CITY OF HOPE NATIONAL MEDICAL CENTER
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DEPARTMENT OF MEDICAL ONCOLOGY AND THERAPEUTICS RESEARCH

TITLE: Randomized Pilot Trial of Oral Cyclophosphamide versus Oral Cyclophosphamide with Celecoxib for Recurrent or Persistent Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

CITY OF HOPE PROTOCOL NUMBER/VERSION: IRB # 03092 **VERSION: 08**

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SITE: Ovary, Fallopian Tube, Peritoneum

HISTOLOGY: Adenocarcinoma

STAGE (If applicable): Recurrent

MODALITY: Chemotherapy/Anti-angiogenesis

TYPE: Phase II

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1.0 OBJECTIVES

The objectives of the study are:

1.1. To assess the response rates in patients with recurrent or persistent epithelial ovarian, fallopian tube or primary peritoneal cancer who are treated with oral cyclophosphamide alone or oral cyclophosphamide with celecoxib.

1.2. To assess the time to disease progression in this group of patients.

1.3. To further describe the toxicities of oral cyclophosphamide with or without celecoxib in the above patient population.

2.0 BACKGROUND AND HYPOTHESIS

2.1. Epidemiology

Ovarian cancer is the fifth most common cancer in women in the United States. Among women who develop gynecologic malignancies, ovarian cancer is the most common cause of death. An estimated 25,400 women in the U.S. will be diagnosed in 2003 and 14,300 will die (1).

2.2. Cancer and Angiogenesis

The standard initial therapeutic approach to advanced ovarian cancer includes debulking surgery followed by chemotherapy (2). Combination chemotherapy has been shown to result in higher remission rates, larger numbers of complete responses, and a longer duration of survival compared to single agent chemotherapy (3). Through the late 1980's and early 1990's the standard combination chemotherapy was cisplatin and cyclophophamide. The optimal treatment for patients having residual disease or who relapse after initial therapy remains unclear and many chemotherapeutic approaches have been tried with variable results. As of yet, there is no second-line chemotherapeutic regimen that is considered standard for these patients (4).

Traditional therapeutic strategies for neoplastic diseases have focused on cytotoxic activity directed at the cancer cell. These approaches have achieved relatively limited success despite aggressive treatment with highly toxic regimens (5). Because tumor growth and metastases are dependent upon the development of vascular supply (angiogenesis) (6-8), therapeutic strategies that target the microvasculature are being evaluated clinically (9). Tumor angiogenesis results from a cascade of molecular and cellular events (7) initiated by the release of angiogenic growth factors (10-11). Tumor cells express a variety of proangiogenic growth factors that diffuse in the direction of pre-existing blood vessels (6; 12). These growth factors activate the normally quiescent vascular cells inducing: (i) proteolytic degradation of the basement membrane (13-14); (ii) migration of endothelial cells towards the angiogenic stimulus (15-16); (iii) endothelial cell proliferation (15; 17; 18); (iv) lumen formation (13; 15; 16; 19);

(v) pericyte capping (15; 20-22); and (vi) production of a new basement membrane. Tumors can also acquire vasculature through vasculogenesis, the formation of blood vessels from progenitor endothelial cells, or angioblasts (23-25). Vasculogenesis was previously thought to be restricted to the embryo (26-27), however, circulating stem cells in peripheral blood have been detected that can differentiate into endothelial cells and contribute to angiogenesis in the adult (28-31).

Pharmacological targeting of the microvasculature in patients with neoplasms represents an attractive therapeutic approach because the inhibition of angiogenesis has been shown to prevent growth (32), and can induce regression of experimental solid tumors (33). Recent data suggests that selective inhibitors of cyclooxygenase-2 (COX-2) are potent inhibitors of angiogenesis (34-35) suggesting the potential utility of these agents in oncology.

2.3. COX-2 and Apoptosis

The increased tumorigenic potential of COX-2 overexpressing cells are also thought to be mediated in part by resistance to apoptosis (36). Treatment with selective COX-2 inhibitors has been shown to induce apoptosis in a variety of cancer cells including colon (37-38), stomach (39), and prostate (40). One mechanism for the pro-apoptotic activity of COX-2 inhibitors has been the down-regulation of Bcl-2 (38). The subcellular localization of COX-2 is perinuclear (41-44) providing a possible link between prostaglandins produced by COX-2 and Bcl-2 transcription (45). Although the precise link between prostaglandin production and Bcl-2 synthesis has not been elucidated, it is interesting to speculate on the potential role of COX-2 in the increased expression of Bcl-2 that results in vascular endothelial cell survival. Human microvascular endothelial cells that overexpress Bcl-2 are refractory to the apoptotic and angiosuppressive properties of thrombospondin-1, and appear to participate in a more vigorous and sustained angiogenic response (46). More recently celecoxib, a potent and selective COX-2 inhibitor was shown to induce apoptosis in human prostate cancer cells by blocking Akt activation, independent of Bcl-2 (47). The role of COX-2 in the potential activation of the survival serine threonine kinase, Akt, is unknown but such an interaction would have important implications for angiogenesis as the Akt system is a critical signaling pathway for vascular endothelial cell survival (48-51).

Selective pharmacologic inhibition of COX-2 represents a viable therapeutic option for the treatment of malignancies. These agents appear to be safe, and well tolerated suggesting that chronic treatment for angiogenesis inhibition is feasible (52-57). Because these agents inhibit angiogenesis they should have at least additive benefit in combination with standard chemotherapy (57). Metronomic dosing regimens of standard chemotherapeutic agents without extended rest periods was shown to target the microvasculature in experimental animal models, and result in significant anti-tumor activity. This antiangiogenic chemotherapy

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regimen could be enhanced by the concurrent administration of an angiogenesis inhibitor (58-59). Given the safety and tolerability of the selective COX-2 inhibitors, and the potent antiangiogenic properties of these agents, the combination of antiangiogenic chemotherapy with a COX-2 inhibitor warrants clinical evaluation.

2.4. Chemotherapy, Chemotherapy Scheduling and Antiangiogenesis

Prior to 1996, cyclophosphamide plus cisplatin was the standard therapy with response rates ranging from 60-80%. Complete responses were achieved in women optimally debulked: however, incompletely resected stage III disease only achieved less than 10% long term disease free control (60). Cyclophosphamide alone has been shown to produce response rates of 33% (61). Previous clinical trials have used doses of IV cyclophosphamide ranging from 500 mg to 1000 mg every 3 to 4 weeks (62).

Preclinical studies have demonstrated consistently that combinations of antiangiogenic and chemotherapeutic compounds have synergistic anti-tumor activity (63-64). It has also been reported that chemotherapeutic agents given at certain doses and schedules may themselves exhibit antiangiogenic effects. Cyclophosphamide is a cell-cycle-nonspecific alkylating agent with activity against many solid tumors including breast, lung, head and neck, prostate cancer and sarcoma (67). In murine models it has been found to reduce angiogenesis by inhibition of endothelial cell proliferation (64). In several recent reports continuous low-dose chemotherapy regimens in combination with angiogenesis inhibitors induced sustained tumor regression in animal tumor models (65-66). In a study involving cyclophosphamide, mice were implanted with Lewis lung carcinoma or EMT-6 breast cancer. Cyclophosphamide treatment with a conventional maximum tolerated dose (MTD) regimen only modestly delayed growth of both tumors in mice. In contrast, when cyclophosphamide was administered at lower doses at more frequent intervals (metronomic doses) tumor growth was significantly impaired, although the tumors eventually progressed (65). The relapse though could be prevented by combination therapy involving similar metronomic dosing of cyclophosphamide with the experimental angiogenesis inhibitor TNP-470. In combination, cyclophosphamide and TNP-470 eradicated aggressive, drug-resistant tumors in 32 out of 38 tumor-bearing mice (65).

Previous clinical trials investigating second-line therapy for patients with recurrent ovarian cancer with oral cyclophosphamide have reported activity. Lokich et al have treated 21 patients with oral cyclophosphamide 150 mg/m^2 for 5 days with infusional cisplatin and reported a response rate of 74%. Toxiciity included nephrotoxicity (38%) and neurotoxicity (24%).(68) Continuous oral cyclophosphamide has been used for the treatment of advanced ovarian cystadenocarcinoma with partial and complete remission rate of 76%.(69)

A City of Hope Phase I Trial of oral cyclophosphamide in combination with celecoxib in patients with advanced malignancies has currently completed

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accrual. The recommended phase II doses are: cyclophosphamide 50 mg po daily and celecoxib 400 mg po bid. MTD has not been achieved and this dosing is well tolerated with 1 grade 3 hematologic toxicity. One of two patients with ovarian cancer responded with resolution of pleural nodules and improvement of CA-125. At dose level 4 one patient with malignant mesothelioma and another with chondrosarcoma both have stable disease.

Single agent cyclophosphamide has known activity against ovarian cancer with response rates of approximately 33%(61). The combination of celecoxib (an antiangiogenic compound) with daily oral cyclophosphamide (chemotherapeutic compound with activity in variety of solid tumors and possible antiangiogenic activity) will exploit the possibility of synergistic antiangiogenic and anti-tumor activity of these compounds without apparent overlapping toxicities. Low doses of daily oral cyclophosphamide at 1 mg/kg/day are used in the treatment of rheumatologic disorders with favorable safety profile (70). Based upon the above data this phase II trial has been designed to evaluate oral cyclophosphamide alone or in combination with celecoxib for patients with recurrent or persistent epithelial ovarian, fallopian tube or primary peritoneal cancer.

3.0 DRUG INFORMATION

3.1. Celecoxib

3.1.1. Celecoxib (Celebrex) is a selective COX-2 inhibitor approved for use in the treatment of osteoarthritis and rheumatoid arthritis.

3.1.2. Dosing information: An oral dose of 100 or 200 milligrams (mg) twice daily is effective in rheumatoid arthritis and osteoarthritis.

3.1.3. Pharmacokinetics: Peak plasma levels occur within 2 hours of an oral dose, and bioavailability is enhanced with a high fat meal. The elimination half-life of celecoxib is approximately 10 hours.

3.1.4. Caution: Headache, dizziness, and minor gastrointestinal disturbances have been reported. Gastrointestinal ulceration or inhibition of platelet aggregation, were not observed with celecoxib in short-term studies.

3.1.5. Clinical applications: celecoxib has demonstrated short-term efficacy in rheumatoid arthritis and osteoarthritis of the knee; the cyclooxygenase-2 selectivity of this agent may reduce the risk of gastrointestinal ulceration and platelet and renal dysfunction compared to traditional nonsteroidal anti-inflammatory agents although this requires confirmation in long-term studies.

3.1.6. Precautions

– Conditions predisposing to gastrointestinal events (history of peptic ulcer, upper gastrointestinal disease, ulcerative colitis, smoking, advancing age, concurrent corticosteroids, alcohol abuse, stress)

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- Patients with bleeding disorders (potential exacerbation)
- Patients with hypertension or other cardiovascular disease (potential for fluid retention)
- Liver disease (pharmacokinetic data lacking)
- Renal impairment (pharmacokinetic data lacking; potential adverse renal effects, particularly in the elderly)
- History of allergic phenomena related to ingestion of other nonsteroidal anti-inflammatory drugs

3.1.7. Adverse Reactions

3.1.7.1 Hematologic Effects

Results of effects on platelets and bleeding time in larger clinical trials have not been published. No significant effect on platelet function, bleeding time or thromboxane B2 levels was observed with doses up to 1200 mg daily in short term (7- to 10-day) studies involving healthy subjects

3.1.7.2 Central Nervous System effects

Headache and dizziness have been reported in short-term studies.

Gastrointestinal Effects

Abdominal discomfort and changes in bowel habits (unspecified) have been reported in short-term studies. In limited endoscopic studies (one week), celecoxib 100 or 200 mg twice daily was not associated with peptic ulceration. Significant adverse gastrointestinal events were not observed in short-term phase II studies.

Data regarding gastrointestinal toxicity (including endoscopic evaluations) from large trials of longer duration are unavailable. Another selective cyclooxygenase-2 inhibitor, melxicam, has been associated with gastrointestinal perforation, ulcer, or bleeding in some patients. It is unclear if the lower cyclooxygenase-2: cyclooxygenase-1 ratio of celecoxib will confer greater safety.

Cardiovascular Effects

FDA Alert 12/17/04: Based on emerging information, including preliminary reports from one of several long term National Institutes of Health (NIH) prevention studies, the risk of cardiovascular events (composite endpoint including MI,

CVA and death) may be increased in patients receiving Celebrex. FDA will be analyzing all available information from these studies to determine whether additional regulatory action is needed.

3.2. Cyclophosphamide (Cytoxan®)

3.2.1. Cyclophosphamide is an alkylating chemotherapeutic agent used in the treatment of variety of solid and hematologic malignancies and autoimmune disorders.

3.2.2. Clinical pharmacology:

Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites by a mixed function microsomal oxidase system. These metabolites interfere with the growth of susceptible proliferating malignant cells. The mechanism of action is thought to involve cross-linking of tumor cell DNA. Cytoxan is well absorbed after oral administration with a bioavailability greater than 75%. The unchanged drug has an elimination half-life of 3 to 12 hours.

It is eliminated primarily in the form of metabolites, but from 5 to 25% of the dose is excreted in urine as unchanged drug. Several cytotoxic and noncytotoxic metabolites have been identified in urine and plasma. Concentrations of metabolites reach a maximum in plasma 2 to 3 hours after an intravenous dose. Plasma protein binding of unchanged drug is low but some metabolites are bound to an extent greater than 60%. It has not been demonstrated that any single metabolite is responsible for either the therapeutic or toxic effects of cyclophosphamide. Although elevated levels of metabolites of cyclophosphamide have been observed in patients with renal failure, increased clinical toxicity in such patients has not been demonstrated.

3.2.3. Indications and Usage:

Malignant diseases - The following malignancies are often susceptible to cyclophosphamide treatment: malignant lymphomas, multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, carcinoma of the ovary, head, and lung, retinoblastoma, and sarcomas.

3.2.4. Toxicities: Alopecia, nausea, vomiting, stomatitis, diarrhea, skin rash, pancytopenia, sterility, decreased gonadal function, hemorrhagic cystitis, syndrome of inappropriate antidiuretic hormone secretion, immune suppression, interstitial pulmonary fibrosis, leukemogenic potential, and at extremely high doses, myocardial necrosis.

3.2.5. Pharmaceutical Data: Cyclophosphamide is available in 100 mg, 200 mg, and 500 mg ampules containing white powder. The drug can be

reconstituted in normal saline or 5% dextrose and water. The drug should be dissolved and given in approximately 250 cc of diluent as rapid iv infusion over 1 hour. It is also available in 25 and 50 mg tablets.

3.2.6. Stability: Store at room temperature. Do not store at temperatures above 90 degrees F.

4.0 STAGING CRITERIA

4.1. Staging will be according to accepted criteria developed by the American Joint Committee on Cancer as specified below and will be used to determine initial stage for descriptive purposes:

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor

T1 Tumor limited to the ovaries
T1a Tumor limited to one ovary; capsule intact, no tumor on ovarian surface
T1b Tumor limited to both ovaries; capsules intact, no tumor on ovarian surface
T1c Tumor limited to one or both ovaries with any of the following: capsule ruptured, tumor on ovarian surface, malignant cells in ascites, or peritoneal washing

T2 Tumor involves one or both ovaries with pelvic extension
T2a Extension and/or implants on uterus and/or tube(s)
T2b Extension to other pelvic tissues
T2c Pelvic extension (2a or 2b) with malignant cells in ascites or peritoneal washing

T3 Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph node metastasis
T3a Microscopic peritoneal metastasis beyond pelvis
T3b Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension
T3c Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis

Regional Lymph Nodes (N):

Regional lymph nodes include hypogastric, (obturator), common iliac, external iliac, internal iliac, lateral sacral, para-aortic, and inguinal.

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

Distant Metastasis (M)

MX Presence of distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis (excludes peritoneal metastasis)

Stage Grouping		T	N	M
Stage	IA	T1a	N0	M0
	IB	T1b	N0	M0
	IC	T1c	N0	M0
Stage	IIA	T2a	N0	M0
	IIB	T2b	N0	M0
	IIC	T2c	N0	M0
Stage	IIIA	T3a	N0	M0
	IIIB	T3b	N0	M0
	IIIC	T3c	N0	M0
		Any T	N1	M0
Stage	IV	Any T	any N	M1

*T = Tumor description, N = Node status; M = Metastases

5.0 ELIGIBILITY CRITERIA

5.1. Inclusion Criteria

5.1.1. Patients with recurrent or residual epithelial ovarian, Fallopian tube, or primary papillary peritoneal cancer, which has been histologically confirmed regardless of prior treatment.

5.1.2. Patients with measurable disease or rising CA-125 to levels at least twice normal. The CA-125 increase must be documented by two independent measurements at least 4 weeks apart.

5.1.3. Patient must have adequate renal function documented by a creatinine < 1.5

5.1.4. Patients must have adequate bone marrow function as evidenced by an absolute neutrophil count of >1.5 x10^9 /L and a platelet count>100 x 10^9 /L.

5.1.5. Patients must have a Karnofsky performance status of 60-100%.

5.1.6. Patients must be at least 18 years of age.

5.1.7. Patient must be capable of understanding the nature of the trial and must give written informed consent.

5.1.8. Patients must have life expectancy of at least three months.

5.1.9. Patients with brain metastases which at the time of study enrollment are controlled and do not require treatment with corticosteroids are eligible.

5.2. Exclusion Criteria

5.2.1. Patients who have had radiotherapy or chemotherapy within three weeks prior to anticipated first day of dosing. Patients must be fully recovered from the acute effects of any prior chemotherapy or radiotherapy.

5.2.2. Patients with unstable or severe intercurrent medical conditions or active, uncontrolled infection.

5.2.3. Patients with a history of allergic reactions to non-steroidal anti-inflammatory drugs.

5.2.4. Patients with history of bleeding peptic ulcer within last 3 months.

5.2.5. Patients undergoing therapy with other investigational agents. Patients must have recovered from all acute effects of previously administered investigational agents and sufficient time must have elapsed since last administration to ensure the drug interactions not occur during this study.

5.2.6. Patients who are allergic to sulfa drugs.

5.2.7. Pregnant women will be excluded from this study due to the potential of harm to the fetus.

5.2.8. Patients with clinically significant cardiovascular disease (e.g. uncontrolled hypertension, myocardial infarction unstable angina), New York heart association grade II or greater congestive heart failure, serious cardiac arrhythmia requiring medication, or grade II or greater peripheral vascular disease. within 1 year prior to study entry. Subjects with hypertension are eligible if their blood pressure h as been normal while on a stable dose of medication for at least one year.

6.0 TREATMENT PLAN

6.1. Patients will be randomized to one of two treatment arms. Arm A consists of oral cyclophosphamide 50 mg daily (each cycle will be 4 weeks) and Arm B consists of oral cyclophosphamide 50 mg daily and celecoxib 400 mg twice daily.

Treatment Schedule:

ARM A

Cyclophosphamide 50 mg po daily

ARM B

Cyclophosphamide 50 mg po daily

Celecoxib 400 mg po twice daily

Cyclophosphamide ----------

Celecoxib ----------

Week 1 Week 2 Week 3 Week 4 Week 1 ……
CYCLE 1 CYCLE 2

6.2. Duration of Therapy

The treatments will continue for all patients having adequate renal and bone marrow as defined for patient eligibility (Sections 5.1.3, 5.1.4). Those patients requiring temporary discontinuation of protocol therapy due to toxicity may have treatment resumed upon resolution of toxicities to ≤ grade 2 using CTCv2.0. A treatment may be stopped for up to 21 days to allow for recovery from toxicities. Patients unable to safely resume treatment at that point will be taken off study.

Criteria for Removal From Treatment

6.2.1. Disease progression.

6.2.2. Treatment delay > 3 weeks.

6.2.3. Unacceptable toxicity.

6.2.4. The patient may withdraw from the study at any time for any reason.

6.3. Patients may not receive concurrent therapy with any other investigational drug, or any other antineoplastic therapy. Standard medical care for the health and comfort of the patient is appropriate.

6.4. After discontinuation of treatment patients will be followed per good medical practice and follow-up information including potential long-term side effects will be obtained until patients' death.

7.0 TOXICITIES MONITORED AND DOSAGE MODIFICATIONS

7.1. Patients will be examined and graded at least once every 4 weeks for subjective/objective evidence of toxicities according to NCI CTC v2.0 which can be found at the CTEP website: http://ctep.info.nih.gov. (see Appendix A).

7.2. Management of Anticipated Toxicities

No hematologic toxicities and neuropathy are expected with celecoxib. Diarrhea, gastritis and gastrointestinal bleeding may occur at higher doses of celecoxib. Toxicities of daily oral cyclophosphamide may include neutropenia, cystitis and alopecia.

7.2.1. Management of celecoxib toxicities

7.2.1.1 Celecoxib has not been reported to cause significant hematologic toxicity. Therefore, no dose modifications in the study drug are required for hematologic toxicity which should be attributed to cyclophosphamide.

7.2.1.1 Non-hematologic toxicity

Grade 1-2 diarrhea will be treated with antidiarrheal agent per investigator's choice, grade 1-2 gastritis will be treated with antacid, H_2 blocker or proton inhibitor per investigator's choice.

7.2.1.1 Other Toxicities

The investigator must use the available data and clinical judgement in deciding whether an adverse event is attributable to celecoxib. The following modifications should be followed in the event of celecoxib-related toxicity:

Grade	Percent of full dose of celecoxib
0-2	100%
3	Hold
4	Hold

7.2.2. Management of Toxicities of Cyclophosphamide

Interruption or delays in the administration of cyclophosphamide will be allowed for up to 3 weeks. In the event of toxicities attributable to

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celecoxib, no dose modification of cyclophosphamide will be required, however, cyclophosphamide will be held until resolution of toxicities (grade ≤2) allows restarting of treatment with cyclophosphamide.

7.2.3. Hematologic Toxicity

The following modifications should be followed for cyclophosphamide-related hematologic toxicity:

Absolute neutrophil count ($x10^6$/L)	Platelets ($x10^6$/L)	Cyclophosphamide dose
≥ 1500	≥ 100,000	100% dose
< 1500	<100,000	*Hold

* Delay treatment for up to 3 weeks. If toxicities have not resolved in 3 weeks then the patient is removed from the protocol. Once toxicities resolve, if the nadir ANC < 300 or platelet count < 30,000 then cyclophosphamide 50 mg will be given every other day. If the hematologic toxicities recur then the patient will be removed from the protocol.

7.2.4. Non-Hematologic Toxicities

Non-hematologic toxicities of cyclophosphamide include fatigue, nausea, vomiting, alopecia, cystitis. The following modifications should be followed in the event of cyclophosphamide-related non-hematologic toxicity (excluding alopecia):

Grade	Cyclophosphamide dose
0-2	100 % dose
3	*Hold
4	*Hold

* If toxicities have not resolved in 3 weeks then the patient is removed from the protocol.

8.0 DATA SAFETY AND MONITORING

8.1. Definition of Risk Level

This is a Risk Level 3 study, as defined in the "Guidance, Policy and Procedures for Data and Safety Monitoring for In-House Trials at City of Hope", http://www.infosci.coh.org/gcrc/doc/dsmp.doc because it is a pilot Phase II clinical trial where the risks are balanced by the potential benefit to subjects and the importance of the knowledge that may result.

8.2 Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT) consisting of the PI, Collaborating Investigator, CRA, protocol nurse, and statistician is responsible for monitoring

the data and safety of this study, including implementation of any stopping rules for safety and efficacy.

Data and safety will be reported to the COH DSMB. Protocol specific data collection will be analyzed at the interim accrual goal for each arm (13 patients). In addition, reporting of data and safety to the DSMB will occur annually using the PMT report.

8.3 Adverse Events

Reporting: Adverse events must be reported to the COH DSMB, IRB and GCRC according to definitions and guidelines at http://www.infosci.coh.org/gcrc/doc/dsmp.doc and http://resadmin.coh.org/doc/irb3810.doc, which are defined below. AEs will be monitored by the PMT. Less than serious adverse events will be reported only at the time of protocol continuation reports. This study will use the Common Toxicity Criteria version 2 (http://ctep.cancer.gov/reporting/CTC-3test.html) to evaluate and grade adverse events

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Adverse Event - An adverse event (AE) is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention. All AEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be recorded on the City of Hope National Medical Center Adverse Events (COH AER) form (http://resadmin.coh.org/doc/irb3820.doc).

Serious Adverse Event- A serious adverse event (SAE) is defined as *any expected or unexpected adverse event* (AE, generally equivalent to CTCAE grades 3, 4 or 5) that is *related or unrelated* to the intervention that results in any of the following outcomes:

- Death
- A life-threatening event
- In-patient hospitalization (not required as part of the treatment) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Causes cancer
- Is an overdose

Certain medical events that may not result in death, be life-threatening, or require hospitalization, may also be considered a serious adverse event when appropriate medical or surgical intervention is necessary to prevent one of the outcomes listed above.

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Unexpected Adverse Event – Any event in which the severity or specificity is not consistent with the risk information described in the protocol, and the event is not anticipated from the subject's disease history or status.

Expected Adverse Event - Any event in which the severity or specificity is consistent with the risk information described in the protocol or is anticipated based on the subject's medical history.

Attribution - For reporting purposes, attribution is the assessment of the likelihood that an AE is caused by the research agent or protocol intervention. The attribution is assigned by the Principal Investigator after considering the clinical information, the medical history of the subject, and past experience with the research agent/intervention. This is recorded using the Adverse Event Report (COH AER) form (http://resadmin.coh.org/doc/irb3820.doc) in one of 5 categories scored as the following: 5=related, 4=probably related, 3=possibly related, 2=unlikely related and 1=unrelated. The attribution is subject to change as follow-up information becomes available, and it can be changed by the DSMB or by the IRB in the process of review.

9.0 STUDY PARAMETERS AND CALENDAR

Assessment	Prior to Therapy	Approx Day 15	Each cycle (every 4 weeks)	Every 2 cycles (every 8 weeks)
History and Physical Exam	X	X [1]	X	
Weight and KPS	X	X [1]	X	
Toxicity using CTC v2.0		X [1]	X	
CBC, Diff, Plts, Na, K, Cl, CO_2, Creatinine, BUN, glucose, Calcium, phosphorus, albumin, LDH, SGPT(ALT),SGOT (AST), Alkaline Phos, Total Bilirubin	X X	X [1]	X X	
Urine Pregnancy Test (if applicable)	X			
EKG	X			
Chest X-Ray,	X			
Tumor markers (if applicable)	X		X	
Tumor Measurements (if applicable)	X			X

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[1]During cycle #1

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1. Disease Status

10.1.1. Measurable disease: Lesions that can be accurately measured in at least one dimension by 1) plain x-ray, CT, MRI or other imaging technique with longest diameter greater than 2 cm or 2) spiral CT with longest diameter 1 cm or greater.

10.1.2. Non-measurable disease: All other lesions including lesion too small to be considered measurable (longest diameter < 2 cm with conventional techniques or < 1 cm with spiral CT), pleural or pericardial effusions, ascites, bone disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed or followed by imaging techniques and cystic lesions. (CA-125, a marker, which has been shown to be highly correlated, with extent of disease is also considered to be evaluable.)

10.2. Objective Status at each evaluation: All measurable lesions up to a maximum of ten lesions representative of all involved organs should be identified as target lesions at baseline. If there are more than ten measurable lesions, the remaining are identified as non-target lesions and are included as non-measurable disease. Measurements must be provided for target measurable lesions while presence or absence must be noted for non-target measurable and non-measurable disease

10.2.1. Complete response (CR): Complete disappearance of all measurable and non-measurable disease. No new lesions. No disease-related symptoms. Normalization of CA-125 and other abnormal lab values. All measurable and non-measurable lesions must be assessed using the same technique as baseline.

10.2.2. Partial response (PR): Defined by either of two sets of criteria outlined below:

1) Greater than or equal to 30% decrease under baseline of the sum of the longest diameters of all target measurable lesions with no new lesions. No progression of non-measurable disease. All measurable and non-measurable lesions must be assessed using the same technique as baseline.

2) A decline in CA-125 by at least 50% confirmed by a second CA-125 four or more weeks later. The reference CA-125 should be measured within 3 weeks prior to starting therapy. No progression of measurable or non-measurable disease during this time period.

10.2.3 Stable: Does not qualify for CR, PR, or progression. All measurable and evaluable sites must be assessed using the same techniques as baseline.

10.2.4 Progression: One or more of the following must occur: 20% increase in the sum of the longest diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using same techniques as baseline. Increase in CA-125 by at least 25% on two sequential measurements 4 weeks apart. Increasing CA-125 alone in patients with coexisting measurable disease shall not define progression when accompanied by responding or stable measurable disease. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration.

10.2.5 Symptomatic deterioration: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

10.2.6 Assessment inadequate, objective status unknown: Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

10.3 Best Response: Calculated from the sequence of objective statuses

a) CR: Two or more objective statuses of CR a minimum of 4 weeks apart documented before progression or symptomatic deterioration.

b) PR: Two or more objective statuses or PR or better a minimum of 4 weeks apart documented before progression or symptomatic deterioration but not qualifying as CR.

c) Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d) Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR. Or unconfirmed CR.

e) Stable: At least one objective status of stable / no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f) Increasing disease: Objective status of progression or symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

g) Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 Time-Related Endpoint Definitions

10.4.1 Survival: Defined as the time from registration to time of death due to any cause. If a patient is not known to have died, survival time is censored at the time of last follow-up.

10.4.2 Progression-free survival: Defined as the time from registration to the first observation of disease progression or death due to any cause. If a patient has not progressed or died, progression-free survival is censored at the time of last follow-up.

10.4.3 Time to treatment failure: Defined as the time from registration to the first observation of disease progression, death due to any cause, or early discontinuation of treatment. If failure has not occurred, failure time is censored at the time of last follow-up.

11.0 STATISTICAL CONSIDERATIONS

Once all pretreatment evaluations have been completed and informed consent obtained, the patient will be registered in the study. The Department of Biostatistics will randomly assign each patient to one of two arms as described above.

Each arm of this randomized pilot trial will be conducted independently. Responders will include patients with best response as either PR, CR, PRNM, or Stable disease. Simon's Two-Stage minimax Phase II design will be used for each arm. We will assume that a true response rate of 20% would warrant further study for an arm, while a true response rate of less than 5% would not warrant any further study of that arm. For each arm, the first stage of accrual will consist of 13 patients. If no responses are seen, that arm will stop accrual, with the conclusion that the regimen is not promising for further study. Provided that one or more responses are observed in the first 13 evaluable patients, continuation of that arm will continue, and an additional 14 evaluable patients will be accrued to that arm during the second stage of accrual. Four or more responses out of the 27 patients will be considered evidence that the regimen warrants further study, provided that other factors such as toxicity and survival also appear to be favorable. Using this design, the probability of correctly declaring that an arm with a true response rate of 20% warrants further study is 0.80 (power), and the probability of falsely declaring that an arm with only a 5% true response rate warrants further study is 0.05 (alpha).

At the conclusion of the conduct of this study, there are four distinct possibilities. Neither arm may prove promising, one arm may prove promising while the other does not, or both arms may prove promising. In the last scenario, the decision on which arm to pursue will be made based on a simple play-the-winner rule, assuming all other factors appear equivalent. In that case, under the null hypothesis of equivalence, there is equal probability of choosing each arm. However, if one arm has a true response rate of 20%, and the other arm a true response rate of 34%, there is an 80% probability of choosing the correct arm.

Exact 95% confidence intervals will be calculated for response rates, and time to treatment failure, duration of response and survival will be estimated using the product-limit method of Kaplan and Meier. Toxicity information recorded will include the type, severity, course at onset, and the probable association with the study regimen. Tables will be constructed to summarize the observed incidence by severity and type of toxicity.

12.0 REGISTRATION GUIDELINES

Registration will be done at City of Hope.

Note: Following registration, randomization will be carried out by Biostatistics at (626) 359-8111, ext. 62468

12.1. Procedures for On-Study and Treatment Deviations

The PI must approve all waivers (i.e.deviations in eligibility) prior to patient registration, and all treatment deviations prior to treatment. The treating physician must contact the PI. Upon approval, the PI must submit an amendment to the protocol to the IRB.

13.0 DATA COLLECTION FORMS AND SUBMISSION SCHEDULE

All data will be collected using COH Biostatistics Information Tracking System (BITS) data collection forms. The completed forms will be submitted to data entry and stored in a secure location.

13.1. The Protocol Nurse will complete the Eligibility Checklist Worksheet at the time of registration.

13.2. Patient Consent Form: At the time of registration, three signed and dated copies of the patient Informed Consent form and the Experimental Subject's Bill of Rights for Treatment Studies must be available for the patient, the patient's medical chart and the Biostatistics Office.

13.3. Confidentiality of Records: The forms will be kept in secure cabinets in the Department of Biostatistics.

13.4. Within four weeks of completion of each course of treatment, the data manager must complete the following:

13.4.1 Within two weeks of registration, the data manager will complete the On-Study Form (Form OS).

13.4.2 Treatment and Adverse Event Form

13.4.3 Supplemental Data Form (if applicable)

13.4.4 Flow Sheets (These are to be submitted along with each treatment form.)

13.4.5 Each time a patient is evaluated for response and/or new follow-up information is obtained the data manager will complete the Response/Off-Study/Follow-Up Form.

14.0 MINORITIES AND WOMEN STATEMENT

This is a Phase II trial in patients with recurrent ovarian, Fallopian tube, or primary peritoneal cancer. As such, only women will be enrolled. Patients of all racial/ethnic groups are eligible for this study if they meet the eligibility criteria outlined in Section 5.0. To date, there is no information that suggests that differences in drug metabolism or disease response would be expected in one group compared to another. Efforts will be made to accrue a representative sample. If differences in outcome appear to be associated with ethnic identity, then a follow-up study will be designed to investigate those differences more fully.

15.0 ETHICAL AND REGULATORY CONSIDERATIONS

All institutional, NCI, Federal, and State of California regulations concerning the Informed Consent form will be fulfilled.

16.0 PATHOLOGY REVIEW

All patients will have advanced malignancy confirmed by review of their biopsy specimens by the Division of Pathology of the City of Hope National Medical Center.

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