blood Count (CBC) with differentials and platelets
- Comprehensive Metabolic Panel (includes sodium, potassium, glucose, BUN, creatinine, calcium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin)

Screening Procedures within 14 days Prior to Starting Treatment

- Serum pregnancy test (for women of childbearing potential only)

Part II: Crossover Eligibility

- Patients randomized and treated on Arm A (standard 30 minute carboplatin infusion) who experience a CTCAE (version 4.0) grade 1 or 2 hypersensitivity reaction may crossover and receive treatment on Arm B (extended 3 hour Carboplatin infusion). Before patients can crossover to Arm B, the following criteria must be met:
    - Currently enrolled on Protocol IRB# 10-184
    - Randomized and treated on Arm A (standard 30 minute carboplatin infusion)
    - Patient experienced a CTCAE (version 4.0) grade 1-2 carboplatin hypersensitivity reaction
      OR
      Patient experienced a CTCAE (version 4.0) grade 3 carboplatin hypersensitivity reaction, and at the discretion of the investigator is appropriate for crossover to Arm B (extended 3 hour carboplatin infusion)

9.0 TREATMENT/INTERVENTION PLAN

9.1 Chemotherapy Administration

Carboplatin Dosing:

Eligible patients will be randomized in a 1:1 manner to receive carboplatin by either standard infusion (Arm A) or extended infusion (Arm B). Carboplatin dosing will follow the Gynecological Medical Oncology and MSKCC institutional guidelines. Dose reductions, modifications, and treatment interruptions will be decided by the Investigator. Carboplatin will be administered as follows:

Arm A:
Per standard MSKCC carboplatin protocol: 100% of carboplatin dose is administered in 250mL of D5W over 30 minutes. Spike infusion bag with secondary set (Braun #V1921), do not prime.

Arm B:
Per desensitization MSKCC carboplatin protocol: Bags 1 and 2 are prepared by the chemopharmacy. Bag 1 contains 10% of the total dose in 100 mL of D5W and Bag 2 contains with 90% of the total dose in 250mL of D5W. 10 mL (1% of total dose) of Bag 1 is infused over the first hour. If there is no evidence of hypersensitivity reaction, the remaining 90 mL (9% of total dose) of Bag 1 is infused over the second hour. If there is still no evidence of hypersensitivity reaction, Bag 2 containing 90% of total dose in 250 mL is infused over the third hour. Spike infusion bag with IMED Alaris 2420 tubing.

Protocol for Extended Infusion Carboplatin (Carbo)	
Infusion time	**Percentage carboplatin infused**
1st hour	1%
2nd hour	9%
3rd hour	90%
Total: 3-hour infusion	100%

Crossover:
Patients treated on Arm A who experience a hypersensitivity reaction will be managed as follows:

Arm A	
CTCAE v4 Grade	**Management**
1 or 2	Crossover to Arm B
3	Crossover to Arm B at the discretion of the treating physician
4	Discontinuation from study

Patients treated on Arm B or who are crossed over to Arm B who experience a hypersensitivity reaction of any grade will be discontinued from study.

Please see Section 5.6.3 for details on the required premedications.

Concurrent Chemotherapy and Bevacizumab:

Patients treated on either Arm may receive concurrent chemotherapy with paclitaxel, docetaxel, pemetrexed, gemcitabine, liposomal doxorubicin or bevacizumab in addition to carboplatin. The decision to use these medications will be left to the discretion of the treating physician. Bevacizumab may be administered with either single agent carboplatin or any carboplatin doublet. The following table describes the recommended dosing, infusion time and schedule for each agent. Modification of all parameters are permitted at the discretion of the Investigator. The cycle length of any liposomal doxorubicin-containing regimen will be 28 days. The cycle length for all other treatment combinations will be either 21 or 28 days, at the discretion of the Investigator.

Suggested Concurrent Chemotherapy Dosing, Infusion Time and Schedule				
Drug	**Dose**	**Infusion Time**	**Cycle Length (Days)**	**Administration Day[b]**
Paclitaxel ("standard" schedule)	135-175mg/m2	3 hours	21[a] or 28	1[b]
Paclitaxel ("weekly" schedule)	60-80mg/m2	1 hour	21[a] or 28	1[b], 8,15[c]
Gemcitabine	800mg/m2	30 minutes	21[a] or 28	1[b], 8
Liposomal Doxorubicin	30mg/m2	Per MSKCC guidelines	28	1[b]
Docetaxel	60-75 mg/m2	1 hour	21 or 28	1[b]
Pemetrexed	375-500 mg/m2	10 minutes	21 or 28	1[b]
Bevacizumab	5-15mg/kg	Per MSKCC guidelines	21 or 28	1[b], 15[d]

a- May be extended to 28 days at discretion of the Investigator
b- For Day 1 of each cycle after Cycle 1, -3/+7 day window is permitted, at the discretion of the Investigator (note: the Investigator may delay Day 1 treatment up to 2 weeks)
c- May be omitted at discretion of the Investigator
d- May be omitted at discretion of the Investigator

Location:

All therapy will be administered in an outpatient setting, under the supervision of a physician and/or chemotherapy nurse, as is standard for chemotherapy administration.

Treatment Course:

Patients will remain on study for up to 8 cycles. Carboplatin will be administered on day 1 of each cycle. Cycles will last 28 days if given in combination with liposomal doxorubicin. The cycle length for all other treatment combinations will be either 21 or 28 days, at the discretion of the Investigator. Dose delays or interruptions (for any reason) of -3 days/+7 days is permitted, at the discretion of the Investigator. The Investigator may delay Day 1 treatment a

maximum of 2 weeks. Any delay/interruption longer than 2 weeks may be considered but the Principal or Co-Principal Investigator must be consulted. If a patient's Day 1 is delayed/interrupted, Day 8 and Day 15 treatments (if applicable) should be scheduled accordingly.

For the secondary endpoint of determining the rate of successful treatment completion in each arm, we will define successful treatment completion if a patient completes at least 5 cycles of carboplatin treatment. If the patient comes off for progressive disease before cycle 5 then the patient would be considered inevaluable for this endpoint. If a patient comes off for any other reason before cycle 5 then the patient would count as a "failure" when calculating treatment completion rates. Discontinuation of non-carboplatin chemotherapy will not be considered "failure." Treatment completion rates will be calculated on evaluable patients.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

		Cycle 1+			
	Pretreatment Evaluation Within 28 Days	**Day 1**[i] +7 Days/- 3 Days	**Day 8**[b] +/- 3 Days	**Day 15**[b] +/- 3 Days	**Post-Study**
Carboplatin		X			
Concurrent Chemotherapy and/or Bevacizumab		X[a]	X[a]	X[a]	
Medical History[c]	X				X
Directed Medical History[d]	X				
Assessment of Baseline Signs/Symptoms	X				
KPS	X	X			X
Height	X				
Weight	X	X			X
Vital Signs[e]	X	X	X	X	X
Physical Exam[f]	X	X			X
Review of Concomitant Medications/ Other Treatments	X	X			X
CBC with differentials and platelets	X	X	X	X	
Comprehensive Metabolic Panel[g]	X	X			
Pregnancy Test[h]	X				
Toxicity Assessment	X	X			X

a-Exact schedule depends on concurrent chemotherapy / bevacizumab defined in Section 9.0
See table "Concurrent Chemotherapy Dosing, Infusion Time and Schedule" in Section 9.1 for details.
b-Only required if patient receiving chemotherapy/bevacizumab on this day
c-Medical history (including demographics, oncologic history, history of other active or resolved disease processes)
d-Directed medical history includes history of drug, food and environmental allergies, history of asthma and history or atopic dermatitis (eczema)
e-Vital signs (temperature, blood pressure, heart rate, respiratory rate)
f- Physical examination including examination of major body systems

g-Comprehensive metabolic panel includes sodium, potassium, glucose, BUN, creatinine, calcium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin.
h-If the patient is of childbearing potential: A serum pregnancy test must be done within 14 days of first treatment per MSKCC guidelines.
i- If screening is completed within 8 days of start, Cycle 1 Day 1 assessments/tests do not need to be repeated.

Clinical Evaluation:
All assessments on day 1 may be performed up to 3 days before the planned start of each cycle (on cycle 1 this may be extended to 8 days before cycle 1, day 1). Patients will have vitals, height (baseline only), weight, KPS, review of concomitant medications, history, physical examination and toxicity assessment recording at this time. Physical evaluation and history will include evaluation for a rash potentially related to carboplatin. Additional nurse or physician visits will be at the discretion of the treating physician.

Laboratory Evaluation:
All laboratory tests on day 1 may be performed up to 3 days before the planned start of each cycle, a CBC with differentials and platelets and comprehensive metabolic panel (including sodium, potassium, glucose, BUN, creatinine, calcium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin). On cycle 1 this may be extended to 8 days before cycle 1, day 1. For regimens including chemotherapy on day 8 and 15, a CBC with differentials and platelets is required prior to each treatment.

For women of childbearing potential: A serum pregnancy test will be performed within 14 days prior to the start of the first cycle in patients of childbearing potential.

Radiologic Evaluation:
As treatment response is not an endpoint for this study, radiologic evaluation will be left to the discretion of the treating physician.

Post-Study Visit:
Following completion of protocol directed treatment, patients will have one post-study visit to assess for any ongoing treatment related toxicity. This evaluation should take place within 3 months of last treatment on study. At this time patients will be assessed with vital signs, KPS, weight, current medications, history, physical exam and toxicity assessment.

11.0 TOXICITIES/SIDE EFFECTS

11.1 Carboplatin Toxicities

Likely

- Fatigue
- Mild nausea or vomiting
- Diarrhea

Less Likely

- Rash
- Numbness, tingling and burning of hands or feet
- Decrease in blood cell counts (white blood cells, red blood cells and platelets)
- Hearing loss or ringing in ears
- Thinning of hair

Rare but Serious

- Allergic reaction, possibly life threatening
- Serious infection

11.2 Paclitaxel Toxicities

Likely

- Fatigue
- Mild nausea or vomiting
- Joint pain and body aches
- Diarrhea
- Temporary loss of hair
- Decrease in blood cell counts (white blood cells, red blood cells and platelets)

Less Likely

- Rash
- Mouth sores
- Numbness, tingling and burning of hands or feet
- Hearing loss or ringing in ears

Rare but Serious

- Allergic reaction, possibly life threatening
- Serious infection

11.3 Gemcitabine Toxicities

Likely

- Fatigue
- Leukopenia
- Thrombocytopenia
- Thinning of hair

Less Likely

- Mild nausea and vomiting
- Pain and irritation along vein during infusion
- Swelling of legs
- Diarrhea
- Constipation
- Mouth Sores

- Rash

Rare but Serious:

- Inflammation of the lungs

11.4 Liposomal Doxorubicin Toxicities

Likely

- Fatigue
- Mild nausea or vomiting
- Pain and irritation along the vein where the drug is given
- Itching, hives, or a red rash at the injection side
- Pink or red urine for the first 48 hours after treatment

Less Likely

- Sensitivity, redness or peeling of the skin on your hands and feet
- Thinning of hair
- Diarrhea
- Mouth sores
- Decrease in blood cell counts (white blood cells, red blood cells and platelets)

Rare but Serious

- Damage to the heart muscle
- Allergic reaction, possibly life threatening
- Serious infection

11.5 Docetaxel Toxicities

Likely

- Fatigue
- Diarrhea
- Hair loss

Less Likely

- Nausea and vomiting
- Mouth sores
- Headache
- Muscle and joint aches
- Ankle swelling
- Rash
- Nail discoloration
- Decrease in blood cell counts (white blood cells, red blood cells and platelets)

Rare but Serious

- Neuropathy
- Allergic reaction

11.6 Pemetrexed Toxicities

Likely

- Low red or white blood cell counts
- Nausea or vomiting
- Constipation
- Loss of appetite

Less Likely

- Low platelet count
- Hair loss
- Diarrhea
- Neuropathy

Rare but Serious

- Severe damage to liver or kidney
- Fever/Infection

11.7 Bevacizumab

Likely

- Hypertension

Less Likely

- Change in voice (hoarseness)
- Proteinuria
- Arthralgia
- Epistaxis

Rare but Serious

- Bowel perforation
- Blood clots
- Transient ischemic attack
- Chest pain
- Allergic reaction causing facial flushing, trouble breathing, low blood pressure

11.8 Management of Adverse Events

All of the therapeutic agents in this trial are commercially available and have FDA approved or NCCN Compendia listed for the treatment of recurrent epithelial ovarian cancer. All treatment combinations are used in routine clinical practice. As a result, the adverse events associated with these treatments will not be collected as part of this protocol. The management of all non-hypersensitivity adverse advents including dose reductions or treatment delays of all agents described in Section 5 are allowed at the discretion of the treating Investigator.

Adverse events collected as part of this protocol include toxicities related to the routine use of premedications and allergic/anaphylaxis hypersensitivity reactions related to carboplatin infusion (the primary endpoint for this study). These adverse events will be graded using the CTCAE Version 4.0 (see Appendix A). These adverse events will be attributed to premedications and carboplatin in the following manner: Definite, Probable, Possible, Unlikely, and Unrelated. Please note that hypersensitivity reactions to carboplatin are typically easy to recognize clinically and occur during the time of carboplatin infusion. Per institutional protocol, carboplatin will not be infused concurrently with other chemotherapy or biologic agents (bevacizumab). It is therefore unlikely there will be difficulty distinguishing carboplatin reactions from paclitaxel, docetaxel, pemetrexed, gemcitabine, liposomal doxorubicin or bevacizumab reactions as these will be temporally separated. Only reactions attributed as definite, probably, possible or unlikely related to carboplatin will count towards the primary endpoint, hypersensitivity rate.

Serious adverse events (SAE) will be reported as described in Section 17.2. A SAE is defined as:

- Is fatal or life-threatening
- Is disabling
- Results in hospitalization or prolongation of hospitalization
- Results in a congenital anomaly or occurrence of malignancy
- Jeopardizes the participant and may require medical intervention to prevent one of the outcomes above

The definition of serious adverse event (experience) also includes important medical event. Medical and scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. The definition of "related" is an adverse event that is attributed as definitely, probably or possibly related to the premedication and/or carboplatin given as part of this protocol. A life-threatening adverse event implies an immediate risk of death from the reaction as it occurred. Life-threatening does not include a reaction that, had it occurred in a more serious form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug induced hepatitis can be fatal.

<u>Hypersensitivity Precautions and Management:</u>
MSKCC guidelines for monitoring and management of hypersensitivity reactions will be observed for all patients treated on study as described in the link below.

http://mskweb5.mskcc.org/intranet/shared/pharmacy/guidelines/Nursing%20Forms/hypersensitivity%20order%20set.htm

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Two outcomes will be assessed: the rate and grade of hypersensitivity reactions to carboplatin and successful completion of planned treatment. These outcomes are defined as follows:

Rate of Hypersensitivity Reactions to Carboplatin: All allergic or anaphylactic reactions to carboplatin of any grade will be counted as an event with exception of reactions attributed as definitely not related to carboplatin.

Successful Completion of Planned Therapy: For the secondary endpoint of determining the rate of successful treatment completion in each arm, we will define successful treatment completion if a patient completes at least 5 cycles of carboplatin treatment. If the patient comes off for progressive disease before cycle 5 then the patient would be considered inevaluable for this endpoint. If a patient comes off for any other reason before cycle 5 then the patient would count as a "failure" when calculating treatment completion rates. Discontinuation of non-carboplatin chemotherapy will not be considered “failure.” Treatment completion rates will be calculated on evaluable patients.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Premature Withdrawals:

Patients who discontinue participation in the clinical study on their own or patients who are withdrawn by the Investigator, for reasons other than those listed below will be defined as premature withdrawals. For the purpose of this study, they will not be considered to have experienced a hypersensitivity reaction but will be considered a “failure” when calculating planned treatment completion (defined as discontinuation of carboplatin treatment prior to 5 cycles for reasons other than disease progression, see Section 12.0 for further details).

Criteria for Stopping Therapy:

- Hypersensitivity Reaction: According to Schema in Section 1.0 and Crossover in Section 9.1
- Substantial non-compliance with the requirements of the study
- Any adverse event which, in the Investigator or treating physician’s opinion, requires termination from the study
- Progression of the underlying cancer unless, at the discretion of the Investigator, continued treatment on the study is deemed appropriate
- Request by the patient or a legal representative/relative to stop the treatment
- The patient uses illicit drugs or other substances that may, in the opinion of the Investigator, have a reasonable chance of contributing to toxicity or otherwise interfering with results
- The development of a second malignancy that requires treatment, which would interfere with this study
- The patient is lost to follow-up
- Treatment delay of greater than 30 days
- Development of an intercurrent illness or situation which would, in the judgment of the

Investigator, affect assessments of clinical status and study endpoints to a significant degree

Criteria for Study Withdrawal:

- Patient decides to discontinue participation in the study. Data generated during their participation in the protocol will be analyzed unless the patient specifically opts to withdraw research authorization.

14.0 BIOSTATISTICS

This is a randomized non-blinded study with the primary objective to determine whether patients treated with extended infusion carboplatin have lower rates of hypersensitivity reaction (HSR) compared to those treated with standard infusion carboplatin. Please refer to Section 15.2 for details regarding randomization. Patients in second or third line treatment setting are eligible. We expect approximately 80% and 20% of patients to be in these two groups respectively. A HSR is defined as any allergic or anaphylactic reaction, regardless of grade, judged unlikely, possibly, potentially or definitely attributed to carboplatin while on study.

Assuming type I error =10%, power 80%, one-sided test aiming to show a decrease from 20% to 5% in HSR rates, the study would require 57 pts in each arm using a test for binomial proportions. Study accrual will be completed in approximately two years assuming 50 pts are accrued per year. Discontinuation from treatment prior to 5 cycles is anticipated to occur very infrequently and therefore patients with early discontinuations will be included in the analysis of the primary endpoint.

Since previous use of carboplatin might affect the HSR rates, randomization will be stratified by previous use of carboplatin (yes/no). The percentage of patients who get at least 1 cycle of carboplatin upfront is 65%, thus we expect each arm to have 37:20 pts in previous carboplatin (yes/no) groups. In addition patients will be stratified based on concurrent paclitaxel or docetaxel use (yes/no). Patients may receive carboplatin alone or in combination with paclitaxel, docetaxel, pemetrexed, gemcitabine, liposomal doxorubicin and bevacizumab at the discretion of the Investigator. No analysis is planned within the taxol stratification factor since we expect this percentage of patients to be small (5-10%).

We will employ continuous significant testing with a significance level=12% to monitor acute reactions (defined as a allergic or anaphylactic reaction of any grade excluding those attributed as definitely not related to carboplatin) within each arm separately and the corresponding stopping boundaries are provided in the table below:

Acceptable Rate of Acute Reactions (Unacceptable rate)	Stopping boundaries Stop if # reactions exceeds (>) the numbers below	Probability of declaring the treatment unsafe due to high number of reactions	Probability of stopping the trial under the unacceptable rate of high number of reactions
15% (≥25%)	5/20 8/30 9/40 13/57	0.69	0.61

For the secondary endpoint of determining the rate of successful treatment completion in each arm, we will define successful treatment completion if a patient completes at least 5 cycles of carboplatin treatment. If the patient comes off for progressive disease before cycle 5 then the patient would be considered inevaluable for this endpoint and will not be included when calculating the secondary endpoint, rate of successful treatment completion. If a patient comes off for any other reason before cycle 5 then the patient would count as a "failure" when calculating treatment completion rates. Discontinuation of non-carboplatin chemotherapy will not be considered “failure.” Treatment completion rates will be calculated on evaluable patients. The rates in the two arms will be compared using two-sample test for binomial proportions.

The analysis of the primary and secondary endpoints will include the 114 evaluable patients that were randomized to each arm prior to crossover. Patients who cross over from Arm A to B will be reported separately both in terms of HSR experience and whether they were able to complete 5 cycles in each arm.

We will perform exploratory analyses to correlate HSR rate within each arm separately to the following: history of drug, food and environmental allergies, history of asthma and history or atopic dermatitis (eczema), number of lifetime platinum cycles, duration since last platinum, and concomitant chemotherapy agent.

Finally, we will also perform a cost-identification analysis to assess the direct medical costs associated with each treatment arm. We will capture the use of all services administered at MSKCC from trial registration to completion of the last cycle of carboplatin. HSRs occur during chemotherapy infusion and are managed immediately within the medical center and as a result, we anticipate that surveying costs outside of MSKCC will be unnecessary. Because the average age of the patients enrolled is anticipated to be 60, health service utilization will be multiplied by unit cost values obtained from Medicare reimbursement schedules for outpatient and inpatient services. Costs will be summed and average direct medical costs estimated for each group. Because cost data are often skewed, we will first examine the distribution of each cost endpoint and apply a non-parametric statistical analysis or other method of handling skewed data as appropriate. The assessment of direct med costs will allow us to perform a limited cost-effectiveness analysis, estimating the incremental cost per HSR.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the written consent/verbal script and a completed Eligibility Checklist must be faxed to PPR.

15.2 Randomization

Patients will be randomized (1:1) to either Arm A: standard 30-minute infusion carboplatin or Arm B: extended 3-hour infusion carboplatin. After all eligibility criteria is established and after consent is obtained, patients will be registered through the Protocol Participant Registration (PPR) system and randomized using the Clinical Research Database (CRDB). Randomization will be accomplished by the method of random permuted block, and patients will be stratified by prior history of carboplatin exposure (yes/no) and concurrent paclitaxel or docetaxel use (yes/no).

Pharmacy will view the patient's randomization assignment in CRDB. The results will not be blinded.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. The data collected for this study will be entered into a secure database (Clinical Research Database – CRDB). Source documentation will be available to support the electronic patient record. The following adverse events will be recorded: allergic hypersensitivity reactions/anaphylaxis, mood disturbance, insomnia, and hyperglycemia. These will be graded using CTCAE Version 4.0 and attributed as Definitely, Probably, Possibly, Unlikely or Unrelated to study treatment. Laboratory data will be tabulated and summarized by descriptive statistics, as well as on the basis of MSKCC specified normal ranges.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*.

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. The patients will be explained the extent of the risks, benefits, toxicities/side effects, alternatives/options for treatment, financial costs/burdens, and the voluntary nature of the study. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines.

Inclusion of Women and Minorities: Because this protocol requires patients to have ovarian, fallopian tube or primary peritoneal carcinoma it will enroll exclusively women. Patients of all races will be accepted into the protocol. Memorial Sloan-Kettering Cancer Center has filed forms HHS 441 (civil rights), HHS (handicapped individual), 639-A (sex discrimination), and 680 (age discrimination); we also take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations.

The proposed study population is as described in section 7.0.

Exclusion of Lactating or Pregnant Women: All women who are being considered for participation in the study and who are child bearing and not surgically sterilized or postmenopausal must be tested for pregnancy within 14 days of the first dose of study medication.

Inclusion of Children in Research

This protocol does not include children younger than the age of 21. Ovary, fallopian tube and primary peritoneal carcinoma rarely occur in this age group.

Benefits: It is possible that this treatment will result in fewer hypersensitivity reactions or shrinkage of the tumor or in a stabilization of an otherwise progressing disease. It is not known, of course, whether these or any other favorable events will occur. It is not known whether this treatment will affect the overall survival of the patients.

Costs: The patient will be responsible for the costs of standard medical care, including all drug administration fees and all hospitalizations, even for complications of treatment.

Incentives: No incentives will be offered to patients/subjects for participation in the study.

Alternatives: For patients with advanced ovarian, fallopian tube or primary peritoneal carcinoma who choose not to participate in this study a range of standard options are available including standard infusion carboplatin, paclitaxel, docetaxel, gemcitabine, liposomal doxorubicin, pemetrexed, topotecan, etoposide, vinorelbine, bevacizumab, palliative surgery or best supportive care. Patients may also be eligible for other investigational studies.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patient's name or any other personally identifying information will not be used in reports or publications resulting from this study.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org containing the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

17.2.1 Sponsor Adverse Events Reporting Definitions

This is not an industry sponsored trial and there is no IND required.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225-49.
2. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 2006;354:34-43.
3. Robinson JB, Singh D, Bodurka-Bevers DC, Wharton JT, Gershenson DM, Wolf JK. Hypersensitivity reactions and the utility of oral and intravenous desensitization in patients with gynecologic malignancies. Gynecol Oncol 2001;82:550-8.
4. Markman M, Kennedy A, Webster K, et al. Clinical features of hypersensitivity reactions to carboplatin. J Clin Oncol 1999;17:1141.
5. Polyzos A, Tsavaris N, Kosmas C, et al. Hypersensitivity reactions to carboplatin administration are common but not always severe: a 10-year experience. Oncology 2001;61:129-33.
6. Morgan JS, Adams M, Mason MD. Hypersensitivity reactions to carboplatin given to patients with relapsed ovarian carcinoma. Eur J Cancer 1994;30A:1205-6.
7. Navo M, Kunthur A, Badell ML, et al. Evaluation of the incidence of carboplatin hypersensitivity reactions in cancer patients. Gynecol Oncol 2006;103:608-13.
8. Schwartz JR, Bandera C, Bradley A, et al. Does the platinum-free interval predict the incidence or severity of hypersensitivity reactions to carboplatin? The experience from Women and Infants' Hospital. Gynecol Oncol 2007;105:81-3.
9. Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, et al. Pegylated Liposomal Doxorubicin and Carboplatin Compared With Paclitaxel and Carboplatin for Patients With Platinum-Sensitive Ovarian Cancer in Late Relapse. J Clin Oncol 2010;28:3323-9.
10. Lee CW, Matulonis UA, Castells MC. Carboplatin hypersensitivity: a 6-h 12-step protocol effective in 35 desensitizations in patients with gynecological malignancies and mast cell/IgE-mediated reactions. Gynecol Oncol 2004;95:370-6.
11. Markman M, Hsieh F, Zanotti K, et al. Initial experience with a novel desensitization strategy for carboplatin-associated hypersensitivity reactions: carboplatin-hypersensitivity reactions. J Cancer Res Clin Oncol 2004;130:25-8.
12. Zanotti KM, Rybicki LA, Kennedy AW, et al. Carboplatin skin testing: a skin-testing protocol for predicting hypersensitivity to carboplatin chemotherapy. J Clin Oncol 2001;19:3126-9.
13. Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol 2008;122:574-80.
14. O'Cearbhaill R, Zhou Q, Iasonos A, et al. The prophylactic conversion to an extended infusion schedule and use of premedication to prevent hypersensitivity reactions in ovarian cancer patients during carboplatin retreatment. Gynecol Oncol 2010;116:326-31.

20.0 APPENDICES

Appendix A: NCI CTCAE Version 4.0, Allergic Reaction and Anaphylaxis Grading

Immune system disorders

	Grade				
Adver.;e Ev ent	1	2	3	4	5
Allergic reacfion	Transie nllflushin!J or ra91, dfever <38 degrsC (<10D 4 deg;rees F); nalention nol indicated	Inlervemion or inf usion inenupfioo indicated; onds promptly to symplomaic treatment (eg., anbrislarrines, NSAIDS- narcotics}; prophyll adic medications indcated for <=2hrs	Prdlonged (e.g., , not rapidly respoosive Go symptomatic medicationandlor bfieii interrupio n of infusion); recurence of symp!oms following initiall illljlrovemeni; hospitalizationindicated lor clinicall sequel ae (eg., renal impairment.	Life-threatening consequences; Illgent interventiorii ndic al ed	Death
Definition: A dsorder characlerized by an adverse l ocal or generalres ponse from exposure to an allergen.					
Anaphyllaxis	-	-	Syllljlfomatc bronchospasm, with or withouturticaria; parenteral interventi011 indicated; a rgy-related edema aioedema; hy pc:ensioo	Life-threatening consequence-s; UJQenll interventio ri ndica!ed	Death
Definition: A dsorder characlerized by an acute i'lfiammatory reacfonre-su-ng from the release of histamine and hislrunine-like substances from masloc'ls, causin g a hypersensitivityimmune response- Oin.ically, ilpres.ents wi1h breathi;n ;difficuly-, dizzines.s, hypotension, cyanosi:s andloss ofconsciousress. andmayllead to cleatl1.					