A PILOT PROSPECTIVE TRIAL OF GENOMIC DIRECTED SALVAGE CHEMOTHERAPY WITH EITHER LIPOSOMAL DOXORUBICIN OR TOPOTECAN IN RECURRENT OR PERSISTENT OVARIAN CANCER WITHIN 12 MONTHS OF PLATINUM-BASED CHEMOTHERAPY.

Coordinating Center: H. Lee Moffitt Cancer Center and Research Institute

Study Chair/PI: Robert M. Wenham, MD, MS
H. Lee Moffitt Cancer Center and Research Institute
12902 Magnolia Drive
Tampa, FL 33612
Ph: 813-745-7205
Fax: 813-745-7228
E-Mail: ROBERT.WENHAM@MOFFITT.ORG

Co-Principal Investigators: Johnathan M. Lancaster, MD, PhD
H. Lee Moffitt Cancer Center and Research Institute
12902 Magnolia Drive
Tampa, FL 33612
Ph: 813-745-4734
Fax: 813-745-7228
E-Mail: JOHNATHAN.LANCASTER@MOFFITT.ORG

Ardeshir Hakam, MD
H. Lee Moffitt Cancer Center and Research Institute
12902 Magnolia Drive
Tampa, FL 33612
Ph : 813-745-1874
E-Mail : ARDESHIR.HAKAM@MOFFITT.ORG

Biostatisticians : Steven Eschrich, PhD
Bioinformatics Core Division
H. Lee Moffitt Cancer Center & Research Institute
Tampa, FL 33612
Ph : 813-745-1303
E-Mail: Steven.eschrich@Moffitt.org

William T. Barry, PhD
Biostatistics and Bioinformatics
Duke Institute for Genome Science and Policy
Duke University Medical Center
Durham, NC 27705
(919) 681-5047
Fax:(919) 668-9335
E-mail: bill.barry@duke.edu

Sub-Investigators: Angeles Alvarez-Secord, MD
Division of Gynecologic Oncology
Duke University Medical Center Box 3079
Durham, NC 27710
(919) 684-3247
Fax: (919) 684-8719
E-Mail: secor002@mc.duke.edu

Sachin Apte, MD, MS
H. Lee Moffitt Cancer Center and Research Institute
12902 Magnolia Drive
Tampa, FL 33612
Ph: 813-745-7205
Fax: 813-745-7228
E-Mail: SACHIN.APTE@MOFFITT.ORG

Responsible Data Manager: Sierra Theodore, RN, CCRC
Gynecologic Oncology Clinical Trials Coordinator
H. Lee Moffitt Cancer Center and Research Institute
12902 Magnolia Drive
Tampa, FL 33612
Ph: 813-745-7272
Fax: 813-745-5860
E-Mail: SIERRA.THEODORE@MOFFITT.ORG

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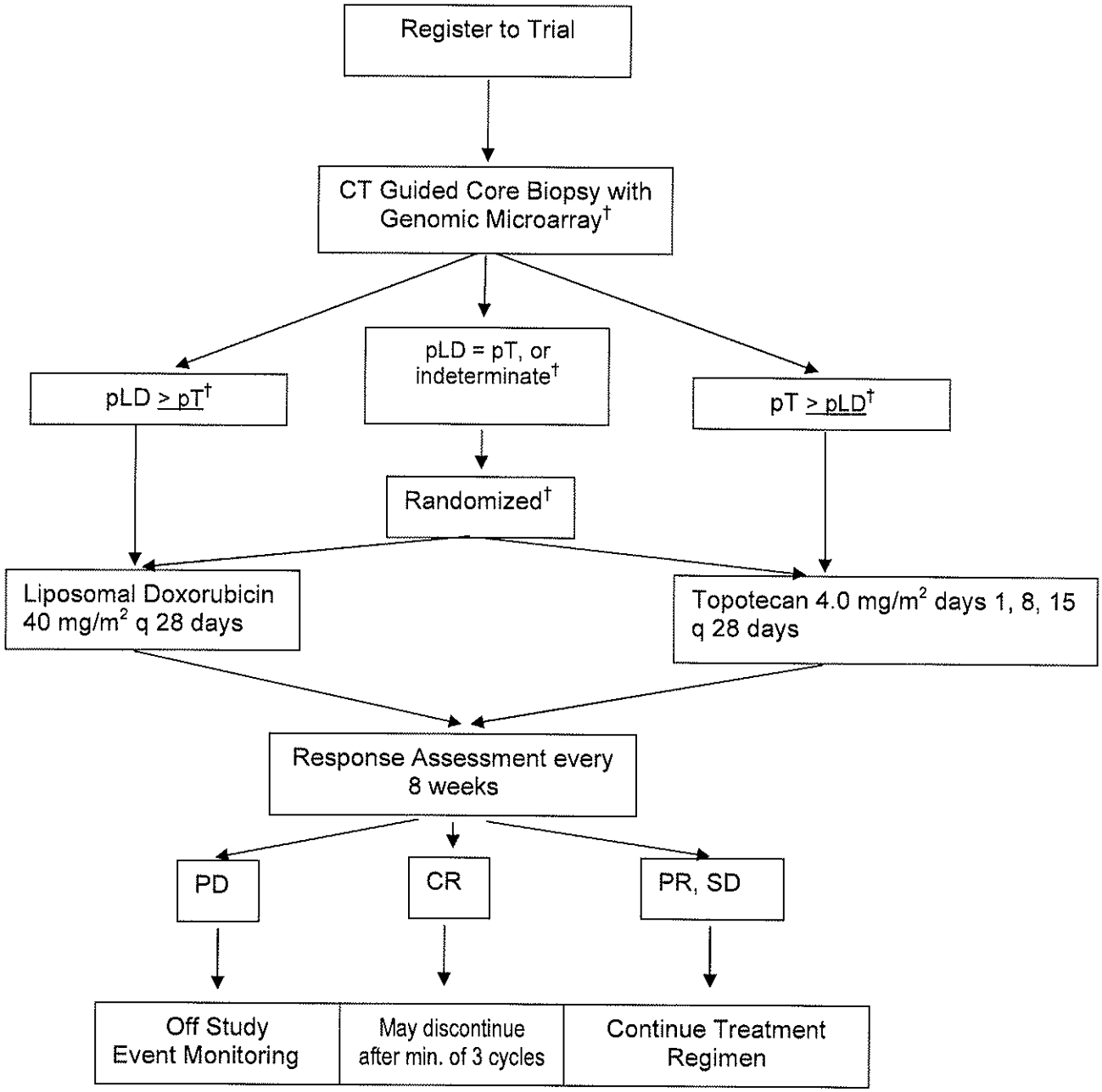
Amendment # 15

TREATMENT SCHEMA



Female patients ≥ 18 yo with recurrent ovarian cancer 0 to 12 months from initial platinum based chemotherapy.

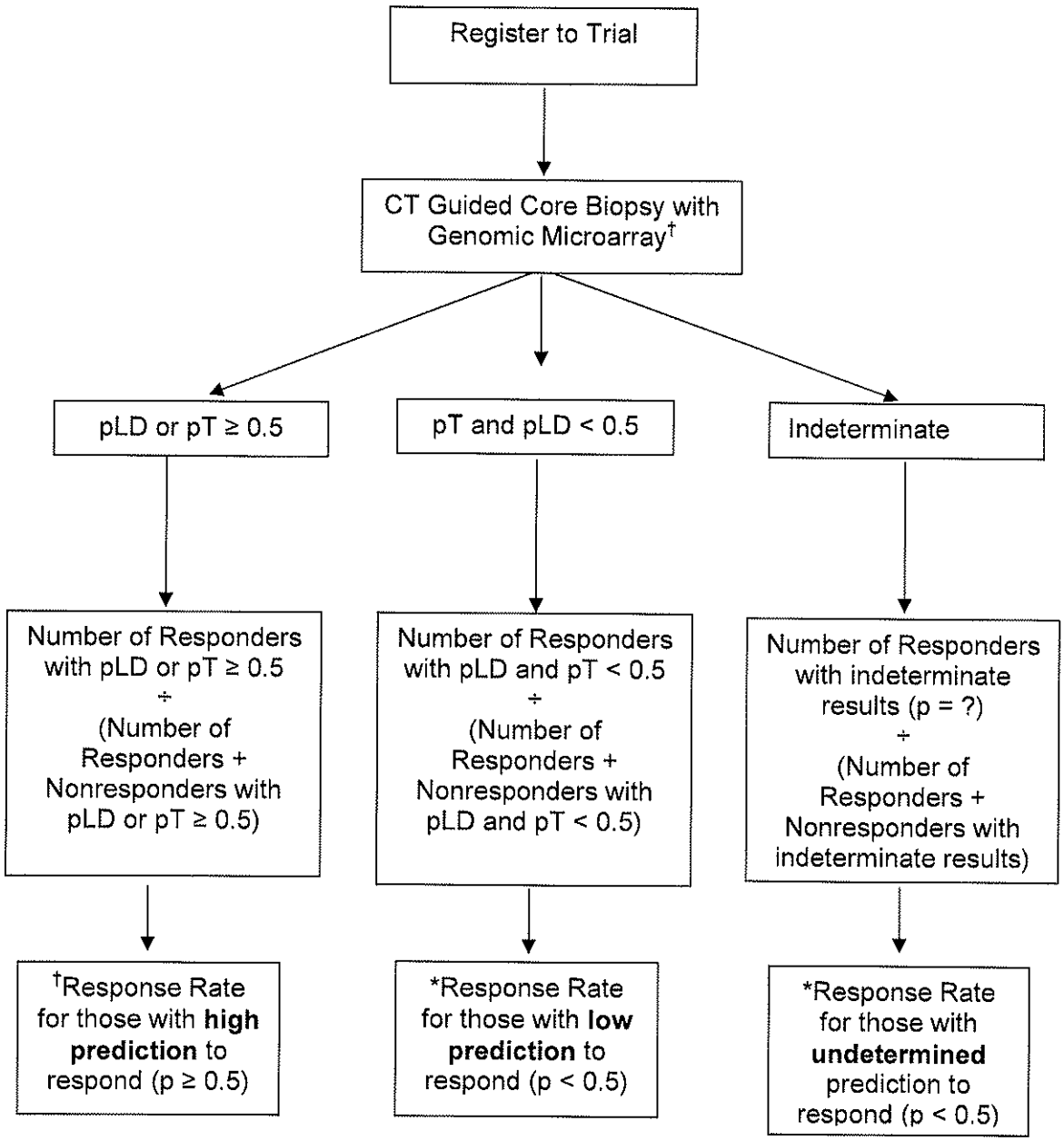
**Full inclusion/exclusion criteria can be found in the protocol.*

Primary Endpoint: Determine the feasibility of a large genomic-directed trial with similar design in ovarian cancer.
†Secondary Endpoints: Response Rate for patients with predictive values ≥ 0.5. and evaluate accuracy of genomic predictions.

pLD = probability of response to liposomal doxorubicin
pT = probability of response to topotecan
PD = progressive disease, CR = complete response, PR = partial response, SD = stable disease.

†Results of Genomic Array Blinded until analysis.

ANALYSIS SCHEMA



Responder = (CR or PR)

Primary Endpoint: Determine the feasibility of a large genomic-directed trial with similar design in ovarian cancer.

†Secondary Endpoint: Response Rate for patients with predictive values ≥ 0.5 and evaluate accuracy of genomic predictions.

*Other analyses are not included in study primary other secondary end points due to power considerations but will be calculated for descriptive purposes only.

pLD = probability of response to liposomal doxorubicin
pT = probability of response to topotecan
PD = progressive disease, CR = complete response, PR = partial response, SD = stable disease.
N = number of patients = 30

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1. OBJECTIVES

1.1. Primary protocol objective:

Determine the feasibility of a large genomic-directed trial with similar design in ovarian cancer.

The primary endpoint for this study is to assess the feasibility of performing an array predicted trial in ovarian cancer patients. A descriptive analysis will be done looking at the success in generating rapid, interpretable genomic array prediction data from biopsied tissue in ovarian cancer patients. From time of consent, biopsy should be obtained within 5 days. The estimated turnaround time for the expression profile is 7-10 days. Including handling time and other factors, a benchmark for success will be that patients will have the information and be able to start treatment within 3 weeks of enrolling on study. We further are anticipating that at about two-thirds (66%) of enrolled patients will have biopsiable tumor in sufficient quantity and quality that will result in an interpretable genomic array. Therefore, we would consider markers of feasibility for a larger trial using genomic directed therapy from biopsies in recurrent ovarian cancer to be:

1. > 60% interpretable genomic arrays leading to successful prediction profiles.
2. >80% of genomic assay results to be within the 3 week time period from enrolling on study.

1.2 Secondary protocol objectives

1.2.1. Determine response rate of array directed chemotherapy (as defined as the proportion of patients achieving complete or partial responses with a predictive score ≥ 0.5 for either chemotherapy)

The chief secondary endpoint is to determine the overall response rate (ORR = CR+PR) for those with a high predictive likelihood of response (defined as the ratio of patients with a CR or PR who had high predictive scores for response to either chemotherapy (≥ 0.5) to all patients who had high (≥ 0.5) predictive scores for either chemotherapy).

1.2.2. Evaluate the accuracy of the chemosensitivity profiles for differentiating doxorubicin and topotecan responsive cancers.

Data will be analyzed to determine the ability of the profile scores to accurately predict a chemotherapy response.

2. BACKGROUND

2.1 Ovarian Cancer

2.1.1 Overview

Ovarian cancer is the fifth leading cause of cancer death among women in the United States and Western Europe and has the highest mortality rate of all gynecologic cancers. *It is estimated that 22,220 new cases of epithelial ovarian cancer will be diagnosed in 2005 and 16,210 women will die of the disease.* Approximately 90% of ovarian cancers are

epithelial in origin. The majority (70%) of epithelial cancers are papillary serous, with less common subtypes including clear cell, mucinous, endometrioid, transitional, and undifferentiated. Approximately 75% of cases of epithelial ovarian carcinoma are diagnosed at advanced-stage (III/IV) with disseminated intra-peritoneal metastases, such that the majority of patients succumb to the disease within 5 years [1]. Despite the fact that 70% of patients will have a complete clinical response to initial therapy, the majority of patients will experience recurrent disease and require salvage therapy[1]. Of the approximately 25,000 new cases of epithelial ovarian cancer diagnosed each year, it is estimated that approximately 70% (~17,500 patients) will receive adjuvant chemotherapy, and the majority of these patients (~14,000) will experience recurrent disease requiring treatment with salvage therapies. Review of Surveillance Epidemiology and End Results (SEER) data suggests that the prevalence of ovarian cancer is approximately 200,000 cases per year [1] and it is likely that approximately 50%, or 100,000, of these women are undergoing active chemotherapy.

2.1.2 Management of Ovarian Cancer

Currently the standard treatment protocol used in the initial management of advanced-stage ovarian cancer is primary cytoreductive surgery, or "debulking", followed by adjuvant chemotherapy with a platinum and taxane. Approximately 70% of patients will have a complete clinical response to this initial therapy, with absence of clinically detectable residual disease on clinical exam, radiologic imaging, or serum CA125 tumor marker. Unfortunately, up to 85% of these cancers recur. Therefore, altogether nearly 90% of advanced stage ovarian cancer patients will receive salvage chemotherapy.

For patients whose recurrence occurs over 1 year from prior platinum chemotherapy, the response rate to retreatment with platinum is over 30%. The response rate is much lower for those considered platinum refractory, defined as progression of disease on an initial platinum-based chemotherapy regimen, or platinum resistant, typically defined as a complete response at completion of initial adjuvant chemotherapy, but recurrence within less than 6 to 12 months. Non-platinum chemotherapies for these refractory and resistant patients typically have a response rate of around 20%.

2.1.3 Salvage Therapy for Patients with Platinum Resistant Disease:

Table 1 lists approved agents that have demonstrated sensitivity during salvage therapy for platinum-resistant recurrent disease.

Drug	Response rate (%)	Cumulative Toxicity
Topotecan	12-19	Myelosuppression
Liposomal Doxorubicin	12-19	Palmar-plantar erythrodysthesia
Carboplatin	10-15	Thrombocytopenia
Paclitaxel	7-17	Peripheral neuropathy
Oral etoposide (VP-16)	27	Secondary leukemias
Gemcitabine	13-22	Myelosuppression

Table 1: Responses (%) to single-agent therapy in recurrent or platinum-resistant ovarian cancer, including cumulative toxicities

Two of the most frequently used salvage agents in these settings are topotecan and liposomal doxorubicin. The preference for these two drugs is based on the combination of tolerability and response, while the decision for which particular of the two drugs is largely empiric. Overall survival of women with platinum- and taxane-resistant ovarian cancer has been estimated based on a retrospective analysis of 111 patients treated in one or more of four nonrandomized phase II trials conducted by the Gynecologic Cancer Program of the

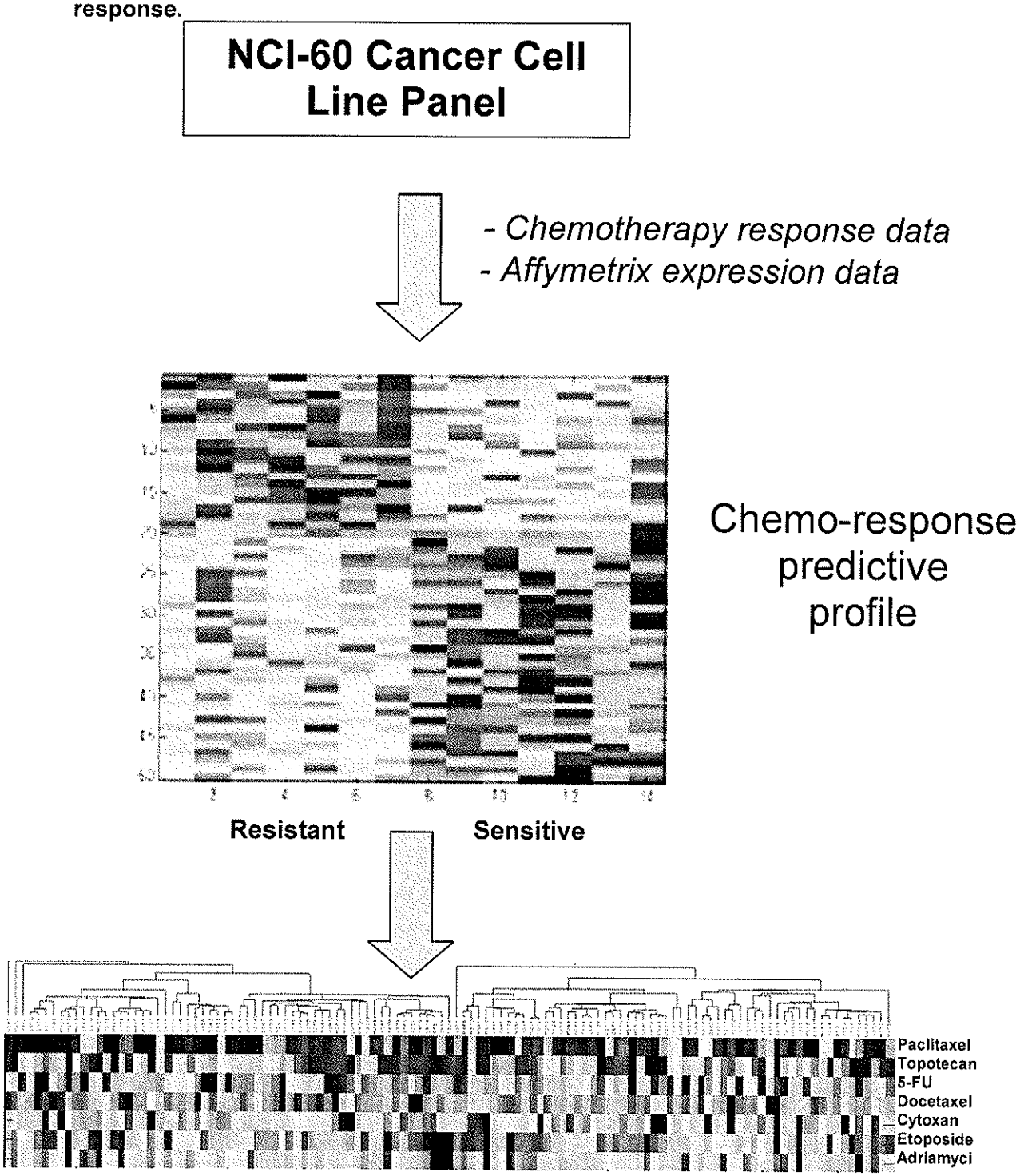
Cleveland Clinic. [2] Duration of survival in patients with platinum/taxane-resistant disease was defined as the time from documentation of both platinum and taxane resistance until death. Median overall survival was 6 months (range, 1–37 months); 32% of patients survived <4 months, and almost three-quarters of patients (73%) died in <12 months. Because many of these patients will likely receive only one agent in this relapsed setting, these statistics highlight the importance of selecting the most effective and well-tolerated agent for patients with resistant ovarian cancer.

2.2 Rationale of Genomic-Directed Therapy

Because of no clear superiority in response rates between a small group of salvage agents (see Table 1), the choice of agent is typically empiric and based on patient and physician preferences. Most often, a patient does not respond to the initial chemotherapeutic choice, and she is switched to the next drug. Unfortunately, each regimen that the patient's cancer is exposed to helps foster the emergence of multidrug resistance, so that subsequent regimens are less likely to induce a response. Therefore, even if a patient's tumor might have been sensitive to a particular drug, that sensitivity may be lost by prior exposure to drugs to which the tumor may not be sensitive. Furthermore, a subset of patients will expire due to progressive disease while on the initial salvage regimen. These facts suggest that the initial choice of chemotherapy is important, and that the ability to predict an individual tumor's response may have a dramatic impact on response and even survival.

We have recently developed preliminary data showing that gene expression profiles within ovarian cancer samples, resected at the time of primary surgical cytoreduction, can be utilized to predict response to therapy. In an analysis of 119 ovarian cancers we developed gene expression profiles that have predictive accuracies in excess of 80% [3]. Further, we have developed genomic signatures predictive of response to chemotherapies using genomic and chemo-response data available for the NCI60 cell line set **[4]** . We have made use of *in vitro* drug sensitivity data generated with the NCI-60 panel of cancer cell lines, coupled with Affymetrix microarray data, to develop gene expression signatures that reflect sensitivity to a series of commonly used ovarian cancer chemotherapeutic drugs (Figure 1).

Figure 1. Illustration of concept of creating predictive profiles for chemotherapy response.

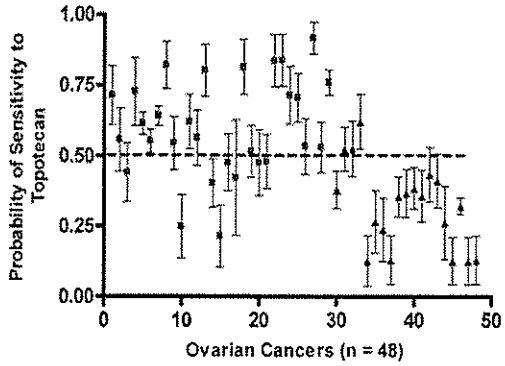


The capacity of the signatures to predict response was validated with response data from an independent set of 15 ovarian cancer cell line studies. We have further shown that a gene expression signature developed from cancer cell lines can accurately predict patients who respond to treatment with predictive accuracies of 82% - 86% in an external validation set of retrospectively collected tumor bank samples. Specifically, our gene expression predictor of response was shown to have an accuracy of 82% for doxorubicin, and 81% in

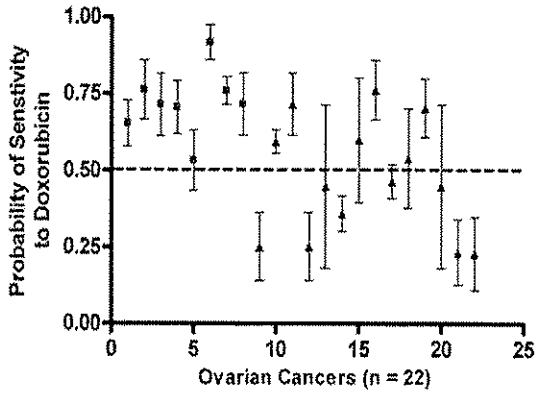
and 81% in predicting response to topotecan (Figure 2).

Figure 2. Accuracy of Genomic Profiles in Predicting Chemotherapy Response using Response Data in Human Ovarian Cancers.

Topotecan
Accuracy: 39/48 (81.3%)
p = 0.002



Doxorubicin
Accuracy: 18/22 (81.8%)
p = 0.01



Red Squares =chemotherapy responders, BlueTriangles =chemotherapy non-responders.

The purpose of this study is to translate these preclinical findings into a clinical trial of genomic-directed therapy. We will determine the response rates to the two most commonly used first-line salvage agents (liposomal doxorubicin and topotecan), by making genomic-directed therapy decisions. We will enroll 30 patients with progressive or recurrent ovarian cancer within 12 months of platinum-based therapy in a pilot trial of genomic-directed salvage therapy. All patients must consent to a biopsy for a frozen tissue sample used for gene expression array analysis that will be used to determine a predictive value for response to liposomal doxorubicin or topotecan. The patients will be treated with the chemotherapeutic agent with a higher predictive score. If the predictive value for each agent is identical for a given subject, the subject will be randomized to one of the two agents. The results of the array analysis will be blinded to the treating investigator and patient. Final analysis of data will be unblinded.

The primary endpoint for this study is to assess the feasibility of performing an array predicted trial in ovarian cancer patients. A descriptive analysis will be done looking at the success in generating rapid, interpretable genomic array prediction data from biopsied tissue in ovarian cancer patients. From time of consent, biopsy should be obtained within 5 days. The estimated turnaround time for the expression profile is 7-10 days. Including handling time and other factors, a benchmark for success will be that patients will have the information and be able to start treatment within 3 weeks of enrolling on study. We further are anticipating that at about two-thirds (66%) of enrolled patients will have biopsiable tumor in sufficient quantity and quality that will result in an interpretable genomic array. Therefore, we would consider markers of feasibility for a larger trial using genomic directed therapy from biopsies in recurrent ovarian cancer to be:

3. > 60% interpretable genomic arrays leading to successful prediction profiles.

4. >80% of genomic assay results to be within the 3 week time period from enrolling on study.

The chief secondary endpoint is to determine the overall response rate (ORR = CR+PR) for those with a high predictive likelihood of response (defined as the ratio of patients with a CR or PR who had high predictive scores for response to either chemotherapy (≥ 0.5) to all patients who had high (≥ 0.5) predictive scores for either chemotherapy).

2.3 Topotecan and Liposomal Doxorubicin in Ovarian Cancer

2.3.1 Topotecan

2.3.1.1 Topotecan Use in Ovarian Cancer

Topotecan has demonstrated efficacy in the treatment of recurrent metastatic ovarian carcinoma. The Food and Drug Administration (FDA) approved dose of topotecan is 1.5mg/m2/day given for the first 5 consecutive days of a 21 day cycle. Topotecan was used as a single agent in patients who failed cisplatin based therapy and had the same response rate as paclitaxel in a European randomized controlled trial. Its activity is demonstrated in both platinum and paclitaxel resistant tumors with response rates ranging from 13-28%. However, in these trials, grade 3-4 neutropenia and thrombocytopenia occurred in greater than 80% and greater than 30% of patients respectively.

2.3.1.2 Rationale for 4 mg/m2 Dose Days 1, 8, 15 q28 days*

The FDA approved dose of 1.5 mg/m2/day x 5 days every 21 days is associated with a high degree of toxicity and is not a dose or schedule commonly used in clinical practice. [5] The toxicity is illustrated in a recent randomized phase III trial comparing topotecan and liposomal doxorubicin in the same patient population as this study.[6] Both arms used the FDA approved doses. Hematologic toxicity was more frequent and usually grade 3 or 4 in the topotecan-treated patients. The majority of patients in the topotecan group (90.2%) experienced hematologic adverse events, and two thirds of these events were grades 3 and 4. The hematologic toxicity in the topotecan arm resulted in a greater utilization of hematopoietic growth factors (granulocyte or granulocyte-macrophage colony-stimulating factor, 29.1% *v* 4.6%; erythropoietin, 23.1% *v* 6.3%), blood transfusions (57.8% *v* 14.9%), and dosing modifications (78.3% *v* 57.3%) when compared with the pegylated liposomal doxorubicin arm. A number of patients treated with topotecan experienced clinical sequelae related to the hematologic toxicity. Nine patients (3.8%) experienced treatment-related sepsis (three of whom died), two experienced sepsis of an unknown relationship to study drug (one of whom died), two withdrew from the study because of sepsis, and two additional patients experienced treatment-related neutropenic fever.

In an effort to decrease toxicity, studies have been done with reduced doses of topotecan in women with relapsed ovarian carcinoma. With a reduction in the dose from 1.5 to 1.25 mg/m2, a significant reduction in grade 3 and 4 hematologic toxicity has been realized, without compromising the efficacy of

therapy. Rodriguez et al. examined a dose of 1 mg/m2/day, again administered daily X 5 and repeated every 21 days in heavily pretreated patients with relapsed ovarian carcinoma. The overall response rate in this trial was 22%, with grade 4 neutropenia occurring in 48.6% of patients and thrombocytopenia and anemia occurring each at a rate of 5.4 %.This ability to maintain efficacy and decrease toxicity provided the rationale for utilizing the lower dose of topotecan employed early in this trial. Furthermore, the administration of topotecan at a dose of 1.25 mg/m2 D1-5 every 21 days has been the most commonly employed dose and schedule in patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer[5, 7]. McGuire reported a 33% response rate and an 11.2 month response duration in 48 patients with platinum-sensitive recurrent ovarian cancer using such a dose and schedule in a previous Gynecologic Oncology Group (GOG) trial.[8]

More recently, weekly topotecan (days 1, 8, 15 of a 28-day dosing schedule) at a dose of 4 mg/m2 by intravenous infusion over 30 minutes has become the generalized 'standard' schedule and the preferred dosing strategy by most gynecologic oncologists over the last few years (personal communication; R. Wenham, B. Karlan). In nonrandomized studies, comparative data from phase 2 studies enrolling platinum-sensitive relapsed or recurrent ovarian cancer patients utilizing topotecan dosed weekly at 4 mg/m2 suggests it is as effective but less toxic than the labeled dose and schedule [7, 9, 10] ----- . For this reason, the present study (20070182) is using topotecan in cohort B at the dose and schedule used by gynecologic oncologists.

*Therefore, there are two regimens of topotecan used in ovarian cancer. The least commonly used is daily x 5 days of a 21 day cycle, which is the FDA labeled regimen, By far the most commonly used regimen in clinical practice by gynecologic oncologists is 4 mg/m2/day on days 1, 8, 15 of 28 day cycle. Patients and their physician will be allowed to choose the regimen they are comfortable with. This will not impact the primary endpoint which is feasibility and should not change the secondary endpoint of response based on published data.

2.3.2 Doxil

2.3.2.1 Liposomal Doxorubicin in Ovarian Cancer

Pegylated liposomal doxorubicin has demonstrated efficacy as a single agent in the treatment of recurrent/relapsed ovarian cancer in several clinical trials. The first of these was a phase II study of 35 patients with platinum- and paclitaxel-refractory ovarian cancer who received pegylated liposomal doxorubicin 50 mg/m^2 every 3 weeks, resulting in a dose intensity of 16.7 mg/m^2 per week. In the event of grade 3/4 toxicities, the dose was reduced to 40 mg/m^2 (or a dose intensity of 13.3 mg/m^2 per week), while the presence of persistent (lasting >3 weeks) grade 1/2 adverse events resulted in an increase in the dosing interval to every 4 weeks.[11] The overall response rate was 25.7% (one complete response [CRs] and eight partial responses [PRs]); however, 13 (37.1%) patients experienced grade 3/4 skin and mucosal toxicities that often necessitated dose modifications.

In a second phase II study, 89 patients with platinum- and paclitaxel-refractory ovarian cancer were treated with pegylated liposomal doxorubicin at a slightly lower dose intensity: 50 mg/m^2 every 4 weeks, or 12.5 mg/m^2 weekly.[12] Tumor response was observed in 16.9% of patients, with one CR and 14 PRs. Dose delays, reductions, or interruptions occurred in 39 (43.8%)

patients, over half of which were required due to adverse events (i.e., hematologic toxicity, HFS [hand-foot syndrome], or stomatitis). The most common treatment-related adverse events were asthenia and HFS, both of which occurred in 41.6% of patients (severity grades 1, 2, or 3).

A subsequent phase III trial was conducted by Gordon and colleagues to compare the safety and efficacy of pegylated liposomal doxorubicin with that of topotecan in 474 patients with relapsed ovarian cancer that recurred after or failed to respond to first-line, platinum-based chemotherapy[6]. Patients were randomly assigned to treatment with pegylated liposomal doxorubicin 50 mg/m^2 every 4 weeks (given as a 1-hour infusion) or topotecan 1.5 mg/m^2/day for 5 consecutive days every 3 weeks (given as a 30-minute infusion) for up to 1 year. Patients were stratified prospectively based on platinum sensitivity and presence/absence of bulky disease. Based on the results of an end-of-study analysis, similar overall response rates and median progression-free and overall survival were observed in both treatment groups.

2.3.2.2 Rationale for 40 mg/m^2 Dose every 28 Days

In the phase III study by Gordon et al. described above, the proportion of patients experiencing grade 1, 2, and 3 adverse events was similar between the two treatment groups; however, fewer patients treated with pegylated liposomal doxorubicin reported grade 4 adverse events (17.2% versus 71.1% with topotecan).[6] Differences were also observed with respect to the nature of toxicities: the most common grade 3/4 nonhematologic toxicities associated with pegylated liposomal doxorubicin were hand-foot syndrome (HFS) (23%) and stomatitis (8%), while hematologic toxicity was the most common event among topotecan-treated patients. A substantial number of patients receiving pegylated liposomal doxorubicin or topotecan required dose modifications (57.3% versus 78.3% respectively; $p < .001$).

The toxicities associated with pegylated liposomal doxorubicin are managed by delaying or reducing the dose, with no apparent loss of antitumor activity. Several studies have suggested that pegylated liposomal doxorubicin administered at a dose of 40 mg/m^2 every 4 weeks rather than 50 mg/m^2 every 4 weeks results in a substantially reduced incidence of hand-foot syndrome (HFS) [13-16] and stomatitis [13-15], without a loss of clinical efficacy. Further investigation has shown that the incidence of HFS is schedule dependent, with shorter dosing intervals leading to increased frequency and severity of occurrence. In contrast, the incidence of stomatitis is dose related, occurring with greater incidence and severity in patients receiving pegylated liposomal doxorubicin doses of 60–70 mg/m^2. These findings suggest that reducing the dose intensity of pegylated liposomal doxorubicin may be used in an effort to maintain efficacy and optimize tolerability. Substantial clinical evidence exists to provide the rationale for a modified dosing schedule of pegylated liposomal doxorubicin 40 mg/m^2 every 4 weeks in patients with recurrent/relapsed ovarian cancer. In fact, this is the dose almost exclusively used in current clinical practice.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have a history of histologically or cytologically confirmed epithelial ovarian cancer with recurrence.

3.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques or as ≥10 mm with spiral computed tomography (CT) scan. See section 9.2 for the evaluation of measurable disease. *Note: Lesions are either measurable or non-measurable using the criteria provided in section 9.*

3.1.3 Patient may have had only 2 prior chemotherapy regimens, with at least one regimen containing platinum, anddisease recurrence or progression occurring between 0 and 12 months (1 to 365 days) from the platinum-containing regimen. Patients who have been treated with consolidation treatment are allowed, and the consolidation will not be considered a separate regimen. Hormonal therapy (i.e. progesterones, estrogens, anti-estrogens, aromatase inhibitors) and immunotherapy will not be considered a prior chemotherapy regimen. Such therapies should be stopped at least 30 days prior to dosing on this trial.

3.1.4 Life expectancy of greater than 6 months.

3.1.5 Eastern Cooperative Oncology Group (ECOG) performance status. 2 or less (Karnofsky. 60%; see Appendix A).

3.1.6 Patients must have normal organ and marrow function as defined below:

- leukocytes . 3,000/μL
- absolute neutrophil count . 1,500/ μL
- platelets . 100,000/μL
- total bilirubin ≤1.5 X institutional upper limit of normal
- aspartate aminotransferase [AST(SGOT)]/alanine aminotransferase [ALT(SGPT)] ≤2.5 X institutional upper limit of normal
- creatinine within normal institutional limits

OR

- creatinine clearance . 60mL/min/1.73m^2 for patients with creatinine levels above institutional normal

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

3.1.8 The measurable disease on CT must be considered amenable to biopsy by Core methods (core biopsy may be radiographically or non-radiographically performed). The potential ability to obtain core material must be reviewed by the Principal Investigator (PI) and/or his designates prior to enrollment.

3.1.9 Patient must consent to biopsy as part of enrolling into trial.

3.1.10 Patients with reproductive potential must use an adequate contraceptive method (e.g. abstinence, intrauterine device, oral contraceptives, barrier device with spermicide or surgical sterilization) during treatment and for three months after completing treatment.

3.1.11 Patients must have a Multiple Gated Acquisition (MUGA) scan or 2-d echocardiogram indicating an ejection fraction of > 50% or institutional standards within 42 days prior to first dose of study drug. The method used at baseline must be used for later monitoring.

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

3.2.2 Patients may not be receiving any other investigational agents concurrently.

3.2.3 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to liposomal doxorubicin or topotecan.

3.2.5 Myocardial infarction within 6 months. History of cardiac disease, with New York Heart Association Class II or greater or clinical evidence of congestive heart failure.

3.2.6 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.7 Pregnant women are excluded from this study. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with liposomal doxorubicin or topotecan, breastfeeding should be discontinued.

3.2.8 Patients with immune deficiency are at increased risk of lethal infections when treated with marrow-suppressive therapy. Therefore, Human Immunodeficiency Virus (HIV)-positive patients receiving combination anti-retroviral therapy are excluded from the study because of possible pharmacokinetic interactions and increased toxicity.

3.2.9 Patients may have had no other malignancies in the prior 5 years other than non-metastatic, locally-controlled, non-melanomatous cutaneous cancers.

3.2.10 Patients who have received radiation to more than 25% of marrow-bearing areas.

3.3 Inclusion of Women and Minorities

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

3.4 Patient Registration

Once clinical eligibility is confirmed, patients must sign an informed consent prior to registration indicating awareness of the investigation nature of the study and expected risks in keeping with the policies of the hospital and Federal regulations (Code of Federal Regulations Part 1X, Subpart B, Sections 50.20-50.27). The study chair will make all determinations of eligibility when there is question of eligibility for a subject. Patient volunteers will not receive any compensation for participation in this trial.

3.5 Removal of Patients From Study

Patients may be removed from the study for any of the following reasons:

- Progression of disease
- Patient non-compliance: defined as any deviation from the protocol without prior agreement of the principal investigator
- Investigator non-compliance: defined as any significant medical or non-medical deviation from the protocol without agreement of the Principal Investigator
- Patient's request to withdraw from the study or refusal of further therapy
- Unacceptable toxicity. A patient may be removed from the study for any complication of treatment that the investigator feels is life threatening.
- If patient does not meet eligibility criteria
- One of the criteria in section 4.3 occurs
- Study is closed

4. TREATMENT PLAN

4.1 Sequence of Events, Possible Risks, and Steps to Minimize Risks

- Pre-study Initial Visit
  - Informed consent
  - Demographics
  - Medical History
  - Concurrent meds
  - Physical exam
  - Vital signs
  - Height
  - Weight
  - Performance status tests to determine patient's ability to perform everyday functions (per ECOG performance status scale in Appendix A)
  - Complete Blood Count w/differential platelets (CBC w/diff, plts)
  - Serum chemistry (albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH,

phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium)
- EKG (as indicated)
- Tumor measurements
- Radiologic evaluation (repeated every 8 weeks)
  - Computed Tomography (CT) scan:
    - Risks include pain, bleeding, injury to surrounding tissues, inadequate tissue collection, nausea, flushing, warmth, salty taste, allergic reaction to contrast dye; discomfort, claustrophobia, exposure to radiation, Kidney damage
    - Pain can be alleviated through the use of analgesics.
    - Standard radiologic protocol for obtaining CTs is followed
  - MRI, x-ray:
    - Risks include: Exposure to loud noises, claustrophobia, localized twitching; removal of metallic objects
    - Steps to minimize risks: Use of earplugs/headphones; steps have been taken to relieve closed in feeling (radiologist can give patient anxiolytics within the standard of care to relieve anxiety); open MRI machine may be used, can discontinue scan
  - Ultrasound:
    - No significant risks
- B-HCG (serum pregnancy test [for women of childbearing potential])
- If patient will be on Liposomal Doxorubicin arm, baseline MUGA or Echo will be done

- Within 5 days of consent, CT-guided tumor biopsy obtained – the equivalent of 2 passes of a 16 gauge core biopsy needle or approximately 20-50 mg of tissue
  - Risks include pain, bleeding, injury to surrounding tissues, inadequate tissue collection, nausea, flushing, warmth, salty taste. Allergic to contrast dye; Discomfort, claustrophobia, exposure to radiation, Kidney damage
    - Pain can be alleviated through the use of analgesics.
  - Biopsy tissue is profiled via genomic microarray (results are blinded until analysis)
  - Tissue handled per section 7.1
- Patient assigned based on results of microarray (see Treatment Schema on page iii and criteria in section 7.2) (pLD>pT = Liposomal Doxorubicin; pT>pLD = Topotecan ; pLD=pT, or indeterminate, randomized to either Liposomal Doxorubicin or Topotecan.
  - Results of microarray and assignment of patient is estimated to be 7-10 days after biopsy
- Treatment must begin within 4 weeks of the baseline evaluations, initial scans, and biopsies.
- Subjects will be evaluated for toxicity at each visit. Subjects will be told to notify the study team in the event any effects are experienced at home. The subject's lab values will be monitored at each visit and discussed with the subject. If the subject is at increased risk for infection or bleeding instructions will be provided to help her lessen the chance that she will experience infection or bleeding.

- If on the Topotecan arm and receiving 4 mg/m2 days 1, 8, 15 q 28 days, the following schedule will be observed:
  - Cycle 1 Day 1
    - Administration of drug
    - Concurrent meds
    - Physical exam
    - Vital signs
    - Weight
    - Performance status
    - CBC w/diff, plts
    - Serum chemistry
    - Adverse event evaluation
  - Cycle 1 Day 8
    - CBC w/diff, plts
    - Vital signs
    -
    - Administration of drug
  - Cycle 1 Day 15
    - CBC w/diff, plts
    - Vital signs
    -
    - Administration of drug
  - Cycle 1 Day 21
    - No visit scheduled
    -
  - Cycle 2 Day 1
    - Medical history
    - Concurrent meds
    - Physical exam
    - Vital signs
    - Weight
    - Performance status
    - CBC w/diff, plts
    - Serum chemistry
    - Adverse event evaluation
  - Cycle 2 Day 8
    - CBC w/diff, plts
    - Vital signs
    -
    - Administration of drug
  - Cycle 2 Day 15
    - CBC w/diff, plts
    - Vital signs
    -
    - Administration of drug
  - Cycle 2 Day 21
    - No visit scheduled
  - Cycle 3 Day 1
      - (+ or – 5 days)
        - Tumor measurement
        - Radiologic evaluation
  -
    - Administration of drug

        - Medical history
        - Concurrent meds
        - Physical exam
        - Vital signs
        - Weight
        - Performance status
        - CBC w/diff, plts
        - Serum chemistry
        - Adverse event evaluation
    - Cycle 3 Day 8
        - CBC w/diff, plts
        - Vital signs
        -
        - Administration of drug
        -
    - Cycle 3 Day 15
        - CBC w/diff, plts
        - Vital signs
        -
        - Administration of drug
    - Cycle 3 Day 21 –
        - No visit scheduled
    - Off study visit
        - Medical history
        - Physical exam
        - Vital signs
        - Weight
        - Performance status
        - CBC w/diff, plts
        - Serum chemistry
        - Adverse event evaluation
        - Tumor measurement
        - Radiologic evaluation

- If on the Topotecan arm and receiving 1.25 mg/m^2 x 5 days q 21 days, the following schedule will be observed:

    Cycle 1 Day 1
        - Vital signs before administration of drug
        - Administration of drug
        - Concurrent meds
        - Physical exam
        - Weight
        - Performance status
        - CBC w/diff, plts
        - Serum chemistry
        - Adverse event evaluation
        - Radiologic evaluation
    - Cycle 1 Days 2-5
        - Vital signs before administration of drug
        - Administration of drug
    - Cycle 2 Day 1
        - Vital signs before administration of drug
        - Administration of drug

        - Medical history
        - Concurrent meds
        - Physical exam
        - Vital signs
        - Weight
        - Performance status
        - CBC w/diff, plts
        - Serum chemistry
        - Adverse event evaluation
    - Cycle 2 Days 2-5
        - Vital signs before administration of drug
        - Administration of drug
    - Cycle 3 Day 1
        - Vital signs before administration of drug
        - Administration of drug
        - (+ or – 5 days):
            - Tumor measurement
            - Radiologic evaluation
        - Medical history
        - Concurrent meds
        - Physical exam
        - Vital signs
        - Weight
        - Performance status
        - CBC w/diff, plts
        - Serum chemistry
        - Adverse event evaluation
    - Cycle 3 Days 2-5
        - Vital signs before administration of drug
        - Administration of drug
    - Off study visit
        - Medical history
        - Physical exam
        - Vital signs
        - Weight
        - Performance status
        - CBC w/diff, plts
        - Serum chemistry
        - Adverse event evaluation
        - Tumor measurement
        - Radiologic evaluation

- If on Liposomal Doxorubicin arm
    - Cycle 1 Day 1
        - Administration of drug
        - Medical history
        - Concurrent meds
        - Physical exam
        - Vital signs
        - Weight
        - Performance status
        - CBC w/diff, plts
        - Serum chemistry

        - Adverse event evaluation
    - Cycle 1 Days 8, 15, 21– no visit scheduled
    - Cycle 2 Day 1
        - Administration of drug
        - Medical history
        - Concurrent meds
        - Physical exam
        - Vital signs
        - Weight
        - Performance status
        - CBC w/diff, plts
        - Serum chemistry
        - Adverse event evaluation
    - Cycle 2
        - (+ or – 5 days):
            - Tumor measurement
            - Radiologic evaluation
        - Days 8, 15, 21 – no visit scheduled
    - Cycle 3 Day 1
        - Administration of drug
        - Medical history
        - Concurrent meds
        - Physical exam
        - Vital signs
        - Weight
        - Performance status
        - CBC w/diff, plts
        - Serum chemistry
        - Adverse event evaluation
    - Cycle 3 Days 8, 15, 21 – no visit scheduled
    - Off study visit
        - Medical history
        - Physical exam
        - Vital signs
        - Weight
        - Performance status
        - CBC w/diff, plts
        - Serum chemistry
        - Adverse event evaluation
        - Tumor measurement
        - Radiologic evaluation
- Subject endpoint (per section 4.4):

  In the absence of treatment delays due to adverse event(s), treatment may continue for unlimited cycles or until one of the following criteria applies:
  - Disease progression,
  - Intercurrent illness that prevents further administration of treatment,
  - Unacceptable adverse event(s),
  - Patient decides to withdraw from the study, or
  - General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

Complete response; following a minimum of 3 cycles, treatment may be continued or discontinued at the discretion of the treating physician and patient.

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4.2 **Chemotherapy Administration**

Treatment may be administered on either an inpatient or outpatient basis at the treating physician's discretion per standard clinical indications. Patients will be permitted to receive chemotherapy at the affiliate sites where they regularly receive care. Radiology, if done at a radiology suite not part of Moffitt or Duke, will be reviewed by the Moffitt PI. All data will be collected and reviewed at the Moffitt Cancer Center. Reported adverse events and potential risks are described in Section 6. Appropriate dose modifications for liposomal doxorubicin and for topotecan are described in Section 5. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Treatment with chemotherapy will continue until progression or one of the criteria for removal (see Section 3.5) is met.

4.3 **Supportive Care Guidelines**

Supportive medications should be given in accordance with institutional guidelines, National Comprehensive Cancer Network (NCCN) guidelines, and/or treating physician's clinical judgment except where explicitly stated in the protocol. This includes, but is not limited to antiemetic, antihistamine, analgesic, anti-inflammatory, or bone marrow support medications. Patients may be transfused as deemed appropriate by the treating physician.

4.4 **Duration of Therapy**

In the absence of treatment delays due to adverse event(s), treatment may continue for unlimited cycles or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Complete response; following a minimum of 3 cycles, treatment may be continued or discontinued at the discretion of the treating physician and patient.

5 DOSING DELAYS/DOSE MODIFICATIONS

All dose modifications will be dose reductions. There will be no dose escalations. Any patient whose treatment is delayed must be evaluated on a weekly basis until adequate hematologic and non-hematologic parameters have been met. Treatment delays are to be kept to a minimum and every effort should be made to maintain the intended schedule. No treatment delays are permitted for other than documented toxicity. If delays of greater than two weeks occur, patient must be taken off study.

Study Drug	2 Level Reduction	1 level Reduction	Initial Dose Level
Topotecan	3.0 mg/m^2	3.5 mg/m^2	4 mg/m^2
Liposomal Doxorubicin	25 mg/m^2	32.5 mg/m^2	40 mg/m^2

5.1 Topotecan

5.1.1 Hematologic toxicity (thrombocytopenia, severe bleeding in association with thrombocytopenia, leucopenia, neutropenia, sepsis or fever/infection with grade neutropenia, anemia)

5.1.1.1 Initial treatment modifications will consist of cycle delay and/or dose reduction as indicated below. The use of hematopoietic cytokines and protective reagents are unrestricted and left to the treating physicians discretion except as noted:

5.1.1.2 Patients will NOT receive prophylactic thrombopoietic agents unless they experience recurrent grade 4 thrombocytopenia after treatment modifications as specified below.

5.1.1.3 Patients may receive erythropoietin for management of anemia AFTER documentation of hemoglobin less than 12 g/dl (Common Terminology Criteria for Adverse Events [CTCAE] v3.0 grade 2).

5.1.1.4 Patients may NOT receive amifostine or other protective reagents, unless indicated in the study design.

5.1.1.5 Treatment decisions will be based on the absolute neutrophil count (ANC) rather than the total white cell count (WBC).

5.1.1.6 Subsequent cycles of therapy will not begin until the ANC is ≥ 1500 cells/mcl (CTCAE v3.0 grade 1) and the platelet count is ≥100,000/mcl. Therapy will be delayed for a maximum of two weeks until these values are achieved. Patients who fail to recover adequate counts within a two week delay will be removed from study.

5.1.1.7 For first occurrence of febrile neutropenia, and/or documented grade 4 neutropenia persisting ≥ 7 days, reduce chemotherapy by one dose level on subsequent cycles. Granulocyte-Colony Stimulating Factor (G-CSF) should be considered for use as per current standard clinical practice guidelines for that and future cycles, unless contraindications preclude its use. In this circumstance, it is recommended that G-CSF (filgrastim) at a dose of 5 mg/kg/day (or equivalent dosing of pegfilgrastim or sargramostim) will be administered subcutaneously starting the day after the last dose of chemotherapy and continuing through hematopoietic recovery. Pegfilgrastim should not be used if the next cycle dose of chemotherapy is to be given within 14 days. Shorter acting agents (e.g. Filgrastim) should be considered in such cases.

5.1.1.8 For recurrent febrile neutropenia, and/or recurrent documented grade 4 neutropenia persisting ≥7 days, a second dose reduction should be done.

Again, prophylactic growth factors should be used unless contraindicated for that patient. Patients with further recurrence of febrile neutropenia, and/or recurrent documented grade 4 neutropenia persisting ≥ 7 days (after initial dose reduction and addition of growth factors) should be removed from study.

5.1.1.9 Patients with grade 4 thrombocytopenia will have a 1 level dose reduction.

5.1.1.10 There will be no dose modifications on the basis of uncomplicated granulocyte nadirs lasting less than 7 days.

5.1.2 Non-Hematologic

5.1.2.1 Gastrointestinal (nausea, vomiting, diarrhea, constipation, abdominal pain, stomatitis, anorexia)

5.1.2.1.1 Use of antiemetics can be used to minimize these

5.1.2.2 Dermatology/skin (alopecia, dermatitis, pruritis, allergic reaction)

5.1.2.2.1 Treat per standard of care of treating physician

5.1.2.3 Constitutional (fatigue, asthenia, fever)

5.1.2.3.1 Treat per standard of care of treating physician

5.1.2.4 Pain (musculoskeletal pain, headache)

5.1.2.4.1 Treat per standard of care of treating physician

5.1.2.5 Pulmonary/respiratory (dyspnea, cough)

5.1.2.5.1 Treat per standard of care of treating physician

5.1.2.6 Hepatic (elevated liver function enzymes)

5.1.2.6.1 Treat per standard of care of treating physician

5.1.2.7 Reproductive (fetal harm)

5.1.2.7.1 Use of birth control during and 3 months after trial

5.2 Liposomal Doxorubicin

5.2.1 Hematologic (neutropenia, thrombocytopenia, anemia)

5.2.1.1 Initial treatment modifications will consist of cycle delay and/or dose reduction as indicated below. The use of hematopoietic cytokines and protective reagents are restricted as noted:

5.2.1.1.1 Patients may receive prophylactic growth factors [filgrastim (G- CSF), sargramostim ([Granulocyte/Macrophage-Colony Stimulating Factor] GM-CSF), pegfilgrastim (Neulasta)] if deemed clinically appropriate.

5.2.1.1.2 Patients will NOT receive prophylactic thrombopoietic agents unless they experience recurrent grade 4 thrombocytopenia after treatment modifications as specified below.

5.2.1.1.3 Patients may receive erythropoietin for management of anemia AFTER documentation of hemoglobin less than 12 g/dl.

5.2.1.1.4 Patients may NOT receive amifostine or other protective reagents, unless indicated in the study design.

5.2.1.2 Treatment decisions will be based on the absolute neutrophil count (ANC) rather than the total white cell count (WBC).

5.2.1.3 Subsequent cycles of therapy will not begin until the ANC is ≥ 1500 cells/mm^3 (CTCAE grade 1) and the platelet count is ≥ 100,000/ul. Initiation of a new cycle will be delayed for a maximum of two weeks until these values are achieved. Patients who fail to recover adequate counts within a two week delay will be removed from study.

5.2.1.3.1 Patients who require a delay of less than 7 days for hematologic toxicity will receive no dose modification. They may have the addition of G-CSF as per standard institutional practice.

5.2.1.3.2 Patients who require a delay of 8-14 days will receive a one level dose reduction of chemotherapy with or without the addition of G-CSF as per standard institutional practice.

5.2.1.3.3 There will be no dose modifications on the basis of uncomplicated granulocyte nadirs lasting < 7 days.

5.2.1.3.4 For first occurrence of febrile neutropenia, and/or documented grade 4 neutropenia persisting ≥ 7 days, reduce chemotherapy by one dose level on subsequent cycles. G-CSF should be considered for use as per current standard clinical practice guidelines for that and future cycles, unless contraindications preclude its use. In this circumstance, it is recommended that G-CSF (Filgrastim) at a dose of 5 mg/kg/day (or equivalent dosing of pegfilgrastim or sargramostim) will be administered subcutaneously starting the day after the last dose of chemotherapy and continuing through hematopoietic recovery. Pegfilgrastim should not be used if the next cycle dose of chemotherapy is to be given within 14 days. Shorter acting agents (e.g. Filgrastim) should be considered in such cases.

5.2.1.3.5 For recurrent febrile neutropenia, and/or recurrent documented grade 4 neutropenia persisting ≥7 days, a second dose reduction should be done. Again, prophylactic growth factors should be used unless contraindicated for that patient. Patients with further recurrence of febrile neutropenia, and/or recurrent documented grade 4 neutropenia persisting ≥ 7 days (after initial dose reduction and addition of growth factors) should be removed from study.

5.2.1.3.6 Patients with grade 4 thrombocytopenia, or grade 3 thrombocytopenia associated with bleeding or platelet transfusion, will have a 1 level dose reduction.

5.2.2 Non-hematologic

5.2.2.1 Palmar-Plantar Erythrodysesthesia

Palmar-plantar erythrodysesthesia is managed by lengthening the dosing interval and dose reduction as noted, based on persistent toxicity on planned date of treatment and based on the worse toxicity grade as above. Patients may be delayed a maximum of 2 weeks from the original planned day of treatment.

Table for Management of PPE

PALMAR-PLANTAR ERYTHRODYSESTHESIA			
Persistent Toxicity on Planned Day of Rx	Week After Dose		
	Week 4	Week 5	Week 6
Gr 1: mild erythema swelling, or desquamation not interfering with daily activities	Re-dose unless patient has experienced a previous Gr 3-4 skin toxicity in which case wait an additional week	Re-dose unless patient has experienced a previous Gr 3-4 skin toxicity in which case wait an additional week	Re-dose at 25% dose reduction; return to 4-week interval or withdraw patient per investigator's assessment
Gr 2: erythema, desquamation, or swelling interfering with but not precluding normal activities; small blisters or ulcerations <2 cm in diameter	Wait an additional week	Wait an additional week	Re-dose at 25% reduction; return to 4-week interval or withdraw patient per investigator's assessment
Gr 3: blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing	Wait an additional week and re-dose at 25% dose reduction	Wait an additional week and re-dose at 25% dose reduction	Withdraw patient
Gr 4: diffuse or local process causing infectious complications, or a bedridden state or hospitalization	Wait an additional week and re-dose at 25% dose reduction	Wait an additional week and re-dose at 25% dose reduction	Withdraw patient

5.2.2.2 Stomatitis

5.2.2.2.1 In the case of stomatitis, the dosing intervals may be increased if necessary for patients to tolerate therapy as noted below. Patients may be delayed a maximum of 2 weeks from the original planned day of treatment. All patients having a grade 3 or 4 toxicity will have a one dose level reduction. Patients should be educated regarding cooling procedures for 3 days after treatment. If side effects occur may use L-Lysine 500 mg 3 tabs 3 x/day and /or prescription mouthwashes.

5.2.2.2.2 Table for Stomatitis Management

STOMATITIS			
Persistent Toxicity on Planned Day of Rx	**Week After Dose**		
	Week 4	**Week 5**	**Week 6**
Gr 1: painless ulcers, erythema, or mild soreness	Re-dose unless patient has experienced previous Gr 3-4 skin toxicity in which case wait an additional week	Re-dose unless patient has experienced previous Gr 3-4 skin toxicity in which case wait an additional week	Re-dose at 25% dose reduction; return to 4-week interval or withdraw patient per investigator's assessment
Gr 2: painful erythema, edema, or ulcers, but can eat	Wait an additional week	Wait an additional week	Re-dose at 25% reduction; return to 4-week interval or withdraw patient per investigator's assessment
Gr 3: painful erythema, edema, or ulcers, but cannot eat	Wait an additional week and re-dose at 25% dose reduction	Wait an additional week and re-dose at 25% dose reduction	Withdraw patient
Gr 4: requires parenteral or enteral support	Wait an additional week and re-dose at 25% dose reduction	Wait an additional week and re-dose at 25% dose reduction	Withdraw patient

5.2.2.3 Hepatotoxicity

5.2.2.3.1 In the event of Grade 2 hepatotoxicity, or Grade 1 hyperbilirubinemia decrease the dose of Doxil one dose level. For Grade 3 or 4 hepatotoxicity or hyperbilirubinemia discontinue Doxil.

5.2.2.4 Cardiac Toxicity

5.2.2.4.1 Development of congestive heart failure that requires medical management or a reduction in Left Ventricular Ejection Fraction (LVEF) below 45% or a decrease of 20% from baseline is an indication to withdraw the patient from study.

5.2.2.5 Hypersensitivity (anaphylaxis, infusion reaction)

5.2.2.6 Gastrointestinal (abdominal pain, nausea, vomiting)

5.2.2.6.1 Use of antiemetics

6 PHARMACEUTICAL INFORMATION

6.1 Topotecan (Hycamtin® NSC #609699) Specific Information

6.1.1 Formulation: Topotecan for injection is supplied as a sterile lyophilized, buffered, light yellow to greenish powder available as single-dose vials. Each vial contains topotecan hydrochloride equivalent to 4 mg of topotecan as free base. The

reconstituted solution ranges in color from yellow to yellow-green and is intended for administration by intravenous infusion.

6.1.2 Storage/Stability: Unopened vials of topotecan are stable until the date indicated on the package when stored between 20-25°C (68-77°F) and protected from light in the original package. Because vials contain no preservative, contents should be used immediately after reconstitution. Reconstituted vials of topotecan diluted for infusion are stable at approximately 20-25°C (68-77°F) and ambient light conditions for 24 hours.

6.1.3 How Supplied: Topotecan is supplied in 4-mg (free base) single-dose vials.

6.1.4 Supplier: Topotecan (Hycamtin) is commercially available from Glaxo SmithKline.

6.1.5 Preparation: Each 4 mg vial is reconstituted with 4 ml Sterile Water for Injection. Then the appropriate volume of the reconstituted solution is diluted in with 0.9% Sodium Chloride Intravenous Solution or 5% Dextrose Intravenous Infusion prior to administration. Because the lyophilized dosage form contains no preservation, the reconstituted product should be used immediately.

6.1.6 Administration: The mixed solution may be infused in a peripheral or central vein over 30 minutes.

6.1.7 Reproductive risks: Topotecan may cause fetal harm when administered to a pregnant woman. The effects of topotecan on pregnant women have not been studied. Patients of child-bearing potential must use an effective form of contraception while receiving treatment with topotecan. Patients who become pregnant during the study should discontinue treatment immediately.

6.1.8 Drug Interactions: Concomitant administration of G-CSF can prolong the duration of neutropenia, so if G-CSF is to be used, it should not be initiated until 24 hours after completion of treatment. See Section 5.1 for treatment modifications based on hematological toxicity.

6.1.9 Adverse effects:

- Hematologic: Thrombocytopenia, severe bleeding (in association with thrombocytopenia), leukopenia, neutropenia, sepsis or fever/infection with grade neutropenia, anemia.
- Gastrointestinal: Nausea and vomiting, diarrhea, constipation, abdominal pain, stomatitis, anorexia.
- Dermatology/Skin: Rash, alopecia, dermatitis, pruritis, allergic reaction.
- Constitutional: Fatigue, asthenia, fever.
- Pain: Musculoskeletal pain, headache.
- Pulmonary/Respiratory: Dyspnea, cough.
- Neurologic: Paresthesia.
- Hepatic: Elevated liver function enzymes.
- Reproductive (fetal harm).
- Nausea/vomiting, loss of appetite, hair loss, mouth sores, higher risk of infection, bruising/bleeding, fatigue, menstrual changes.

6.2 Liposomal Doxorubicin DOXIL® (NSC #712227) Specific Information

6.2.1 Formulation: Doxil is supplied as a liquid in sterile vials each containing 20 mg doxorubicin hydrochloride at a concentration of 2.0 mg/mL.

6.2.2 Solution Preparation: Dilute the DOXIL in 5% Dextrose Injection, United States Pharmacopeia (USP) (D5W). For doses ≥ 12 mg and ≤ 90 mg, dilute in 250 mL of D5W. For doses ≥ 90 mg, dilute in 500 mL of D5W. Once the DOXIL has been diluted it must be kept refrigerated at 2° to 8 °C and administered within 24 hours of mixing. Ordinarily, the drug will be administered by intravenous infusion over 1 hour. However, because of occasional acute reactions to the first dose, that initial

infusion can be administered more slowly if necessary. Infusion may be given through a peripheral vein or a central line.

6.2.3 Storage: Store DOXIL in a refrigerator at 2° to 8°C. Avoid freezing.

6.2.4 Stability: Once the DOXIL has been diluted it must be kept refrigerated at 2° to 8°C and administered within 24 hours of mixing.

6.2.5 Supplier/How Supplied: Commercially available. Johnson & Johnson Pharmaceuticals, Inc.

6.2.6 Administration: See Sections 4.1 and 6.2.2.

6.2.7 Adverse Effects:

- Dermatologic: Mucositis/Stomatitis, palmar-plantar erythrodysesthesia, rash, radiation recall, rarely alopecia
- Hematologic: Neutropenia, thrombocytopenia, anemia
- Hypersensitivity: Anaphylaxis, infusion reaction
- Gastrointestinal: Abdominal pain, nausea, vomiting
- Cardiotoxicity: Cardiotoxicity is rare with DOXIL compared to doxorubicin with a reported incidence of 0-9%.
- Nausea/vomiting, loss of appetite, hair loss, mouth sores, higher risk of infection, bruising/bleeding, fatigue, menstrual changes

6.2.8 Handling and Disposal: DOXIL should not be mixed with other drugs until specific compatibility data are available. The presence of any bacteriostatic agent, such as benzyl alcohol, may cause precipitation of DOXIL. Caution should be exercised in handling DOXIL solution. The use of gloves is recommended. If DOXIL comes into contact with skin or mucosa, immediately wash thoroughly with soap and water. DOXIL should be handled and disposed of in a manner consistent with other anti-cancer drugs. DOXIL is an irritant. DOXIL extravasations should be handled per institutional guidelines.

7. CORRELATIVE/SPECIAL STUDIES

7.1 Tissue Collection, Core Processing and Expression Analysis

The tissue samples will be generated at Moffitt Cancer Center (MCC) and Duke University. There are three possible tissue types that could be submitted for processing: tissue from surgical resection, core biopsy or ascites. At MCC the Tissue Core (TC) will be involved in sample collections and initial processing.

7.1.1 Samples collected at MCC:

The protocol coordinator will notify the Tissue Core and pathologist assigned to the study (Dr. Hakam), using a Case Notification Form, specifying the date, time and location of the tissue collection procedure.

Surgical resection: Upon notification, the Tissue Core representative will collect tissue (normal and tumor) samples into labeled bag and snap-freeze it in accordance with Tissue-Core standard operating procedures. Tissue ischemic time should not exceed 15 minutes; immediately after collection the tissue sample will be embedded in OCT media and sectioned. H&E slide is created and subsequently evaluated by the pathologist for tumor type and content. Based on slide review, the tissue macrodissection will be performed to ensure harvest of at least 60% of diseased tissue. Only high-content tumor tissue will be used for RNA extraction, QC and gene expression analyses.

Core biopsy: Upon notification, the Tissue Core representative and pathologist will assist the radiologist in sample collection during routine CT-guided biopsy. The amount of tissue collected should be equivalent to 20-50 mg. Prior to core sample freezing (within 15 minutes) the pathologist

will perform diff-quick on the touch-prep to assess tumor content in the harvested sample. Tissue core with > 60% of the tumor content will be used in subsequent processing.

Ascites: Ascites will be harvested only if solid tissue is inaccessible for biopsy. No less then 20 ml of fluid should be collected in 50 cc conical tube. Immediately after collection, the cell suspension will be spun at 1500xg. The pellet will be washed once with PBS and frozen in -80C pending RNA extraction and QC.

7.1.2 Samples collected at Duke University:

Surgical resection: Tissue should be collected in a labeled bag and snap frozen in liquid nitrogen within 15 minutes of harvest. The samples should remain frozen in -80 C freezer until shipping.

Core biopsy: Individual cores should be collected in a labeled 2ml cryovial and snap frozen in liquid nitrogen within 15 minutes of harvest. Prior to sample freezing, touch preps should be performed for each core and labeled accordingly, allowing association of the frozen core with the touch prep. The core biopsies should remain frozen in a -80 C freezer, and slides at room temperature until shipping.

Ascites: It should be processed as described above. Cell pellet should remain frozen until shipping.

7.1.3 Sample labeling and shipping

Sample Labeling: Specimens should be labeled with the assigned study number issued by the MCC study coordinator, the date of collection, time lapse from collection to freezing, and the specimen type and name of the sending institution. Please contact Sid Kamath at 813. 745-6629 for the case study number.

Sample Shipping: Prior to shipping samples, please email Michelle Egerman to coordinate the shipment.

Email address: michelle.egerman@moffitt.org.

All samples should be shipped to the following address:

Moffitt Cancer Center
12902 Magnolia Dr.
Tampa, Fl. 33612
Room 3040
Mail stop: MCC-CORE

All frozen samples should be sent on dry ice. Touch prep slides should be sent at room temperature.

7.1.4 RNA extraction and QC

The selected tissue samples will be processed for RNA using Qiagen, mimi-RNeasy kit. RNA quality will be tested on Nano-chips using Agilent Bioanalyzer.

7.1.5 Microarray analyses

RNA will then be prepared, probe generated, and used for hybridization to Affymetrix U133 Plus 2.0 GeneChip arrays (http://www.affymetrix.com/products/arrays/specific/hgu133plus.affx). All procedures will be performed in a MIAME (minimal information about a microarray experiment) compliant fashion, as defined in the guidelines established by Microarray and Gene Expression Data (MGED) Society (www.mged.org) [17, 18]. The Affymetrix CEL files will be added to the MCC Ovarian Genomic Directed Therapy Database. Raw microarray data is deposited by MCC Microarray Core Facility personnel into a password-protected genomic database that is established on a dedicated MCC network drive for this study. Only personnel in the MCC Microarray Core Facility and the study Bioinformatician will have access to this database. Neither the PI, the clinical personnel, nor other laboratory personnel will have access to this database.

Any residual tissue or ascites will be stored in the laboratory and under the oversight of Dr. Johnathan Lancaster at H. Lee Moffitt Cancer Center and Research Institute. Dr. Lancaster will oversee the storage of that tissue, which, if subsequently used, would only be used for Institutional Review Board (IRB)-approved studies.

7.2 Generation of Chemosensitivity Predictor, Turnaround Time and Treatment Assignment

The predictive models for Doxil and topotecan as defined in our previous work ([19] will be implemented to assess the predictive response of a clinical trial sample. In order to predict the clinical trial samples, we have identified a sample set to serve as a reference batch based on similarity in data characteristics of the samples in this batch to the new clinical trial being assayed at this time that best approximate the samples being collected in the prospective validation study. This is assessed by principal component analysis in which measures of similarity (e.g. Spearman rank correlation) were used to determine the optimal set of samples; in this trial we are going to use 24 arrayed ovarian cancer samples as the reference set.

For each incoming sample, the raw Affymetrix CEL file for that sample is combined with the reference set CEL files and measurements of probe intensities are converted into transcriptome-levels estimates of gene expression using the RMA algorithm [20] The incoming sample and reference set are then subject to joint global normalization to the training dataset using a procedure that adjusts the mean and standard deviation of expression in every gene to be equivalent across the two datasets. These pre-processing steps are performed in the R/Bioconductor environment and numeric data for the new samples is exported so that another statistical software runs the algorithm for determining the predicted classification. Each new sample is treated precisely the same and thus the data environment for normalization is constant (the patient samples in the study do not 'accumulate' as part of the reference set).

After the pre-processing steps and normalization, the predictive model, as defined in our previous work [19] is applied to the post-processed sample to generate a probability score. Importantly, all aspects of the model are fixed and based on previous work that defined optimal parameters. These parameters are coded in the software so that each run of the model is identical and based on precisely the same parameters every time. The analysis process generates a log that details the metrics of sample quality, data quality, and results of the predictions which are evaluated to determine if a sample meets quality control standards. For all evaluable samples, the continuous probability score based on the model is converted into a classification of chemo-sensitivity based upon the decision rules defined for the trial. Those with a score greater than or equal to 50% will be assigned to the agent of higher predictive score. Those below 50% will be randomly assigned to one of the two drugs. In the case that the above analysis fails to generate a successful profile, the patients in the experimental arm will be randomized to one of the two treatments in equal proportions. All prediction scores will be kept blinded to patient and treating investigator until the conclusion of the trial. All results will be imported into a secured database and physician is notified of response status. Raw microarray data is deposited by MCC Microarray Core Facility personnel into a password-protected genomic database that has been established on a dedicated MCC network drive for this study. Only personnel in the MCC Microarray Core Facility and the study Bioinformaticians will have

have access to this database. Neither the PI, the clinical personnel, nor other laboratory personnel will have access to this database.

The estimated turnaround time for the expression profile is 7-10 days. From time of consent, biopsy should be obtained within 5 days. Including handling time and other factors, all patients will be able to start treatment within 3 weeks of enrolling on study.

7.3 Disease Response Evaluation and Data Collection

Disease response will be followed using Response Evaluation Criteria in Solid Tumors (RECIST) criteria for response. CA-125 tumor markers will be obtained, but responses for this study will be based on the radiographic findings. A descriptive summary will be made of tumor markers in correlation with genomic predictions and radiographic responses in the final analysis. Patients will have repeat computed tomographic imaging at 8 week intervals. In addition to response and time to progression, data will be collected regarding timeliness of biopsies, gene array processing, and adverse events due to biopsies or treatment.

8. STUDY CALENDAR

Baseline evaluations are to be conducted within 4 weeks prior to administration of protocol therapy. Initial scans and biopsies must be done within 4 weeks prior to the start of therapy. Repeat scans will be at 8 week (+ or – 5 days) intervals beginning with cycle 1 day 1. All laboratory evaluations must be done within 5 days of treatment. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Response will not be assessed prior to the 8 week scan, even if scans are obtained for other reasons in the interim. All patients must receive at least 2 cycles of chemotherapy to determine response.

	Pre-Study	C1 D1	C1 D8	C1 D15	C1 D21	C2 D1	C2 D8	C2 D15	C2 D21	C3 D1	C3 D8	C3 D15	C3 D21	Off Study[d]
Topotecan[a]		X	X	X		X	X	X		X	X	X		
Informed consent	X													
Demographics	X													
Medical history	X					X					X			X
Concurrent meds	X	X----------												X
						----------X								
Physical exam	X	X				X					X			X
Vital signs	X	X	X	X		X	X	X			X	X		X
Height	X													
Weight	X	X				X					X			X
Performance status	X	X				X					X			X
CBC w/diff, plts	X	X	X	X		X	X	X		X	X	X		X
Serum chemistry[b]	X	X				X					X			X
EKG (as indicated)	X													
Adverse event evaluation		X ----------												X
		----------X												
Tumor measurements	X	Tumor measurements are repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X[d]
Radiologic evaluation	X	Radiologic measurements should be at baseline and then every 8 weeks.												X[d]
B-HCG	X[c]													

a: *Topotecan*: Starting dose 4.0 mg/m2 days 1, 8, 15 q28 days days given i.v. per protocol. Maximum BSA = 2.0. (The only variation may be the alternative regimen given elsewhere: 1.25 mg/m2 x 5days q 21 days; evaluation dates are unchanged.)

b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.

c: Serum pregnancy test (women of childbearing potential).

d: Off-study evaluation. Two consecutive measurements taken 4 weeks apart must be used to document response or progressive disease (if the patient is removed from study for this reason.)

	Pre-Study	C1 D1	C1 D8	C1 D15	C1 D21	C2 D1	C2 D8	C2 D15	C2 D21	C3 D1	C3 D80	C3 D15	C3 D21	Off Study[d]
Liposomal Doxorubicin[a]		X				X				X				
Informed consent	X													
Demographics	X													
Medical history	X	X				X				X				X
Concurrent meds	X	X---------- ----------X												
Physical exam	X	X				X				X				X
Vital signs	X	X				X				X				X
Height	X													
Weight	X	X				X				X				X
Performance status	X	X				X				X				X
CBC w/diff, plts	X	X				X				X				X
Serum chemistry[b]	X	X				X				X				X
EKG (as indicated)	X													
Adverse event evaluation		X ---------- ----------X												X
Tumor measurements	X	Tumor measurements are repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X[d]
Radiologic evaluation	X	Radiologic measurements should be performed every 8 weeks.												X[d]
B-HCG	X[c]													
MUGA or Echo	X[e]													

a: *Doxil* Dose 40 mg/m2 every 28 days given i.v per protocol. Maximum BSA = 2.0
b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.
c: Serum pregnancy test (women of childbearing potential).
d: Off-study evaluation. Two consecutive measurements taken 4 weeks apart must be used to document progressive disease if the patient is removed from study for this reason.
e: Baseline and repeated after each 5 cycles or per institutional guidelines.

9. MEASUREMENT OF EFFECT

For the purposes of this study, patients should be reevaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

9.1 Definitions

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [21]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

9.1.1 Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (CT, Magnetic Resonance Imaging [MRI], x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

9.1.2 Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

9.1.3 Target lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

9.1.4 Non-target lesions

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Non-target lesions

include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

9.2 Guidelines for Evaluation of Measurable Disease

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.*

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

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

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

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

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

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Furthermore, such evaluation is not considered as necessary standard of care for this cancer. Therefore, the utilization of such techniques for objective tumor response will not be performed

for this purpose. Information obtained if surgery is being performed for another indication (e.g. bowel obstruction) may be used and placed in context to validate other measures of response by the judgment of the principal investigator.

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

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

9.3 Response Criteria

9.3.1 Evaluation of target lesions

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

9.3.2 Evaluation of non-target lesions

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

existing non-target lesions

Although a clear progression of "non-target" lesions only is exceptional, in such circumstances the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

9.3.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see section 9.3.1).

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

Note:

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

- X In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be

investigated (fine needle aspirate/biopsy) before confirming the complete response status.

9.4 Confirmatory Measurement/Duration of Response

9.4.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed 4weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks (see section 9.3.3).

9.4.2 Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

9.4.3 Duration of Stable Disease

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

9.5 Response Review

There will be a simultaneous review of the patients' files and radiological images at the termination of study in order to confirm responses.

10. REGULATORY AND REPORTING REQUIREMENTS

The descriptions and grading scales found in the revised National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 3.0. A list of adverse events that have occurred or might occur (Reported Adverse Events and Potential Risks) can be found in Section 6 (Pharmaceutical Information). *A copy of the CTCAE version 3.0 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) web site (http://ctep.cancer.gov/reporting/ctc.html).*

The protocol will be conducted in accordance with the protocol submitted to and approved by the United States Army Medical Research and Materiel Command's (USAMRMC) Office of Research Protection (ORP), Human Research Protection Office (HRPO) and will not be initiated until written notification of approval of the research project is issued by the USAMRMC ORP HRPO.

The knowledge of any pending compliance inspection/visit by the FDA, Office of Human Research Protection (OHRP), or other government agency concerning clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements will be reported immediately to USAMRMC ORP HRPO.

10.1 Adverse Event Reporting

Adverse event reporting per University of South Florida (USF) IRB and Moffitt Protocol Monitoring Committee (PMC) guidelines remain operant at the Moffitt Cancer Center. Adverse events at other sites should follow their local institutional guidelines. In addition, all serious adverse events (SAEs) should be reported to the clinical trials coordinator at H. Lee Moffitt Cancer Center, 813-745-7272, within 5 business days. Also, all unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study should be promptly reported by phone (301-619-2165), by email (hsrrb@det.amedd.army.mil), or by facsimile (301-619-7803) to the United States Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO). A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and materiel Command, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

The data will be collected for analysis with the current trial. These toxicities will be also be reviewed by the principal investigators or designees to make decisions regarding delaying, reducing, or omitting the next cycle of therapy, or discontinuing the patient from study.

10.1.1 Expedited Reporting Guidelines

SAEs must be followed until resolution or deemed irreversible. All relevant follow-up information must be promptly reported and recorded on the Study Flow Sheet.

10.1.2 Expedited Adverse Event Reporting Exclusions

Individual institutional rules may have priority and should be followed at that institution. All grade 4 and 5 events should be reported within 5 business days.

10.2 Data Reporting and Monitoring Plan

Data obtained in the course of this study will be stored in a password protected manner under the supervision of Robert M. Wenham, M.D. and Johnathan M. Lancaster, M.D., Ph.D. for an indefinite length of time but no less than that which is required by institutional, federal, state, and local guidelines. Data to be collected is: Eligibility criteria (section 3.1), Exclusion criteria (section 3.2), the signed informed consent, all results from pre-study initial visit and all subsequent tests/evaluations as listed in section 8 (Study Calendar), any supportive medications given/prescribed/recommended (section 4.3), dosing levels, any deviations

from the protocol and the reason, any unexpected or adverse events, disease response per section 7.3, any measurements as noted in Section 9, results of microarray analysis.

No results of the genomic and/or microarray data will be shared with the patients, but all other clinical data will be shared with the patient by the treating physician as clinically indicated.

10.2.1 **Investigators**

As principal investigator, Robert M. Wenham, M.D. will provide global oversight to all facets of the trial. This includes regulatory issues such as budgeting, IRB, consents, adverse event monitoring, protocol violations, data collection and analysis, and progress reports. It also includes assuring the genomic microarray translational component is incorporated into the trial as described in the protocol section and that timely and accurate communication occurs between investigators. He will also be responsible for all conflict resolution and troubleshooting. At least once every month meetings will be conducted to review progress including technical aspects, accrual goals, adverse events, and identification of performance improvement items. Dr. Wenham has no conflict of interest to disclose.

Johnathan M. Lancaster, M.D., Ph.D. will be the translational scientist responsible for performing and analyzing the genomic microarrays. Part of this will include ensuring the integrity of collected specimens, rapid and accurate performance of Affymetrix microarray, and the timely communication of those results to the other investigators. Dr. Lancaster has extensive experience with the techniques and the microarray platform described which has led to peer-reviewed publications and the preliminary data for this trial. Dr. Lancaster is part of the Risk Assessment, Detection, and Intervention Program at the H. Lee Moffitt Cancer Center. The Moffitt Cancer Center and the collaborating institution have pending patent applications (which may become issued patents) related to one or more parts of this study. These patent applications relate to Dr. Lancaster's research. This means that it is possible that the results of this study could lead to personal profit for the Moffitt Cancer Center, the collaborating institution, and/or Dr. Lancaster. This project has been carefully reviewed to help assure that Dr. Lancaster's professional judgment will not be compromised. Dr. Lancaster will comply with all Cancer Center policies, and the study will be monitored to ensure patient safety.

Ardeshir Hakam, M.D. is a clinical gynecologic pathologist who will be involved in the review of pathologic materials for patients enrolled on this trial. He will be responsible for confirming the diagnosis of accepted pathologic types of ovarian cancer, as well as reviewing biopsy specimens for the percent of the sample containing malignant cells. Dr. Hakam has no conflict of interest to disclose.

Steven Eschrich, Ph.D. is a biostatistician in Moffitt's Bioinformatics Core Division. Dr. Eschrich will be responsible for analysis of all relevant data for statistical accuracy and conclusions.

Angeles Alvarez-Secord, M.D. is a sub-investigator located at Duke

University. Dr. Alvarez-Secord will be responsible for identifying, screening, recruiting, and treating patients on this trial located at Duke University Medical Center and forwarding the relevant patient data collected per this protocol in a manner that will protect patient confidentiality. She will also direct the collection of biopsy material from these patients and supervise the shipment of the biopsy per the protocol section 7.1. Dr. Alvarez-Secord has no conflict of interest to disclose. As part of the responsibilities assumed by participating in this trial, Dr. Alvarez-Secord agrees to maintain and have available for monitoring adequate case records (accurate source documents and case review forms [CRFs]) for the patients treated under this protocol. In addition, he agrees to maintain all administrative documents, e.g. IRB correspondence, investigational product and supplies shipment manifests, monitoring logs, or Moffitt Cancer Center/designee correspondence.

William T Barry, PhD is an Assistant Professor at Duke who has implemented automated analysis systems within various ongoing Duke Institute for Genome Science and Policy clinical trials involving the chemotherapeutic predictive models that will be used within this trial. He will be responsible for providing his expertise in designing the automation parameters of the statistical analysis.

Sachin Apte, M.D., M.S. is a sub-investigator located at the Moffitt Cancer Center who will be responsible for identifying, screening, recruiting, and treating patients on this trial. Dr. Apte has no conflict of interest to disclose.

Sierra Theodore, R.N., CCRC, is a clinical trials coordinator at the Moffitt Cancer Center. She will be responsible for collection and reporting of information and data that is collected from patients who have been consented to this trial at Moffitt and at Duke through the use of Adverse Event (AE) forms, CRF forms, End of Study forms, and Informed Consent forms. Ms. Theodore has no conflict of interest to disclose.

10.2.2 **Data Safety Monitoring Plan**:

The Principal Investigator of the study will be responsible for the conduct of the trial. In this capacity, the PI or the PI's designee will hold monthly meetings to review study conduct with study personnel including the regulatory specialist, clinical trials coordinators and accruing physicians. Communication between the PI and co-PI will occur at least monthly or when any significant change findings or adverse events occur.

All adverse event reports should be per the policies and guidelines of the local institutional protocol monitoring committee and the responsible local Institutional Review Board. In addition, all adverse event reports should be forwarded to the Principal Investigator of this study.

The CTC will be responsible for screening eligibility of patients with investigators, registering patients for the protocol, and assigning a registration number to them upon completion of the eligibility labs etc. Subsequently, the CTC or designate will guide the evaluation of the patients through protocol treatment.

All response data will be entered into a spreadsheet and reviewed by the PI. If there is a discrepancy, the PI will review the data to determine response.

A serious adverse event is any adverse drug experience occurring at any dose that:

1. Results in death
2. Is life-threatening
3. Results in in-patient hospitalization or prolongation of existing hospitalization
4. Results in a persistent or significant disability/incapacity; or in congenital anomaly/birth defect

There are no early stopping rules for this study because the two drugs used in this study represent standard of care, the choice is typically empiric, and the results of genomic-directed decision for therapy, at worst, should do no worse than patients given these drugs randomly off study.

10.2.3 Institutional Review Board

No subject is to be enrolled on this protocol until the Center's Institution Review Board has approved it. The protocol will be conducted in accordance with the protocol submitted to and approved by the USAMRMC ORP HRPO and will not be initiated until written notification of approval of the research project is issued by the USAMRMC ORP HRPO.

Major modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the USAMRMC ORP HRPO as soon as the deviation is identified.

Any deviation to the protocol that may have an effect on the safety or rights of the subject or the integrity of the study must be reported to the USAMRMC ORP HRPO as soon as the deviation is identified. In the event of a protocol deviation, the procedures set forth by the USF IRB (policy #704) will be followed.

A copy of the approved continuing review report and the local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available. A copy of the approved final study report and local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available.

If the protocol is modified, terminated, or extended, the procedures set forth by the USF IRB (policy #703 and 705) will be followed.

10.2.4 **Monitoring**

For subjects at the Moffitt Cancer Center, Corporate Compliance will perform audits on the study, and report findings to the Protocol Monitoring committee.

Per DoD Directive 3216.1, all greater than minimal risk studies require a Medical Monitor. Dan M. Sullivan, MD will serve as the medical monitor for this study. His role in this research study will be to comment on the outcomes of any unanticipated problem involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol. In the case of a serious adverse event or death, Dr. Sullivan will comment on the relationship to participation in the study. He will also indicate whether he concurs with the details of the report provided by the principal investigator.

10.2.5 **Informed Consent**

The investigator is responsible for patient care and for obtaining consent by the patient. Written informed consent must be obtained prior to entry of any patient. Volunteers will be identified by their physician, who will be one of the investigators listed on the informed consent. The subject's treating physician, in reviewing the treatment options with the potential volunteer, will mention this study if she is potentially eligible based upon the available clinical information and her history. If the physician and potential subject determine she would like to be screened for participation in the study, the study coordinator is called to review the screening and study procedures with the potential subject and the informed consent document is given to the patient. After discussion with her physician (who is also a study co-investigator) of the risks and potential benefits of study participation (along with the other required elements within CFR 50.25) the study subject is given time to make her decision. After the study subject decides to participate in the research study she denotes this decision by signing the informed consent in the presence of study staff. Volunteers will be consented at one of the approved sites listed on the informed consent that have activated this trial. Patients will have an indefinite amount of time to consider participation. However, the opportunity to participate may be limited by any changes in the patient's eligibility criteria and whether the trial remains open. Patients will be able to discuss their choice with significant others or their physicians.

We do not know if the patient volunteers will benefit by taking part in this study. We do not know if the experimental procedure will help the patient's disease. We are doing this study to develop a reliable method for selecting the treatment to which a woman is most likely to respond, based on pre-treatment genomic microarray analyses of her own tumor tissue. We do not know if the microarray analysis will accurately predict a chemotherapy to which the patient will respond. This research study should help us learn more about whether this procedure will improve treatment decisions in the future.

Physicians will be recruiting their own patients. The issue of coercion is not expected to be an issue since the physician will not receive a financial benefit for enrolling patients and given the expected level of reimbursement from private

insurance/Medicare/Medicaid, there is no significant financial benefit to the physician. The study team will interact with the patient as a team and individually. The subject will be repeatedly told that they can tell any member of the study if they have any questions or concerns about participating in the research study. They can also indicate to any member of the study team if they wish to quit the project at any time. This will allow the subject to express their concerns to other individuals if they feel they cannot do so to the physician.

Patients will not need to take any special precautions as part of their participation in this trial.

Subjects may withdraw from the protocol at any time in any manner verbal or written by notifying any member of the research team, including their physician. If a subject withdraws, her data will be maintained and used in analysis as detailed in section 11. If a patient withdraws, her treatment will not be affected.

10.2.6 **Hospital/Clinic Records**

Hospital records for patients on this study are the responsibility of the investigator. Accurate and complete study records will be maintained and made available for review by the sponsors of the trial, representatives of the U.S. Army Medical Research and Materiel Command as a part of their responsibility to protect human subjects in research, health care personnel involved in this study, the IRB, Department of health and Human Services (DHHS), and the FDA. Records will be stored in a confidential manner so as to protect the confidentiality of subject information. The electronic medical record system is password protected and can only be accessed from within the Moffitt firewall. All data that is recorded on paper case report forms are kept in a research area. When not in use, the case report forms are located within a file cabinet that is locked or within a locked area.

10.2.7 **Case Report Forms**

See Appendix.

Subject information will be recorded on case report forms, which will be kept in locked cabinets or a locked area in the Program offices. Any data stored on Moffitt Cancer Center's network system is password protected and is access-limited. Firewalls are in place to prevent outside incursions. Records will be kept in accordance with federal, state, and local regulations, as well as sponsor requirements. At the regulated time, all records will be shredded.

10.2.8 **Investigator Study Files**

The principal investigator is responsible for maintaining study files after final study closure in a manner and time period as mandated by the FDA. The following documents should be kept in the study files:

A completed, signed FDA Form 1572 (Statement of Investigator) and copies of all current curricula vitae of all sub investigators listed on the Statement of the Investigator.

- The original protocol and all amendments
- Final IRB approval, annual renewals and all IRB correspondence
- Blank Case Report Forms

- Copy of all IRB approved Informed Consent forms with applicable version date
- Updated laboratory certification and laboratory values (covering entire time of study)
- Copy of all patient's signed informed consent forms
- The final completed case report form for all patients

10.3 Cooperative Research and Development Agreement (CRADA)/ Clinical Trials Agreement (CJA)

Any manuscripts reporting the results of this clinical trial will include the Principal Investigator, Co-Principal Investigator, Statistician, Study pathologist, and the top accruing Sub-investigators in order up to the maximum number of authors allowed by the publisher. Final decision of all issues relating to the publication will belong to the Moffitt PI.

11. STATISTICAL CONSIDERATIONS

11.1 General Ethical and Statistical Considerations

Consideration was given to whether it was appropriate to blind results of the genomic predictions until the analysis of data. Patients enrolled in the trial would have typically received either liposomal doxorubicin or topotecan as standard of care for treatment in this clinical setting. Unblinding of the results would likely have led to the exclusion of patients with predictive profiles under 50%; with the possibility of treating physicians employing alternative salvage chemotherapy agents. Therefore, these patients who would have otherwise received these preferred salvage drugs (topotecan or liposomal doxorubicin), might now be given other, perhaps less preferred, alternative salvage drugs based on assumptions about this assay that we are just now attempting to validate. Including these patients means that patients on any arm of the trial would never be receiving less than usual standard of care. If our hypothesis is correct, we have no risk of worsening patient outcome compared to standard care; but we have a strong chance at improving the outcome for a significant proportion of patients. An additional benefit of blinding the results will be to prevent bias in estimating response by the investigators.

This is a pilot study with results that should give information necessary to explore the results further in larger prospective studies. The response rate for genomic-directed therapy will be the *combined response rate* for both topotecan and liposomal doxorubicin patients with predictive profiles of ≥0.5. This is possible since our prior data of 119 ovarian cancer patients demonstrates that almost exactly equal proportions of those with predictive profiles ≥0.5 will be assigned to topotecan or liposomal doxorubicin. Moreover, even if this were not the case, we also know that the historical response rates for these two chemotherapies are nearly identical in this population at around 20%.

11.2 Sample Size/Accrual Rate

The present trial is a pilot study. The primary endpoint of the trial is to determine feasibility of a larger trial. To do so we will describe 1) the time required from enrollment to information from the genomic prediction array available to the investigator for initiation of treatment and 2) the number of successful biopsies and successful assays. Consideration for the number of patients needed for the trial is based on giving a reasonable description of the primary objectives above, as well as some information to calculate a response rate for those with a high predictive likelihood ratio. Published data regarding liposomal doxorubicin and topotecan response rates in exactly this type of population is available from both phase II and phase III trials (3-11) and provides us with an historical response rate (H_o) of about 20%. We have calculated the positive predictive values (PPV) of response based upon a predictive profile cutoff of >0.5. Given the prior preclinical data, 67% of patients (roughly 2/3rds) will be predicted to have a high likelihood of response to either topotecan or doxorubicin, (and in roughly equal proportions of patients to each drug). To have a clinically interesting result, we will estimate a conservative response rate of 40% for the two drugs combined when the predictive ratio is greater than or equal to 0.5.

By enrolling 30 patients, we expect about 2/3rds, or 20 patients, to have interpretable assay results. This assumes that one-third will be unable to be biopsied or have uninterpretable or indeterminate assay results. Note that indeterminate results are those that, despite successful biopsy and collection of tumor tissue, are uninterpretable due to limitations of the assay either from sample degradation, high levels of background noise, or other problems. Of the 20 patients, our data suggests that two-thirds, or about 13, will have a predicted likelihood ratio of ≥ 0.5 for one of the 2 chemotherapies. We will generate a response rate with 95% confidence interval. Given 13 evaluable patients with relative risk (RR) ratios of ≥ 0.5, a 40% response rate will allow 90% confidence interval of (0.18, 0.62).

11.3 Feasibility

We plan to successfully complete this trial within18 months by accruing at the H. Lee Moffitt Cancer Center and Duke University Medical Center, with the possibility of adding other approved sites that may reduce the anticipated trial completion date. This may include any of the H. Lee Moffitt Cancer Center's approved Moffitt Research Network sites and/or Duke University Medical Center. Duke University Medical Center and most of Moffitt's approved Research Network sites have access to a local IRB. Before the site could open this trial, we will provide the protocol and the informed consent for submission to their IRB as per that IRB's policy. Additionally, we would ensure that USAMRMC ORP HRPO reviews and approves the site. Moffitt would then provide oversight of their regulatory, study initiation visits, monitoring, and in general act as a liaison between the Moffitt PI/coordinator and the site PI/coordinator. Before a site can be designated as a Moffitt approved Research Network site, it must undergo an approval process that includes site inspection. All Moffitt approved Research Network sites follow our policies, and Moffitt has staff who provide education, act as a resource, and provide oversight to those sites.

At each site, the principal investigator who has been approved to activate this

trial will be responsible for screening, recruiting, consenting, and treating the patient volunteers and will be responsible for sending tissue collected per the specific protocol instructions in section 7.1 and reporting the patient-associated data collected per Section 8. With enrollment of approximately 2 per month from both Moffitt and Duke, accrual will be reached before the 18 month target. We have an established collaborative relationship between the medical centers for gynecologic oncology and genomic science protocols. While we have a firm commitment and vested interest from investigators at Duke to accrue patients to this trial, the H. Lee Moffitt Cancer Center is the principal site. The primary direction and control, as well as all translational science and data analysis will be performed at the H. Lee Moffitt Cancer Center.

11.4 Statistical Analysis

For each group, the overall response rate (secondary endpoint) will be calculated with a 2-sided 95% confidence interval. Fisher exact test will be used to test difference of response rates between groups. The primary endpoint will be done using simple descriptive statistics of rates of successful biopsies, array analyses, and times from enrollment to biopsy, biopsy to analysis, and analysis to treatment. For expression data, the gene-expression sensitivity profiles will be assessed for their ability to assign patients into the appropriate category. Although the trial will attempt to validate the profiles in a prospective manner, the data obtained will also provide a further opportunity for remodeling profiles for future studies. Expression data will be obtained on all patients enrolled in the trial. This will allow us to evaluate the accuracy of the predictor for all the patients enrolled. We will use the binary regression predictive model used in our previous work [19].

11.5 Reporting and Exclusions

11.5.1 **Evaluation of toxicity.** All patients will be evaluable for toxicity from the time of their biopsy. Information regarding biopsy complications and chemotherapy treatments will be collected.

11.5.2 **Evaluation of response.** All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the exception of those who received no chemotherapy) will be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug

administration does not result in exclusion from the analysis of the response rate.

All conclusions should be based on all eligible patients. Sub-analyses will then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.).

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Consent to Take and Store Additional Samples

We are asking you to let us to take and store additional samples of your tumor or tumor DNA for use in the future research studies.

These samples may be used for a variety of purposes. We may use these samples to help us:

- Learn more about your disease.
- Learn how treatment with Doxil or Topotecan works.
- Find new ways to help people feel better.
- Someday, learn how to treat or cure ovarian cancer.

It is your choice. You do not have to agree to this. There will be no penalty if you don't agree. You can still take part in the main study that was explained to you.

____ I give my consent to take, store, and use samples of my tumor or tumor DNA for future research studies.

____ I do not give my consent to take, store, and use samples of my tumor or tumor DNA for future research studies.

_____ _____

Signature Date

_____

Printed name

_____ _____

Signature of Person Obtaining Consent Date

_____

Printed Name of Person Obtaining Consent

APPENDIX A

Performance Status Criteria

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

APPENDIX B

MULTICENTER GUIDELINES

Responsibility of the Protocol Chair

- The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center (Moffitt Cancer Center)

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval).
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.