Local Protocol #: UC IRB13-1235

A RANDOMIZED PLACEBO CONTROLLED PHASE II TRIAL OF METFORMIN IN CONJUNCTION WITH CHEMOTHERAPY FOLLOWED BY METFORMIN MAINTENANCE THERAPY IN ADVANCED STAGE OVARIAN, FALLOPIAN TUBE AND PRIMARY PERITONEAL CANCER

Coordinating Center: *The University of Chicago*

Principal Investigator:

S. Diane Yamada, M.D.
University of Chicago Medicine
5841 S. Maryland Avenue, MC 2050
Chicago, Il 60637
773-702-6721
Fax: 773-702-5411
sdyamada@uchicago.edu

Co-Investigators:

Gini Fleming, M.D.
University of Chicago Medicine
5841 S. Maryland Avenue, MC 2115
Chicago, IL 60637
773-702-6712
Fax: 773-702-3163
gfleming@medicine.bsd.uchicago.edu

Iris Romero, M.D.
University of Chicago Medicine
5841 S. Maryland Avenue, MC 2050
Chicago, IL 60637
773-702-6722
773-702-5411
iromero@babies.bsd.uchicago.edu

Ernst Lengyel, M.D., Ph.D.
University of Chicago Medicine
5841 S. Maryland Avenue, MC 2050
Chicago, IL 60637
773-702-6722
Fax: 773-702-5411
elengyel@uchicago.edu

Statisticians:

Theodore Karrison, PhD
Department of Health Studies
University of Chicago Medicine
5841 S. Maryland Avenue, MC 2007
Chicago, IL 60637
Ph. 773-702-9326
Fax. 773-702-1979
karr@uchicago.edu

Matthew J. Maurer
Division of Biomedical Statistics and Informatics
Mayo Clinic
200 First Street
Rochester, MN 55905
Ph. 507-266-2064
maurer.matthew@mayo.edu

Principal Investigators at Participating Sites:

Sean C. Dowdy, M.D.
Mayo Clinic
200 First Street SW
Rochester, MN
Ph. 507-266-0225
dowdy.sean@mayo.edu

Gustavo C. Rodriguez, M.D.
NorthShore University Health System
2650 Ridge Avenue
Walgreen Building #1507
Evanston, IL 60201
Ph. 847-570-2639
grodriguez@northshore.org

James A. Wallace, M.D.
Ingalls Memorial Hospital
1 Ingalls Drive
Harvey, IL 60426
Ph. 708-339-4800
james.wallace@uchospitals.edu

Charles Leath III, M.D.
University of Alabama
1700 6th Ave South
10th Floor Women and Infants Center, Suite 10250
Birmingham, AL 35233
Ph. 205-934-4986
cleath@uabmc.edu

Rodney Rocconi, M.D.
University of South Alabama
1660 Springhill Avenue
Mobile, AL 36604
Ph. 251-665-8000
rocconi@health.southalabama.edu

Michael Goodheart, M.D.
University of Iowa
200 Hawkins Drive
31506 PFP
Iowa City, IA 52242
Ph. 319-356-2015
michael-goodheart@uiowa.edu

James L Wade, III, M.D.
Decatur Memorial Hospital
Clinical Research Department
2300 N. Edward Street
Decatur, IL 62526
Ph. 217-876-6600
jlwade3@sbcglobal.net

Other Participating Sites:

Northwest Community Hospital
Arlington Heights, IL
Ph. 847-618-1000

Protocol History

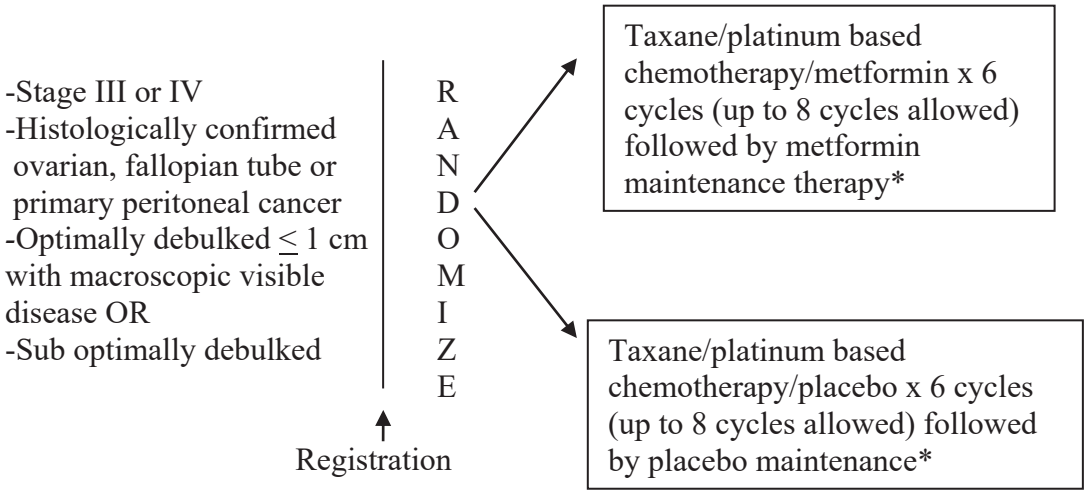
Version Date	Description of Action
1/28/14	**Original Submission**
4/29/14	**Amendment #1**
12/15/14	**Amendment #2**
5/11/15	**Amendment #3**
9/18/15	**Amendment #4**
6/29/16	**Amendment #5**
10/11/16	**Amendment #6**
04/12/17	**Amendment #7**
01/16/18	**Amendment #8**
12/04/18	**Amendment #9**
11/15/19	**Amendment #10**

This study is being conducted by institutional members of the Personalized Cancer Care Consortium (PCCC), as well as additional sites.

SCHEMA

Target population:
-Primary epithelial ovarian, fallopian tube or primary peritoneal cancer, stage III or IV
-Primary cytoreductive surgery with macroscopic residual disease (optimally debulked ≤ 1 cm with visible residual disease) OR suboptimally debulked OR
-Planned for neoadjuvant chemotherapy

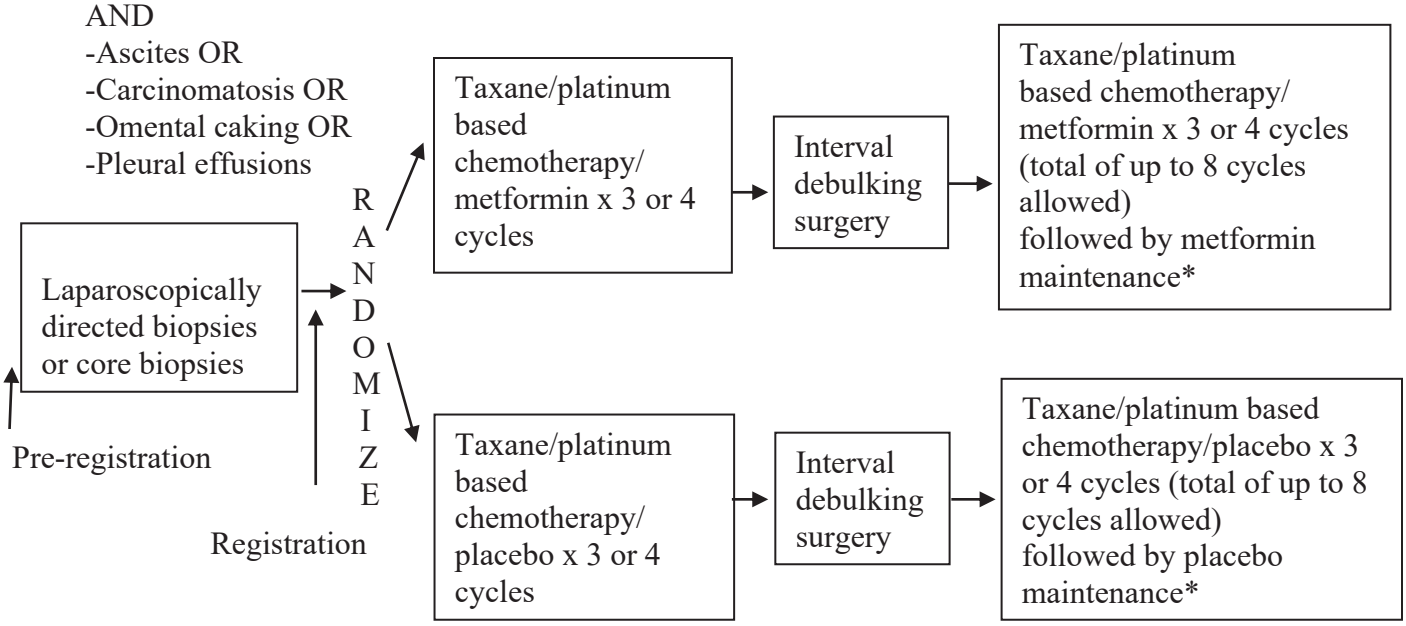
Primary cytoreductive surgery followed by adjuvant therapy



*Olaparib maintenance therapy allowed

Neoadjuvant chemotherapy followed by interval debulking surgery (IDS)—PARTICIPATING in correlative tissue collection substudy

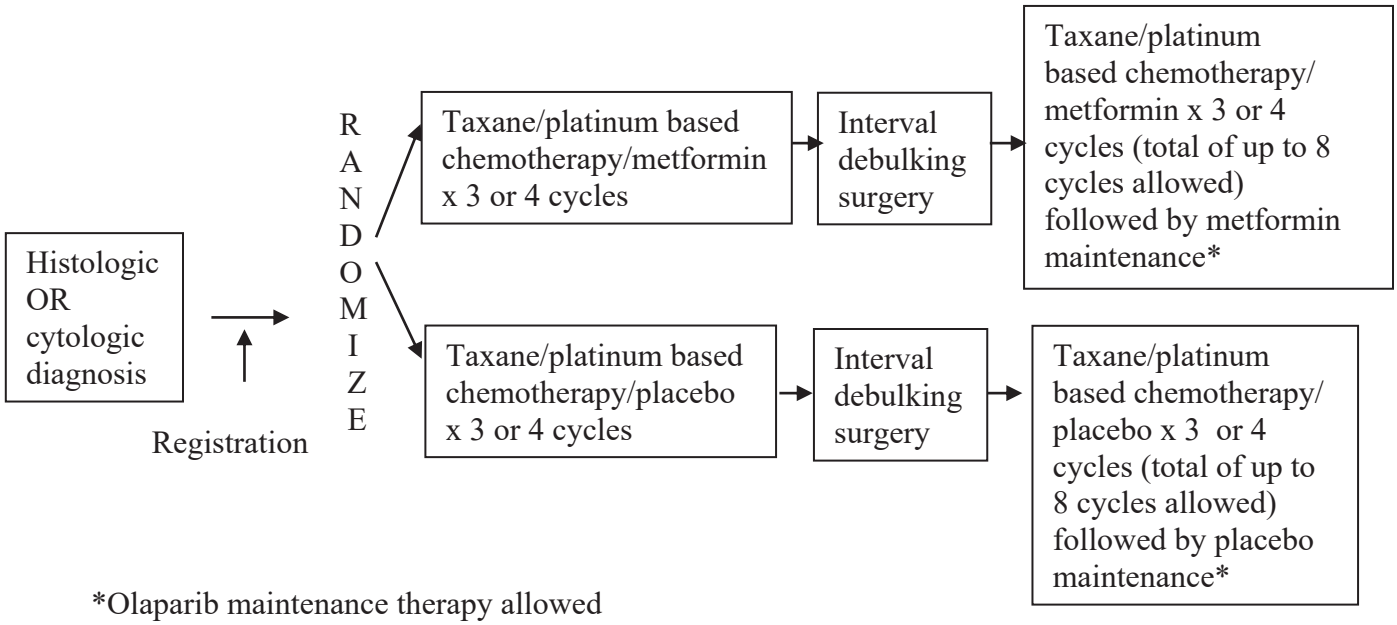
-Investigator suspects stage III or IV ovarian, fallopian tube, or primary peritoneal cancer:
-CA125>250 OR CA125:CEA ratio > 25 OR CA125 ≤ 250 with no evidence of GI cancer
AND
-Ascites OR
-Carcinomatosis OR
-Omental caking OR
-Pleural effusions



*Olaparib maintenance therapy allowed

Neoadjuvant chemotherapy followed by interval debulking surgery (IDS)-
NOT PARTICIPATING in correlative tissue collection substudy

-Presumed stage III or IV based on ascites, peritoneal carcinomatosis, omental caking
-Histologically confirmed carcinoma consistent with ovarian, fallopian tube or primary peritoneal cancer:
  -Cytology OR FNA OR core biopsies OR surgically directed biopsies showing adenocarcinoma
-CA125 >250 OR CA125:CEA ratio > 25 OR CA125 ≤ 250 with no evidence of GI cancer



*Olaparib maintenance therapy allowed

Acceptable chemotherapy regimens will include:

1. R1: IV paclitaxel 175 mg/m2 plus IV carboplatin AUC 5-6 every 21 days
2. R2: IV docetaxel 75 mg/m2 plus IV carboplatin AUC 5-6 every 21 days
3. R3: IV paclitaxel 80 mg/ m2 day 1, 8, and 15 plus IV carboplatin AUC 5-6 day 1 every 21 days

Acceptable alternative chemotherapy regimens for elderly patients ≥ 70 will include:

1. R4: IV paclitaxel 135 mg/m2 plus IV carboplatin AUC 5* plus optional G-CSF every 21 days
2. R5: IV paclitaxel 60 mg/m2 day 1, 8, and 15 plus IV carboplatin AUC 5* day 1 every 21 days (day 15 paclitaxel optional)
3. R6: IV paclitaxel 60 mg/m2 plus IV carboplatin AUC 2 day 1, 8, and 15 every 21 days

*Patients for whom the physician deems carboplatin AUC 5 to be unsafe may be treated with AUC 4.

Subjects can receive a total of 8 cycles of chemotherapy

Metformin dose will be 850 mg po q day starting on day 1 of chemotherapy then increased to 850 mg po BID as tolerated.

Total duration of metformin/placebo is for 2 years from date of randomization or until radiologic progression of disease or intolerance to metformin.

Olaparib maintenance therapy allowable for BRCA germline mutation carriers. Total duration is for 2 years from completion of chemotherapy or progression of disease, whichever comes first.

Planned total sample size: 160 (80% power to detect 5 months improvement in median progression free survival (PFS) with α=0.15, allowing for 10% dropout.

Primary endpoint: Progression free survival

Secondary endpoints:

-Biochemical response rate
-Overall survival
-Time to biochemical progression
-Toxicity

Ancillary endpoints:
-Correlative biomarkers

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objective

To determine if the addition of metformin to standard adjuvant or neoadjuvant chemotherapy plus extended metformin beyond standard chemotherapy increases progression free survival when compared to 6 cycles of standard chemotherapy alone in non-diabetic subjects with stage III (with any gross residual disease) or stage IV ovarian, primary peritoneal, or fallopian tube carcinoma.

1.2 Secondary Objectives

To determine whether the addition of metformin to standard chemotherapy plus extended metformin beyond standard chemotherapy increases the time to biochemical progression when compared to chemotherapy alone

To compare biochemical (CA-125) response rates in the two arms

To describe and compare toxicities in the two arms

To compare overall survival in both arms

1.3 Exploratory Objectives

To elucidate metformin's molecular mechanism of action in ovarian, fallopian tube or primary peritoneal cancer by: (i) determining whether metformin's anti-cancer effects are mediated by systemic metabolic changes, a direct effect on tumor cells, or both, and (ii) testing the metabolic and proteomic alterations induced in biospecimens from non-diabetic patients prospectively treated with standard chemotherapy in conjunction with metformin compared to placebo.

2. BACKGROUND

2.1 Standard management of ovarian, fallopian tube and primary peritoneal cancer

Currently, the standard treatment for ovarian, fallopian tube and primary peritoneal cancer, hereafter referred to as OvCa, consists of aggressive surgery to remove all visible tumor and six cycles of a platinum and taxane containing chemotherapy regimen followed by close surveillance. Despite initial response rates of over 80%, the majority of women with advanced stage disease will suffer a recurrence (1,2). Ultimately, OvCa has the highest fatality to case ratio of all the gynecologic malignancies which has stimulated a range of approaches to improve outcome. For those patients with stage III disease who have been optimally debulked (surgically cytoreduced) to less than 1 cm of residual disease, intraperitoneal chemotherapy has demonstrated a significant survival benefit over intravenous chemotherapy with median

progression free survival (PFS) of 23.8 months compared to 18.3 months with IV therapy and median overall survival (OS) of 65.6 months vs 49.7 months with IV therapy (3). In the suboptimally debulked patient population, however, PFS and OS have remained relatively constant with the last significant improvement occurring with the addition of paclitaxel to platinum based chemotherapy. GOG 111, which incorporated paclitaxel into frontline therapy with cisplatin, improved median PFS to 18 months from 12 months and OS to 38 months from 24 months over a non-paclitaxel containing regimen (4). Despite the investment of significant resources, new drug development in OvCa has been slow. Introduction of the last new drug, liposomal doxorubicin (Doxil®), occurred 14 years ago. GOG 182/ICON 5 was a randomized phase III multi-institutional trial that incorporated liposomal doxorubicin, or gemcitabine as a triplet regimen with paclitaxel and carboplatin or topotecan, or gemcitabine as a sequential doublet regimen with paclitaxel and carboplatin. This strategy of adding a third cytotoxic agent to the backbone of paclitaxel and carboplatin intravenously did not yield an improvement in PFS (15.4-16.4 months) or OS (39.6-44.2 months) over paclitaxel and carboplatin alone (5, 6). In addition to adding cytotoxic agents (GOG 182/ICON5), other strategies to augment PFS in suboptimally debulked patients have included the use of molecularly targeted agents (GOG 218, ICON7) to frontline therapy. The addition of bevacizumab, an anti-angiogenic agent, to paclitaxel and carboplatin and as maintenance therapy did improve PFS by nearly 3 months in GOG 218 but did not change OS (7). Similar results were obtained in the ICON7 study (8). Given the cost of bevacizumab, its use in the upfront setting has not been deemed cost effective (9). Other strategies in this patient population have included using a dose dense chemotherapy approach. The Japanese GOG performed a randomized phase III study in patients with stage II to IV disease utilizing weekly paclitaxel at 80 mg/m2 on days 1, 8, and 15 of a 21 day regimen in conjunction with carboplatin AUC 6 on day 1 as compared to intravenous paclitaxel and carboplatin on day 1 of a 21 day regimen. The long term results for those patients with 1 cm of residual disease showed a significant improvement in PFS: 17.6 months with the weekly dose dense regimen as compared to 12.1 months with the q 21 day regimen. OS also increased to 51.2 months from 33.5 months with the dose dense regimen (10).

Standard chemotherapy regimens for OvCa patients include adjuvant paclitaxel and carboplatin IV q 21 days and dose dense paclitaxel day 1, 8 and 15 with carboplatin day 1 IV q 21 days. In patients with large volume disease, a neoadjuvant chemotherapy approach with 3 cycles of paclitaxel and carboplatin IV followed by an interval debulking procedure and another 3 cycles has also been deemed equivalent to primary cytoreduction followed by paclitaxel and carboplatin IV q 21 days (11). Elderly patients may experience increased toxicity with standard doses of chemotherapy. In a retrospective analysis, reduced doses of chemotherapy appeared to be better tolerated in patients over the age of 70 (12). These reduced doses of chemotherapy are currently being evaluated for toxicity in GOG 273. Despite an increase in the percentage of patients who attain 5 year survivals, patients with stage III and IV disease, particularly those with a large initial tumor burden, those with poorer performance status and those who are suboptimally debulked, continue to have the worst outcome and new approaches to therapy, that are cost effective, warrant investigation.

2.2 Metformin

A protective effect of metformin against cancer was initially suggested by observational studies describing decreased cancer risk and increased survival among diabetic patients using metformin compared to individuals not using metformin (13-15). In a meta-analysis of these studies metformin use was associated with a 31% decrease in cancer risk (17). While provocative, these retrospective observational studies have inherent limitations (i.e. recall and allocation bias, confounding) and the metformin literature has been criticized for time related biases (18). A study using Women's Health Initiative data was able to partly overcome these limitations. The study prospectively collected data on metformin use and using a time-dependent exposure analysis, found that diabetic women on metformin had a lower incidence of breast cancer (19). Building on the observational studies, several pre-clinical studies have now been published indicating that metformin inhibits growth of cancer cell lines (20-22), decreases tumor growth in pre-clinical models (23-25), and may increase chemosensitivity when added to chemotherapy in breast (25), endometrial (23, 26), and OvCa (22,27-29). Retrospective studies in breast (30) and lung cancer (31) have found higher rates of response to neoadjuvant chemotherapy among metformin users.

The University of Chicago and the Mayo Clinic have independently shown in retrospective studies that patients with diabetes who use metformin have a significantly better prognosis and their tumors are more sensitive to chemotherapy than those who have not used metformin (32, 33). Moreover, our pre-clinical studies, using OvCa cell lines and mouse models, suggest that metformin inhibits tumor growth, alters the interaction between cancer cells and stromal cells in the tumor microenvironment, and sensitizes tumor cells to platinum/paclitaxel chemotherapy by modifying OvCa cell metabolism (Figure 1).

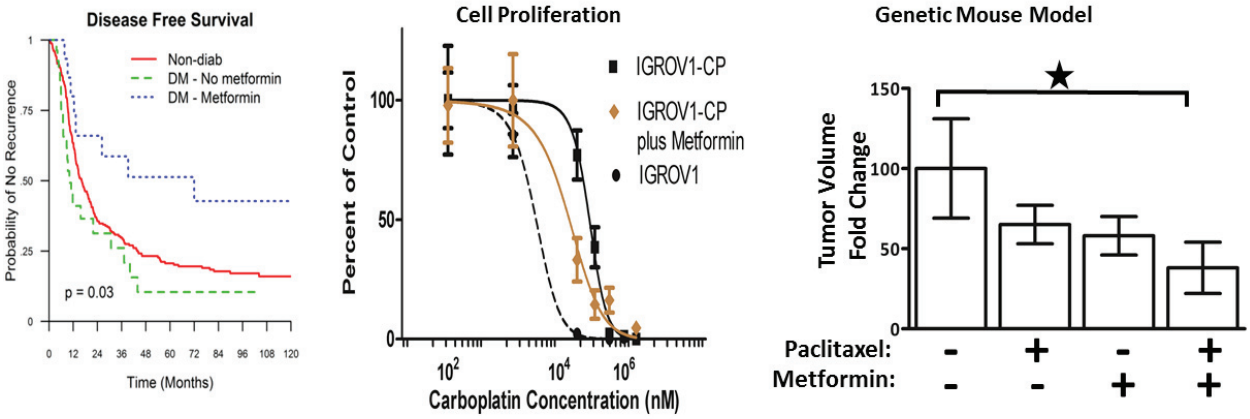


Fig. 1. Metformin added to chemotherapy increases cytotoxicity. **(A)** Using a retrospective cohort OvCa patients were divided into 3 groups: non-diabetics (n=297) and diabetics not using metformin (n=28) and using metformin (n=16). Disease free survival was evaluated using Kaplan-Meier estimates. **(B)** Carboplatin resistant (IGROV1-CP, box symbol) and sensitive (IGROV1, circle symbol) OvCa cells were treated with increasing concentrations of carboplatin for 72 hrs and proliferation was measured using MTT assays. Resistant cells were then treated with carboplatin plus 10mM metformin and MTT assay repeated (diamond symbol). **(C)** OvCa was induced in Kras/Pten genetic mice, 2 weeks later mice were treated with: vehicle control (n=21), paclitaxel alone (3 mg/kg IP weekly, n=25), metformin alone (100 mg/kg/day in water, n=18), or paclitaxel plus metformin (n=18). After nine weeks of treatment mice were sacrificed and primary tumor weight was measured and compared between treatment and control mice. Bar reports mean ± s.e.m. Star = 0.02.

In addition to the retrospective studies that correlate metformin use with improved survival, one prospective study is also suggestive of an association with improved recurrence free survival. Among diabetic patients on the MIMOSA trial of abagovomab, a murine monoclonal antibody directed against CA125, those patients who received metformin had a HR for recurrence free survival (RFS) of 0.42 [CI: 0.175-1.002], p=0.05. Median OS had not been met in the metformin patients with a HR = 0.295 [CI: 0.109-0.803], p=0.02 compared to diabetic patients not receiving metformin (34, 35). Therefore, the existing body of literature supports the theory that metformin has both a protective and therapeutic effect in cancer.

The mechanisms mediating metformin's effects are unclear. The vast majority of the pre-clinical work has been completed using supra-physiologic doses (mM range) of metformin, leaving the true *in vivo* cancer targets of the diabetes drug largely unknown. The need for higher concentrations of metformin to elicit a response *in vitro* may be partially explained by the artificial metabolic environment of mammalian cell culture (high levels of insulin, glucose and growth factors). However, a recent study has shown that that when combined with chemotherapy, physiologically attainable concentrations (μM range) of metformin reduced proliferation and apoptosis) in OvCa cell lines (36).

Our group at the University of Chicago has performed *in vitro* studies to examine the effect of the combination of chemotherapy and metformin on cellular proliferation. In the resistant cell line (IGROV-CP) the addition of metformin to carboplatin increased the cytotoxic effect of carboplatin (Fig. 1B). In addition, treatment with paclitaxel plus metformin increased cytotoxicity versus paclitaxel alone (data not shown). These findings were corroborated *in vivo* using the *LSL*-K-ras$^{G12D/+}$Pten$^{loxP/loxP}$ genetic mouse model (37) where Kras is activated and Pten is deleted in ovarian surface epithelial cells, leading to OvCa (38). Mice treated with carboplatin or paclitaxel plus metformin and metformin alone had significantly lower tumor volume than control treated mice (Fig. 1C). These preliminary results are consistent with other pre-clinical reports in OvCa (27, 28) and breast cancer (25) which demonstrated that metformin increased cytotoxicity when added to chemotherapy *in vitro* and decreased tumor burden in mouse models when added to chemotherapy.

Mechanistic studies of metformin in cancer have focused on the activation of AMPK by the tumor suppressor liver kinase b1 (LKB1) and the subsequent inhibition of mTOR (39, 40). However, the metabolic effects of metformin are far-reaching and include modifications in insulin, glucose, and lipid metabolism through inhibition of the canonical AMPK pathway (41), as well as an increasing number of newly recognized unique targets. For example, metformin has increased activity in the setting of p53 loss of function (23). Since p53 is involved in mediating

the energy-conserving response to AMPK activation, its loss probably heightens metformin-induced energy stress on cancer cells. Most serous OvCa have mutations in p53 (42) and it would seem plausible that metformin might be more active against p53-deficient cells. Another unique aspect of cancer cell energetics is that normal cells generate ATP through oxidative phosphorylation, while tumors rely on aerobic glycolysis to generate energy (43). In addition, the metabolic stress induced by metformin on cells may make them particularly vulnerable to chemotherapy. In OvCa, we have found that one reason why OvCa cells metastasize to the omentum is the availability of high-energy lipids in omental adipocytes. OvCa cells induce lipolysis in adipocytes which then transfer lipids to cancer cells, leading to increased utilization of lipids through fatty acid oxidation (44). Given the bioenergetic changes found in cancer cells, the fact that almost all serous OvCa have p53 mutations, and the significant metabolic effects of metformin, there is a solid biologic rationale to support the possibility that metformin could serve as a metabolic therapeutic for the treatment of OvCa.

2.3 Rationale for combination therapy and maintenance therapy

The observational and retrospective studies in OvCa subjects suggest that those who received metformin in conjunction with chemotherapy have an improvement in survival. Presumably, the diabetic patients in these retrospective studies also continued metformin after the completion of their chemotherapy as well, in essence, receiving "maintenance" metformin. Our *in vitro* and *in vivo* studies would support the synergistic effect of metformin when administered with chemotherapy. This supports the rationale for the use of metformin in conjunction with adjuvant or neoadjuvant chemotherapy.

In xenograft models of breast cancer, metformin has been shown to kill cancer stem cells and prolong remission (45). More specifically, in OvCa, metformin has been shown to reduce the percentage of ALDH+ ovarian cancer stem cells (CSC) both *in vitro* and *in vivo*. Metformin, even as a single agent, slowed the growth of OvCa CSC *in vivo* (46). Preliminary results of an ongoing randomized phase III trial of maintenance metformin in non-diabetic patients with early stage breast cancer have demonstrated expected metabolic effects in the metformin group with acceptable tolerance and no adverse metabolic events (47). In addition to the systemic metabolic effects that metformin may have on the OvCa environment, a maintenance strategy will address the potential role metformin may play in eradication of CSC and suppression of CSC growth. In sum, this clinical trial will lay the groundwork to determine whether metformin is an effective cancer therapeutic in patients with OvCa.

In 2018, the SOLO1 study was published, a randomized phase III trial analyzing the use of PARP maintenance therapy with olaparib vs placebo as maintenance therapy after completion of chemotherapy in those with BRCA germline or somatic mutation carriers. The vast majority of patients had germline BRCA mutations. The study showed a significant difference in PFS for those who received olaparib. At 41 months median follow-up, the hazard ratio for disease progression or death at 3 years was 60% vs 27% (HR 0.30, 95% CI 0.23-0.41, $p<0.001$). The median PFS in the olaparib group was 49.9 months vs 13.8 months in the placebo group (67). Use of olaparib maintenance therapy in stage II-IV ovarian, fallopian tube, and primary

peritoneal cancer patients who have experienced a complete clinical or partial remission is listed as acceptable standard maintenance therapy in the NCCN guidelines version 1.2019 (68).

2.4 Correlative Studies Background

The goal of the correlative studies in this clinical trial is to begin identifying novel biomarkers and molecular mechanisms of metformin in OvCa. Given a patient population that is newly diagnosed with advanced stage OvCa, administration of chemotherapy is considered a vital component of initial treatment. Metformin/placebo administration in conjunction with chemotherapy for primary treatment is a unique approach and will allow for an analysis of metformin effect. Towards this end, biospecimens (tumor sample and fasting serum) will be collected during the clinical trial for exploratory biomarker studies. Currently, the precise molecular mechanism of action by which metformin exerts its anticancer effects is unclear. It is hypothesized that metformin may act directly on cancer cells or its beneficial effects may be a result of reduction of systemic insulin and glucose levels. Mirroring clinical trials of metformin in breast cancer (48), the clinical trial correlative studies will focus in these two areas as outlined in detail below:

Systemic effects: In diabetes, metformin's primary effect is reducing gluconeogenesis in hepatocytes resulting in reduced systemic glucose levels and ultimately reduction of systemic insulin levels. It is plausible that the systemic effects of metformin mediate its anticancer effects since insulin has been shown to be mitogenic and elevated insulin levels are associated with worse prognosis (49). In addition, elevated glucose levels have been associated with increased risk and mortality in cancer in general (50) and ovarian cancer specifically (51, 52).

Tumor effects: Novel biomarkers and molecular mechanisms will be discovered using paired pre and post-Rx specimens from a prospective clinical trial. In addition to reducing systemic insulin and glucose, metformin alters lipid metabolism through the canonical AMPK pathway (53). In preliminary studies, we have found that almost all OvCa cell lines tested (8/10) expressed the metformin transporter OCT1 and LKB1, and that metformin activates AMPK, a finding also reported by others (29). When activated, AMPK inactivates the key regulatory enzyme in lipid metabolism, acetyl CoA carboxylase (ACC), leading to decreased fatty acid synthesis (regulated by fatty acid synthase, FASN). To determine whether these metformin effects are present in OvCa, we completed several experiments with SKOV3ip1 OvCa cells, which express OCT-1. Metformin increased inactivated ACC and decreased FASN levels. To further understand the effect of metformin in OVCA, tumor microarrays (TMA) will be constructed using 5x5mm cores of tumor samples from participants in the clinical trial. The TMAs will be stained for metformin targets and the level of expression will be compared between treatment arms and correlated with clinical outcome. . In the candidate driven approach described above, we expect that metformin targets will be differentially expressed in biospecimens collected before and after metformin treatment, and that the primary biological effect of metformin in this setting will be a direct effect on signaling pathways in tumors. For an unbiased approach, the OvCa proteome before and after chemotherapy/metformin will be quantified in the paired tumor samples using quantitative proteomics. This validated and reproducible proteomic approach will allow us to identify novel proteins and pathways that change with chemotherapy alone *versus* chemotherapy

with metformin.

3. PATIENT SELECTION

3.1 Eligibility Criteria for Pre-Registration (subjects undergoing neoadjuvant chemotherapy who might be candidates for correlative tissue collection substudy and are being registered prior to histologic confirmation)

3.1.1 A reasonable suspicion of ovarian cancer by the treating oncologist is required, evidenced by abdominal carcinomatosis, omental caking, pleural effusions or ascites AND an elevated CA125 > 250 OR CA125:CEA ratio > 25 OR CA125 $\leq$ 250 with no evidence of GI cancer.

3.1.2 Age ≥18 years

3.1.3 ECOG performance status ≤2

3.1.4 Patients must have normal organ and marrow function as defined below (labs within 4 weeks of preregistration):

- leukocytes ≥3,000/mcL
- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL
- total bilirubin ≤ upper normal institutional limits (except for patients with Gilbert's Disease who are eligible despite elevated serum bilirubin level)
- AST(SGOT)/ALT(SGPT) ≤2.0 × institutional upper limit of normal
- creatinine ≤ institutional upper limit of normal (ULN)
  OR
- creatinine clearance ≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.
- blood glucose ≤ 126 mg/dL fasting or ≤140 mg/dL nonfasting

3.1.5 Signed written pre-registration informed consent document

3.2 Exclusion Criteria For Pre-Registration

3.2.1 Subjects with known diabetes and those taking metformin, sulfonylureas, thiazolidenediones or insulin for any reason.

3.2.2 Patients who are receiving any other investigational agents.

3.2.3 Subjects with comorbidities that would limit their two year survival for reasons other than ovarian cancer.

3.2.4 Concurrent active invasive malignancy or one previously diagnosed with a greater than 30% chance of recurrence in the next two years.

3.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to metformin.

3.2.6 Subjects must not have conditions associated with increased risk of metformin-associated lactic acidosis, including New York Heart Association Class III or IV congestive heart failure, history of acidosis of any type, alcoholic liver disease, or habitual intake of 3 or more alcoholic beverages per day.

3.2.7 Uncontrolled intercurrent illness including, but not limited to, ongoing or active major infection, unstable angina pectoris, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 Pregnant or nursing women are excluded from this study because the safety of metformin in pregnancy has not been established.

3.3 Eligibility Criteria for Registration

3.3.1 Subjects must have histologically confirmed carcinoma consistent with ovarian, fallopian tube, or primary peritoneal carcinoma (any of these three are referred to in this protocol as "ovarian cancer (OvCA)" OR a cytological diagnosis of carcinoma. The following histologic subtypes are included: serous, endometrioid, undifferentiated, clear cell, mixed, transitional, malignant Brenner tumor or adenocarcinoma NOS. Subjects eligible for this study may be in one of three surgical categories: 1) status post primary debulking surgery 2) undergoing neoadjuvant chemotherapy at a site not participating in correlative tissue collection sub study OR 3) undergoing neoadjuvant chemotherapy at a site participating in correlative tissue collection sub study.

3.3.2 Subjects undergoing primary debulking surgery must have stage III or IV disease and have undergone surgery to include, at a minimum, removal of the uterus, ovaries and fallopian tubes. These patients may be optimally debulked (less than 1 cm residual disease) but must have grossly visible macroscopic residual disease OR be suboptimally debulked.

3.3.3 Subjects for whom neoadjuvant chemotherapy followed by interval cytoreductive surgery is planned must have fine needle aspirate (FNA) or other cytology showing adenocarcinoma OR core biopsies OR surgically directed biopsies showing adenocarcinoma AND CA125 over 250 OR CA125:CEA ratio > 25 OR CA$\leq$ 250 with no evidence of GI cancer. They should have presumed stage III or IV disease, generally based on abdominal carcinomatosis, omental caking, pleural effusions or ascites.

3.3.4 The subject and her physician must agree to 6 cycles (a total of up to 8 cycles will be allowed) of one of the standard of care regimens allowed on this protocol. These regimens (starting dosage) include:

< 70 years of age:

-R1: IV paclitaxel 175 mg/m2 and carboplatin AUC 5-6 every 21 days
-R2: IV docetaxel 75 mg/m2 and carboplatin AUC 5-6 every 21 days
-R3: IV paclitaxel 80 mg/m2 day 1, 8, and 15 and carboplatin AUC 5-6 day 1 every 21 days.

≥70 years of age may (but not required to) choose one of the following alternative regimens:

-R4: IV paclitaxel 135 mg/m2 plus IV carboplatin AUC 5 plus optional G-CSF every 21 days
-R5: IV paclitaxel 60 mg/m2 day 1, 8, and 15 plus IV carboplatin AUC 5 day 1 every 21 days (day 15 paclitaxel optional)
-R6: IV paclitaxel 60 mg/m2 plus IV carboplatin AUC 2 day 1, 8, and 15 every 21 days

Use of granulocyte colony stimulating factor is permitted, but additional chemotherapy agents (e.g. gemcitabine) or biologic agents (e.g. bevacizumab) are not. Dose modifications for patients ≥ age 70 are allowable as indicated above. Patients ≥ age 70 for whom the physician deems carboplatin AUC 5 to be unsafe may be treated with AUC 4.

3.3.5 Age ≥18 years

3.3.6 ECOG performance status ≤2

3.3.7 Patients must have normal organ and marrow function as defined below (labs within one week of registration if patient postop, otherwise within two weeks of registration):

- leukocytes ≥3,000/mcL
- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL
- total bilirubin ≤ upper normal institutional limits (except for patients with Gilbert's Disease who are eligible despite elevated serum bilirubin level)
- AST(SGOT)/ALT(SGPT) ≤2.0 × institutional upper limit of normal
- creatinine ≤ institutional upper limit of normal (ULN)
  OR
- creatinine clearance ≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.
- blood glucose ≤ 126 mg/dL fasting or ≤ 140 mg/dL nonfasting

3.3.8 Women of child-bearing potential must agree to use an effective method of birth control on trial, as the safety of metformin in pregnancy has not been established. An effective method of birth control includes surgical sterilization of woman or her partner, abstinence, or two barrier methods (e.g. condom plus diaphragm); or hormonal methods of birth control (oral contraceptives or intrauterine device).

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

3.4 Exclusion Criteria for Registration

3.4.1 Mucinous adenocarcinoma, borderline tumors.

3.4.2 Subjects who will undergo intraperitoneal chemotherapy

3.4.3. Subjects receiving neoadjuvant chemotherapy for whom interval debulking surgery (assuming adequate response to therapy) is not planned.

3.4.4 Subjects receiving chemotherapy regimens not specified in the inclusion criteria

3.4.5 Subjects should not be participating in other clinical trials of interventions designed to reduce risk of ovarian cancer recurrence or plan to receive off –protocol maintenance therapy (e.g. paclitaxel or bevacizumab). Use of olaparib in BRCA genetic mutation carriers per FDA approval is allowable.

3.4.6 Subjects with known diabetes, fasting glucose over 126 mg/dL or random glucose over 140 mg/dL and those taking metformin, sulfonylureas, thiazolidenediones or insulin for any reason. Either fasting OR random glucose may be used to determine eligibility.

3.4.7 Patients who are receiving any other investigational agents.

3.4.8 Subjects with comorbidities which would lead to a clinical expectation that they will not survive two years for reasons other than ovarian cancer.

3.4.9 Concurrent active invasive malignancy or one previously diagnosed with a greater than 30% chance of recurrence in the next two years.

3.4.10 History of allergic reactions attributed to compounds of similar chemical or biologic composition to metformin.

3.4.11 Subjects must not have conditions associated with increased risk of metformin-associated lactic acidosis, including New York Heart Association Class III or IV congestive heart failure, history of acidosis of any type, alcoholic liver disease, or habitual intake of 3 or more alcoholic beverages per day.

3.4.12 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.

3.4.13 Pregnant or nursing women are excluded from this study because the safety of metformin in pregnancy has not been established.

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Eligible subjects will be entered on study centrally by the University of Chicago study coordinator. All sites should call the study coordinator at (773) 834-1746 or PhaseIICRA@medicine.bsd.uchicago.edu to verify availability of a slot.

For subjects who undergo primary debulking surgery or neoadjuvant chemotherapy *not* on the tissue collection substudy, registration will take place after histologic confirmation consistent with OvCa. For subjects undergoing neoadjuvant chemotherapy *and* the tissue collection substudy, pre-registration will be required prior to obtaining baseline research samples. Registration will then take place after histologic confirmation of OvCA. Following registration, patients should begin randomized protocol treatment within 14 business days. Study medication does not need to commence exactly on day 1 of chemotherapy. The specific chemotherapy regimen, dosing schedule, and number of cycles of chemotherapy will be declared at the time of registration. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration but prior to randomization, the patient's registration on the study will be cancelled. The study coordinator/CRA should be notified of cancellations as soon as possible.

4.2 Registration Process

When a potential patient has been identified, notify the CRA via phone or email to ensure registration on the study (773) 834-1746 or PhaseIICRA@medicine.bsd.uchicago.edu. Reservations for potential subjects will only be held for subjects who have signed consent for that particular study.

When registering a subject, the following must occur:

- Confirm that the institution has current IRB approval of the correct version of protocol/consent and has an annual update on file.
- Submit all required materials (Eligibility Checklist, Source documentation, & signed consent form) to confirm eligibility and required pre-study procedures to the CRA a

minimum of 48 hours prior to the subject's scheduled therapy start date or a minimum of 24 hours prior to planned biopsy or procedure in the case of pre-registration.

- Source documentation includes copies of all original documents that support each inclusion/exclusion criteria. The eligibility checklist does not serve as source documentation but rather as a checklist that original source documentation exists.
- Communicate with the above CRA to ensure all necessary supporting source documents are received and the potential subject is eligible to start treatment on schedule. If there are questions about eligibility, the CRA will discuss it with the PI. The PI may clarify, but not overturn, eligibility criteria.
- Submit specific chemotherapy regimen, dosing schedule, and number of cycles of chemotherapy to be administered for the subject
- Confirm registration of subjects by obtaining a subject study ID number from the CRA via phone, fax or email.
- The date the patient is randomized will be considered the patient's "OnStudy Date." The patient's subject ID will be assigned and a confirmation of registration will be issued by the CRA on this date. Subjects that sign consent and do not go "OnStudy" will be recorded in the database with the date they signed consent and the reason for not going "OnStudy" (e.g., Ineligible, Screen Failure or Withdrawn Consent).

5. TREATMENT PLAN

5.1 Agent Administration

This is a randomized placebo-controlled study. Metformin HCl tablets 850 mg, and placebo tablets will be purchased by the Mayo Clinic or the University of Chicago. The University of Chicago will coordinate distribution to the site pharmacies. Each bottle provided to subjects by the site will be labeled with a protocol number, dosing and storage instructions, and the expiration date, when required. The contents of the label will be in accordance with all applicable regulatory requirements.

Treatment is expected to be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Suggested dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Subjects participating in this trial will fall into one of three categories:

- Patients with a histologic diagnosis of OvCa who have undergone primary debulking and will be randomized to standard chemotherapy with metformin or placebo followed by metformin or placebo maintenance
- Patients with a strong suspicion of OvCa who will participate in the correlative tissue collection substudy and undergo tissue biopsy prior to neoadjuvant therapy, where interval debulking and tissue collection is performed after three cycles of chemotherapy. If for any reason, a patient pre-registered turns out not to have ovarian cancer, they will not be registered to treatment. If, for any reason, the subject

undergoes debulking (e.g. a laparoscopy performed upfront shows disease to be more resectable than previously believed) and macroscopic residual disease remains, they can be registered to the trial and receive adjuvant therapy.

- Patients with a histologic or cytologic diagnosis consistent with OvCa who will be randomized to undergo neoadjuvant chemotherapy +/- metformin and interval debulking followed by metformin or placebo maintenance who will not participate in the correlative tissue collection substudy.

At the time of registration, the treating physician will designate which of the following standard chemotherapy regimens the patient will receive:

- R1: IV paclitaxel 175 mg/m2 plus IV carboplatin AUC 5-6 every 21 days x 6 cycles (a total of up to 8 cycles will be allowed)
- R2: IV docetaxel 75 mg/m2 plus IV carboplatin AUC 5-6 every 21 days x 6 cycles (a total of up to 8 cycles will be allowed)
- R3: IV paclitaxel 80 mg/ m2 day 1, 8, and 15 plus IV carboplatin AUC 5-6 day 1 every 21 days x 6 cycles (a total of up to 8 cycles will be allowed)

Acceptable chemotherapy regimens for elderly patients $\geq$ age 70 will include any of the above AND the following alternative regimens:

- R4: IV paclitaxel 135 mg/m2 plus IV carboplatin AUC 5* plus optional G-CSF every 21 days x 6 cycles (a total of up to 8 cycles will be allowed)
- R5: IV paclitaxel 60 mg/m2 day 1, 8, and 15 plus IV carboplatin AUC 5* day 1 every 21 days (day 15 paclitaxel optional) x 6 cycles (a total of up to 8 cycles will be allowed)
- R6: IV paclitaxel 60 mg/m2 plus IV carboplatin AUC 2 day 1, 8, and 15 every 21 days x 6 cycles (a total of up to 8 cycles will be allowed)

Please be advised that the treating physician must declare at the time of registration whether 6 or 8 cycles will be given.

Please be advised that as soon as the treating physician is aware of a BRCA mutation and plans to administer PARP maintenance therapy after completion of chemotherapy, the study team should be notified.

*Patients for whom the physician deems carboplatin AUC 5 to be unsafe may be treated with AUC 4.

Throughout this protocol, any of the above chemotherapy regimens will be referred to as "standard chemotherapy regimen".

Subjects will be randomized in a 1:1 ratio to receive one of the following treatments:

Arm 1: Metformin 850 mg po (with food) BID with standard chemotherapy x 6 to 8 cycles followed by metformin 850 mg po BID. Metformin will be continued for two calendar years

from the date of randomization.

Arm 2: Placebo tablet po (with food) BID with standard chemotherapy x 6 to 8 cycles followed by placebo tablet BID. Placebo will be continued for two calendar years from the date of randomization.

5.1.1 Methods of Chemotherapy Administration

Note that the following are guidelines. Minor alterations, for example in the duration of infusion, premedications, or dose modifications of the standard of care agents are not considered protocol deviations.

- Paclitaxel 175 mg/m2 day 1 of a 21 day cycle will be infused IV over 2-3 hours.
- Paclitaxel 60-80 mg/m2 days 1, 8 and 15 of a 21 day cycle will be infused over approximately 1 hour.
- Patients may switch to docetaxel from a paclitaxel regimen for neuropathy.
- Docetaxel 75 mg/m2 day 1 of a 21 day cycle will be administered IV over approximately 1 hour.
- Due to the risk of immediate hypersensitivity reaction, paclitaxel should be the first drug infused in any combination
- Carboplatin will be administered as a 30-60 minute infusion, following paclitaxel (or docetaxel) administration.
- All drugs are dosed based on subject's actual BSA. BSA is only recalculated if there is a +/- 10% weight change (up or down).
- Dosing of carboplatin:

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

$$\text{Creatinine clearance Cl (ml/min)} = \frac{[140\text{-age(years)}] \times \text{weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/dl)}}$$

The initial dose of carboplatin must be calculated using GFR. In the absence of new renal obstruction or other renal toxicity greater than or equal to CTC Grade 2 (serum creatinine > 1.5 x ULN), the dose of carboplatin will not be recalculated for subsequent cycles, but will be subject to dose modification as noted.

In patients with an abnormally low serum creatinine (less than or equal to 0.8 mg/dl), due to reduced protein intake and/or low muscle mass, the creatinine clearance should be estimated using minimum value of 0.8 mg/dl. If a more appropriate (higher) baseline creatinine value is available within 4 weeks of treatment, that value may also be used for the initial estimation of GFR.

CALVERT FORMULA:

Carboplatin dose (mg) = target AUC x (GFR + 25)

Note: the GFR used in the Calvert formula should not exceed 125 ml/min.

Maximum carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min

The maximum allowable doses of carboplatin are:

AUC 6 = 900mg
AUC 5 = 750 mg

5.1.2 Metformin Administration

USE ONLY STUDY SUPPLY OF METFORMIN

Metformin will be taken with food ideally on day 1 of the standard chemotherapy regimen. Subjects will undergo a "ramp up" to protocol dose. A proposed schedule is as follows:

- 1 tablet (850 mg) po daily for one week, then
- 1 tablet (850 mg) po bid for 2 years from the date of randomization

A pill calendar (Appendix C) will be provided for each subject. The participating institution's study nurse will make telephone contact with the subject one week after starting metformin/placebo. The study nurse will assess compliance and toxicity to ensure that the subject increases the medication to twice daily. The major side effects of metformin which limit tolerance are gastrointestinal (nausea, abdominal bloating, diarrhea). During the initial study period, subjects should be encouraged to take the tablets with food. Pills are not to be crushed or split, prior to taking, for any reason. If the subject is unable to increase the study medication because of toxicity, the study nurse at the participating institution should make recommendations to improve medication tolerance. This may include encouraging the subject to take the medication with food in addition to ramping up slowly by taking the medication every other day or once per day for an additional week until a twice per day dose can be tolerated . Breaks are allowed to ascertain the cause of unpleasant symptoms. The highest tolerable metformin/placebo dose should be recorded and administered for the remainder of the study.

The subject will maintain a pill calendar for each dose of medication. The pill calendar and pill bottles will be returned to the study nurse. A pill count will be performed by the site pharmacist in order to calculate milligrams of medication taken.

5.1.3 <u>Pre-medication:</u>

5.1.3.1 Paclitaxel

For all courses where paclitaxel is to be administered it recommended that a preparative regimen be employed one hour prior to the treatment regimen on that day to reduce the risk of

hypersensitivity reaction.

This regimen should include standard dose (s) of dexamethasone (either IV or po), an anti-histamine H_1 (diphenhydramine 25-50 mg IV or po, or an equivalent dose of an alternate H_1 blocker such as loratidine or fexofenadine) and a standard dose of anti-histamine H_2 IV such as cimetidine, ranitidine or famotidine). For those subjects who are at risk for hypersensitivity reactions or cannot tolerate the preparative regimen, nab-paclitaxel can be substituted.

5.1.3.2 Docetaxel

It is recommended that subjects be premedicated with dexamethasone 8 mg orally taken the night before, morning of, and evening after each treatment (total dose, 24 mg/3wk).

5.1.4 Anti-emetic regimens

Nausea and vomiting may be a significant side effect of each regimen. The following representative anti-emetic regimens are suggested:

- Ondansetron 8-32 mg IV 30 minutes prior to administration of chemotherapy and dexamethasone 10-20 mg IV 30 minutes prior to drug administration or
- Granisetron 10 mcg/kg IV (or 2 mg po) 30 minutes prior to chemotherapy, with or without lorazepam 0.5-2.0 mg IV 30 minutes prior to chemotherapy

5.1.5 Surgery

For subjects undergoing primary debulking surgery, standard chemotherapy and study medication should be started as soon as reasonable after recovery from surgery but must be started within 14 business days of registration. Study medication does not necessarily need to commence on day 1 of chemotherapy.

For subjects undergoing neoadjuvant chemotherapy, interval debulking surgery must be performed after cycle 3 or 4 of standard chemotherapy as soon as nadir counts permit but within 6 weeks of completion of cycle 3 or 4. If a subject is unable to undergo interval debulking, they do not need to be removed from study, however, the study CRA and PI should be notified. Subjects enrolled in the correlative tissue collection substudy who are unable to undergo interval debulking should also be reported to the study CRA and PI. **FOR PATIENTS ON THE TISSUE COLLECTION SUBSTUDY, METFORMIN MUST BE GIVEN ORALLY ON THE MORNING OF INTERVAL DEBULKING SURGERY AND THE TIME OF MEDICATION ADMINISTRATION AS WELL AS TIME OF TISSUE COLLECTION RECORDED.** For patients on the correlative tissue collection substudy, at least 5 mm^3 of tissue must be collected and submitted. The elimination of metformin is rapid with a half-life ranging from 1.7 hours to 3 hours. Therefore, in order to assess the effects of metformin on the tissue, administration prior to surgery is essential. Please refer to section 9.2 for detailed guidelines on serum and tissue collection.

For patients undergoing interval debulking surgery, metformin should be restarted at the time of discharge from the hospital or as soon as the patient is able to restart oral medication.

5.2 General Concomitant Medication and Supportive Care Guidelines

Metformin has not been demonstrated to inhibit or induce CYP enzymes. However, the elimination of metformin is dependent on renal function. Renal dysfunction increases the risk of lactic acidosis. This should be considered when subjects are taking ACE inhibitors, loop diuretics, non-steroidal anti-inflammatory drugs, cyclosporine, aminoglycosides or receiving IV contrast dye. Metformin is a substrate for transporters such as plasma monoamine transporters (PMAT), organic cation transporters (OCT) as well as efflux transporters which include the multidrug and toxin extrusion antiporters (MATEs). SNPS in genes encoding these transporters may affect the pharmacokinetics of metformin. Such medications include pyrimethamine, an anti-protozoal agent, which inhibits MATE1 and MATE2-K and OCT-2 at high *in vitro* concentrations. This drug can decrease the clearance of metformin and increase the AUC.

Metformin/placebo should be held if the subject's creatinine is elevated over the institutional normal limit. Medication may resume if the creatinine reaches baseline. The subject's medication list should be reviewed for possible effect on renal function that may increase the toxicity of metformin.

If the subject is scheduled for any CT scans requiring intravenous contrast material, metformin/placebo should not be taken for 24 hours prior to the investigation nor for 48 hours after the procedure. Study medication may be resumed at full dose (without ramp up) provided there is no concern about renal function. If there is concern about renal function, creatinine should be checked prior to resumption of study medication.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment with metformin or placebo as a single agent will continue to complete a total duration of 2 calendar years *from the date of randomization* (approximately 28 "cycles" of single agent metformin/placebo where a cycle is counted as three weeks of daily therapy) 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.

5.4 Duration of Follow Up

Subjects will be followed for progression and survival until the last patient randomized on study receives a total of 2 years (from date of randomization of that last patient) of metformin/placebo.

5.5 Criteria for Removal from Study

Subjects will be removed from study therapy when any of the criteria listed in Section 5.3 applies. The reason for removal from study therapy and the date the patient was removed must be documented in the Case Report Form. Patients discontinuing therapy will continue to be followed per protocol to ascertain time to progression and secondary outcomes. A patient who withdraws consent to be followed must provide the withdrawal of consent in writing.

Subjects in the neoadjuvant chemotherapy cohort who do not undergo interval debulking surgery will remain on study. Subjects participating in the correlative tissue collection substudy who forego an interval debulking will also remain on study; however, if clinically appropriate, they may undergo core biopsies to fulfill the correlative tissue endpoint.

5.5 Criteria for Unblinding of Study Medication

A subject's attending physician will be unblinded only if the treatment information is critical for making immediate therapeutic decisions for the subject (e.g. if withholding the treatment information would put the subject at risk of serious adverse events or death). In this case, the attending physician should immediately contact the study chair at 773-845-5014.

When a toxicity occurs, the site may request to know the actual treatment received to manage the subject. The appropriateness of this request will be determined by the study chair depending upon the type and grade of the toxicity and the availability of therapeutic options.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 General guidelines for hematologic toxicity - institutional guidelines may be used, and failure to follow these guidelines for standard of care agents does not constitute a protocol violation

6.1.1 Treatment decisions will be based on the absolute neutrophil count (ANC) and not the total white cell count (WBC).

6.1.2 Lower limits for ANC and platelet count
With cytotoxic chemotherapy. Day 1 of a subsequent cycle of cytotoxic chemotherapy will not be administered until the ANC$\geq$1000 cells/mcl if growth factor is planned, and 1,500 cells/mcl if it is not, and the platelet count is $\geq$100,000/mcl. All cytotoxic treatment will be delayed for a maximum of 3 weeks until these values are achieved. METFORMIN/PLACEBO MAY BE CONTINUED DURING THIS TIME AS LONG AS THERE ARE NO CONTRAINDICATIONS.

For patients receiving paclitaxel day 1, 8 and 15, the day 8 and day 15 ANC should be ≥ 500 cells/mcl and the platelet count ≥ 50,000/mcl to receive paclitaxel. If not given, these doses are eliminated and not made up.

6.1.3 Use of hematopoietic cytokines and protective agents

It is anticipated that myelosuppression may be a side effect of each regimen. Myeloid growth factors (either filgrastim or pegfilgrastim) can be used utilizing NCCN and/or ASCO guidelines as a reference. If myeloid growth factors are used, it is recommended that filgrastim (dose as per institutional standard) be administered subcutaneously daily starting 24-72 hours after the last dose of chemotherapy and continuing through hematopoietic recovery or pegfilgrastim will be administered at 6 mg subcutaneously (one dose per treatment cycle) 24 to 72 hours after the last dose of chemotherapy. Administration of growth factors on the same day as chemotherapy is not recommended. Pegfilgrastim is not recommended for chemotherapy regimens given less than every 2 weeks.

6.1.4 Patients will not receive prophylactic thrombopoeitic agents or erythropoietin stimulating agents.

6.2 Suggested modifications for hematologic toxicities - institutional guidelines may be used, and failure to follow these modifications for standard chemotherapy agents does not constitute a protocol violation

6.2.1. Dose limiting neutropenia (DLT-ANC) is defined by the development of febrile neutropenia, prolonged grade 4 neutropenia lasting ≥ 7 days, delay of treatment for more than 7 days because of neutropenia, ANC < 1,000 cells/mcl on day 1, or omission of day 8 or day 15 on a weekly paclitaxel regimen because of neutropenia. Febrile neutropenia is defined within the CTC AE as a disorder characterized by an ANC < 1,000 cells/mcl and a single temperature of > 38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than one hour.

6.2.2. Dose limiting thrombocytopenia (DLT-PLT) is defined by any occurrence of grade 4 thrombocytopenia (< 25,000/mcl) or bleeding associated with grade 3 thrombocytopenia (< 25,000 to <50,000/mcl), delay of treatment on day 1 of a cycle by more than 7 days because of thrombocytopenia, platelet count of < 100,000/mcl on day 1, or inability to give day 8 or day 15 paclitaxel due to thrombocytopenia. There will be no modifications for uncomplicated grade 3 thrombocytopenia except as listed above.

Table A. Modification Instructions for Dose Limiting Hematologic Toxicity-every 3 week regimen				
DLT-ANC	DLT-PLT	First Occurrence	Second Occurrence	Third Occurrence
Yes	No	Reduce carboplatin by one AUC unit (and docetaxel by 10 mg/m2 if subject is on docetaxel)	Add G-CSF* and maintain all current drug doses	Reduce paclitaxel dose by 50 mg/m2 vs change scheduling vs discontinue cytotoxic chemotherapy**
Yes	Yes	Reduce carboplatin by one AUC unit (and docetaxel by 10 mg/m2 if subject is on docetaxel)	Add G-CSF* and reduce carboplatin by one AUC unit (and docetaxel by 10 mg/m2 if subject is on docetaxel)	Reduce paclitaxel dose by 50 mg/m2 vs change scheduling vs discontinue cytotoxic chemotherapy**
No	Yes	Reduce carboplatin by one AUC unit (and docetaxel by 10 mg/m2 if subject is on docetaxel)	Reduce carboplatin by one AUC unit (and docetaxel by 10 mg/m2 if subject is on docetaxel)	Reduce paclitaxel dose by 50 mg/m2 vs change scheduling vs discontinue cytotoxic chemotherapy**

* See section 6.1.3
** Specific management of cytotoxic chemotherapy dosing is left to the discretion of the investigator.

Table B: Modification Instructions for Dose Limiting Hematologic Toxicity-weekly regimen				
DLT-ANC	DLT-PLT	First Occurrence	Second Occurrence	Third Occurrence
Yes	No	Reduce carboplatin by one AUC unit (and docetaxel by 10 mg/m2 if subject is on docetaxel)	Omit day 15 paclitaxel and administer G-CSF after day 8 paclitaxel	Reduce carboplatin by one AUC unit and give G-CSF after day 8 paclitaxel.**
Yes	Yes	Reduce carboplatin by one AUC unit (and docetaxel by 10 mg/m2 if subject is on docetaxel)	Omit day 15 paclitaxel and administer G-CSF after day 8 paclitaxel and reduce carboplatin by one AUC unit	Reduce day 1 paclitaxel dose**
No	Yes	Reduce carboplatin by one AUC unit	Reduce carboplatin by one AUC unit	Discontinue cytotoxic chemotherapy**

** Specific management of cytotoxic chemotherapy dosing is left to the discretion of the investigator.

6.3 Metformin Toxicity

The major side effects of metformin which limit tolerance are gastrointestinal (nausea, abdominal bloating, diarrhea). During the ramp up period, subjects should be encouraged to take the tablets with food. Subjects should have less than or equal to grade 1 GI toxicity attributable to metformin in order to dose escalate. The dose escalation process is left to the treating physician. In most cases, if the medication dosing is increased slowly, it is tolerable. Possible modifications to ensure compliance include taking the medication every other day or once per day for an additional week until a twice per day dose can be tolerated. Because some of the GI side effects may be attributable to the cytotoxic chemotherapy, breaks of up to 2 weeks consecutively, are allowable to ascertain the cause of unpleasant symptoms which should subside after the first week if attributable to the chemotherapy. The highest tolerable dose of metformin/placebo should be administered and recorded on the pill calendar. Subjects will stay on study at the highest tolerable dose. Supportive care with anti-emetics should be provided. If the subject is unable to tolerate any dose of metformin in conjunction with chemotherapy, they will stay on study and may attempt to start metformin during the maintenance phase after completion of chemotherapy.

Nausea/Vomiting/Distention/ Bloating/Diarrhea Gastrointestinal-Other	**Management/Next Dose for Metformin**	**Investigator Action**
≤ Grade 1	No change in dose	Subject should be encouraged to remain on full dose and take medication with food. Supportive care should be encouraged with anti-emetics and/or anti-diarrheal medications.
Grade 2 (or higher)	Hold until ≤ Grade 1. Dose should be adjusted to maintain ≤ grade 1 symptoms	If symptoms are present in week 1 of the 21 day cycle and may be attributable to the chemotherapy, hold metformin/placebo for 2 weeks, then resume dose at 1 tablet per day and increase as tolerated. Dose adjustment for subsequent cycles is left to the treating physician to maintain symptoms ≤ grade 1. For persistent grade ≥ 3 report as AE
Recommended management: anti-emetics Loperamide 4 mg at first onset, followed by 2 mg with each loose movement until diarrhea-free for 12 hours (maximum dosage 16 mg/24 hours). Adjunct anti-diarrheal therapy is permitted and should be recorded when used.		

Event	**Grade**	**Investigator Action**
Hepatic dysfunction: AST or ALT > 3.0X ULN	Consult CTC AE for precise grading	Continue study medication. Study medication is not associated with liver toxicity or exacerbation of liver toxicity.
Renal dysfunction Creatinine ≥ institutional ULN	Please consult your institution's ULN and CTC AE for precise grading	Hold study drug for creatinine ≥ institutional ULN If elevated creatinine is due to reversible process (i.e. dehydration, treatable infection), investigator may resume metformin when creatinine is within institutional normal limit.
Acidosis (Lactate ≥ 5.0 mM) (pH< 7.3)	Grade 3	Stop study drug and do not re-start. Report as a serious adverse event.
Skin reactions Major-generalized urticarial, bullous rashes, exfoliative dermatitis	Generalized	Stop study drug and do not restart
Steven Johnson Syndrome	Localized	If the rash is thought to be possibly, probably or definitely related to study medication, discontinue the study medication.
Hospitalization for any reason	As per grade of event causing hospitalization	If hospitalization is possibly, probably or definitely related to study medication, hold study drug for up to 4 weeks. The investigator will determine when it is safe to re-start. If hospitalization is not related to study medication, the investigator may continue the study medication. Hospitalization > 24 hrs, report as SAE

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. An adverse event is defined as any untoward medical event in a subject enrolled in a clinical trial. The event does not necessarily have a causal relationship with the study agent. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

7.1 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **Special AE expedited reporting:**
  AEs for metformin should undergo expedited reporting if they include lactic acidosis or signs of metformin overdose (grade ≥3 nausea, vomiting, abdominal pain, malaise, myalgia, mental status change, renal insufficiency, cardiovascular compromise, hypoglycemia or hyperglycemia).

- **Attribution** of the AE:
  - Definite (5) – The AE *is clearly related* to the study treatment.
  - Probable (4) – The AE *is likely related* to the study treatment.
  - Possible (3) – The AE *may be related* to the study treatment.
  - Unlikely (2) – The AE *is doubtfully related* to the study treatment.
  - Unrelated (1) – The AE *is clearly NOT related* to the study treatment.

7.2 Adverse Event Definitions

7.2.1 Adverse Event

An adverse event is an unexpected medical problem that happens during treatment with a drug or other therapy. Adverse events do not have to be caused by the drug or therapy, and they may be mild, moderate, or severe.

7.2.2 Serious Adverse Events

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death

2) Life-threatening (e.g. places subject at immediate risk of death, this does not include events that might have caused death if they occurred a greater severity)
3) Results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.

Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.2.3 Unexpected Events

Unexpected events are those not listed at the observed specificity or severity in the protocol, informed consent, investigator brochure, or FDA-approved package insert. An event is considered unexpected if it is listed as occurring within the class of drugs or otherwise expected from the drug's pharmacological properties but which has not been previously observed with this specific investigational agent.

7.3 Adverse Event Reporting Requirements

7.3.1 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported using the Serious Adverse Event Reporting Form discussed below must also be reported in routine study data submissions.**

7.3.2 Serious Adverse Event Reporting **to** the Coordinating Center

Use the UCCCC protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

All serious adverse events and all adverse events that have been specified to require expedited reporting in section 7.1 occurring on this study require expedited reporting to the University of Chicago Comprehensive Cancer Center (UCCCC) Clinical Trials Office (CCTO). The responsible Research Nurse or other designated individual at the treating site should report the SAE to the CCTO by the end of the business day when s/he becomes aware of the event. Events occurring after business hours should be reported to the CCTO by 12pm (noon) the next business day. Reports should be made using the eVelos database 'Serious Event Report' Form.

All serious adverse events should also be reported to the local IRB of record according to their policies and procedures.

7.3.3 Serious and Unexpected Adverse Event reporting **by** the Coordinating Center

The designated UCCCC Regulatory Manager will notify all participating sites of all serious and all unexpected as well as both serious and unexpected adverse reactions that occur on this clinical trial and which are reported to the UC Institutional Review Board (IRB).

8. PHARMACEUTICAL INFORMATION

8.1 Metformin

Chemical Name: N,N-dimethyl biguanide hydrochloride

How Supplied: Metformin 850 mg or placebo will be supplied as white to off-white tablets

Stability: 2 year expiration

Storage: Store at room temperature (15º to 30ºC) in well-closed containers

Route of administration: orally, with food

Mechanism of action: Metformin HCL is a biguanide derivative producing an antihyperglycemic effect only when there is insulin secretion. It has no effects on the pancreatic beta cells. The mode of action is not fully understood. It has been postulated that metformin may potentiate the effect of insulin or reduce hepatic gluconeogenesis.

Pharmacokinetics. Metformin absorption is relatively slow and may extend over about 6 hours. The drug is excreted in urine at high renal clearance at about 450 mL/min. The initial elimination is rapid with a half-life varying between 1.7 and 3 hours. The terminal elimination phase, which accounts for about 4 to 5% of the absorbed dose is slow, with a half-life between 9 and 1 hours. Metformin is not metabolized. Its main sites of concentration are the intestinal mucosa and the salivary glands. The plasma concentration at steady-state ranges about 1-2 mcg/mL.

Certain drugs may potentiate the effect of metformin HCl, particularly sulfonylurea type of drugs in the treatment of diabetes. Co-administration of metformin and sulfonylurea antidiabetic drugs could produce a hypoglycemic reaction if they are given in patients already receiving other drugs which, themselves, can potentiate the effects of sulfonylureas. Examples of these drugs include: long-acting sulfonamides, tubercolostatics, phenylbutazone, clofibrate, monoamine oxidase inhibitors, salicylates, probenicid and propranolol. Metformin is negligibly bound to plasma proteins.

Adverse Effects: Lactic acidosis (estimated incidence 3 cases/100,000 patient years, fatal in 50% of cases), gastrointestinal toxicities (> 1/10 diarrhea, nausea, vomiting, abdominal bloating, flatulence, anorexia, metallic taste), rash (<1/10,000, subnormal vitamin B12 (9% after 6

months), hepatic dysfunction (<1/10,000), elevations in TSH (<1/10,000). Modest weight loss (up to five pounds) is common. Hypoglycemia does not normally occur when metformin is administered although extreme caloric restriction or excessive physical activity without adequate caloric intake may rarely lead to hypoglycemia.

8.2 Study Drug Compliance

Subjects should be given clear instruction about how to take their study medication. Patients will self-administer the medication. A pill calendar (Appendix C) will be given to the patient upon registration in the study. The calendar will be kept in the subject's institutional research chart and submitted to the study CRA at regular intervals. The patient will return their study medication bottles at their regularly scheduled visit, when new bottles will be dispensed. At regular intervals, the bottles will be returned to the site pharmacy for a pill count. After completion of standard chemotherapy, the pill calendar and pill bottles can be collected at every 3 month visits. Subjects should make a notation of missed medication doses on the pill calendar. Subjects must return all containers and any remaining tablets at the end of the study.

8.3 Return and Retention of Study Drug

Sponsor:
University of Chicago
5815 S. Maryland Ave.
Chicago IL, 60637

Return and retention of study drug used will be kept in a locked limited access room. Accountability records for the study drug will be maintained and readily available for inspections by regulatory authorities at any time. All study supplies and associated documentation will be regularly reviewed and verified. An Investigational Drug Accountability Log will be used for drug accountability. For accurate accountability, the following information will be noted when drug supplies are used during the study:

1. Study identification number
2. Patient identification number
3. Lot number(s) dispensed for that patient
4. Date and quantity of drug dispensed
5. Any unused drug returned by the patient

Before disposal/destruction, final drug accountability and reconciliation of empty and partially used drug must be performed. Drug will be destroyed at the study site in accordance with the Investigational Drug Services Standard Operating Procedures and/or Destruction of Investigational Medications Policy. Only sites that cannot destroy unused drug on-site will be required to return their unused supply of investigational product to the sponsor site for destruction.

8.4 Paclitaxel (NSC #673089)

Formulation: Paclitaxel is supplied as a 6 mg/mL, non-aqueous solution in multi-dose vials containing 30 mg/5mL, 100 mg/16.7 mL, or 300 mg/50 mL of paclitaxel. In addition to 6 mg of paclitaxel, each mL of sterile non-pyrogenic solution contains 27 mg of purified Cremaphor® EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

Storage: Unopened vials of paclitaxel are stable to the date indicated on the package when stored between 20 to 25^0 C (68 to 77^0 F). Protect from light.

Preparation: Paclitaxel must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride for Injection, USP;5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25^0 C/77^0 F) and room lighting conditions.

NOTE: In order to minimize patient exposure to the plasticizer DEHP, which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should be stored in bottles (glass, polypropylene) or plastic (Polypropylene, polyolefin) bags and administered through polyethylene-lined administration sets.

Paclitaxel should be administered through an inline filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® or IVEX-HP®, which incorporate short inlet and outlet PVC-coated tubing, has not resulted in significant leaching of DEHP.

All patients should be premedicated with corticosteroids, diphenhydramine, and H_2 antagonists prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Patients who experience severe hypersensitivity reactions to paclitaxel should not be re-challenged with the drug.

Adverse Effects: Consult the package insert for the most current and complete information.

Supplier: Commercially available both from Bristol-Myers Squibb Oncology as well as generic manufacturers. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

8.5 Docetaxel (Taxotere® RP-56976, NSC #628503)

Formulation: Docetaxel is supplied as a sterile, non-pyrogenic, non-aqueous viscous solution in single dose vials containing 20 mg/0.5 mL or 80 mg/2 mL of docetaxel. Each mL contains 40mg docetaxel (anhydrous) and 1040mg polysorbate 80.

Docetaxel requires dilution prior to use. A sterile, non-pyrogenic single dose diluent is supplied for this purpose. The diluent for docetaxel contains 13% (w/w) ethanol in water for injection and is supplied in vials.

Storage: Unopened vials of docetaxel are stable to the date indicated on the package when stored between 2 and 25^0 C (36 and 77^0F). Protect from light.

Preparation: Docetaxel must be combined with its supplied diluent (final concentration = 10mg/mL) and then further diluted prior to infusion. Docetaxel should be diluted in 0.9% Sodium Chloride for Injection, USP or 5% Dextrose Injection, USP to produce a final concentration of 0.3 to 0.74 mg/mL. The fully prepared docetaxel infusion solution should be used within 4 hours (including the infusion duration).

NOTE: In order to minimize patient exposure to the plasticizer DEHP, which may be leached from PVC infusion bags or sets, the final docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic (polypropylene, polyolefin) bags and administered through polyethylene-lined administration sets.

All patients should be premedicated with oral corticosteroids for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

Adverse Effects: Consult the package insert for the most current and complete information.

Supplier: Commercially available from Aventis. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

8.6 Carboplatin (Paraplatin® - NSC #241240)

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

Storage: Unopened vials of carboplatin are stable to the date indicated on the package when stored at 25^0C (77^0F). Excursion from 15 to 30^0C (59 to 86^0 F) are permitted. Protect from light. Carboplatin multi-dose vials maintain microbial, chemical, and physical stability for up to 14 days at 25^0C following multiple needle entries.

Preparation: Carboplatin aqueous solution can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water or 0.9% Sodium Chloride for Injection, USP. When prepared as directed, carboplatin aqueous solutions are stable for 8 hours at room temperature (25^0C/77^0F). Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solution be discarded 8 hours after dilution.

Calvert Formula for Carboplatin (AUC) Dosing

Total dose (mg)=target AUC (in mg/mL/minute)*[GFR(in mL/minute)+25]

NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must NOT be used for the preparation or administration of carboplatin.

Adverse Effects: Consult the package insert for the most current and complete information.

Supplier: Commercially available both from Bristol-Myers Squibb as well as generic manufacturers. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies

The goal of the correlative studies in this clinical trial is to begin identifying novel biomarkers and molecular mechanisms of metformin in OvCa. Towards this end, bio specimens (tumor sample and fasting serum) will be collected during the clinical trial for exploratory biomarker studies. Currently, the precise molecular mechanism of action by which metformin exerts its anticancer effects is unclear. It is hypothesized that metformin may act directly on cancer cells or its beneficial effects may be a result of reduction of systemic insulin and glucose levels. Mirroring clinical trials of metformin in breast cancer (48), the clinical trial correlative studies will focus in these two areas as outlined in detail below:

For a comprehensive evaluation of metformin's effects in OvCa, the correlative studies will be completed in three types of biospecimens (Figure 2):

- Longitudinally collected serum samples. Longitudinal collection will allow for assessment of metformin's effects on key signaling pathways over time.
- Tumor collected from subjects prior to treatment with metformin or placebo. Analysis of basal expression of metformin targets in these samples and correlation with therapeutic response may identify potential predictive biomarkers for use in future phase III trials.
- Paired tumor and serum specimens (specimen #1: treatment naïve and specimen #2: chemotherapy±metformin). Profiling of paired samples will give us a unique opportunity to identify changes in molecular markers induced by metformin use, an approach that will help clarify the molecular mechanisms of action of metformin in OvCa.

Figure 2

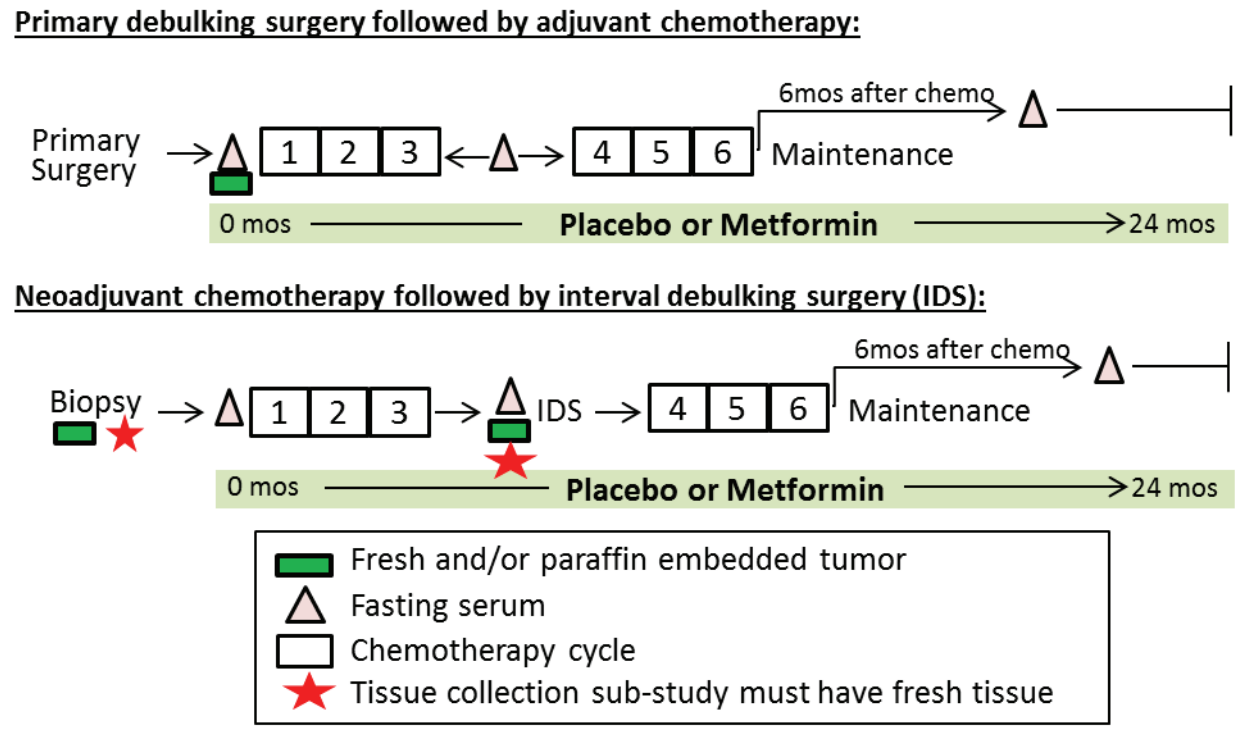


Fig. 2. Collection of biospecimens.

To test metformin's systemic effects in OVCA the following assays will be performed and results correlated with clinical outcomes:

- Insulin: will be measured using chemiluminescent immunoassay on a Siemens Immulite 2000.
- C- reactive protein: will be measured using chemiluminescent immunoassay on a Siemens Immulite 2000.
- Glucose: will be measured using the yellow springs instrument 2300
- HOMA score: To quantify insulin resistance, homeostatic model assessment (HOMA) scores (fasting insulin μ/ml X fasting glucose (mmol/22.5)) will be calculated.

These analyses will be completed in the University of Chicago Clinical Resource Center core laboratories and Diabetes Research Training Center Laboratories at University of Chicago. All methods for serum measurements have been widely used and are accepted methods in clinical trials. The facility is very experienced in these methodologies and has been operational for 40 years.

Tumor effects: To further understand the effect of metformin on the tumor, OVCA tumor microarrays (TMA) will be constructed using 5x5mm cores of tumor samples from participants in the tissue collection substudy of the clinical trial. The TMAs will be stained for the following metformin targets and the level of expression will be correlated with clinical outcomes:

- AMPK: One of metformin's primary molecular effects is activation of AMPK signaling. AMPK maintains cellular energy balance by activating ATP producing processes and inhibiting pathways that consume ATP.
- ACC: Through canonical AMPK signaling, one primary cellular target of metformin is lipid metabolism. Metformin inhibits acetyl CoA carboxylase (ACC) activity, the key regulatory enzyme in fatty acid synthesis which catalyzes the irreversible conversion of acetyl-CoA to malonyl-CoA.
- P70S6K: Also, through canonical AMPK signaling, metformin inhibits protein synthesis by inhibiting mammalian target of rapamycin (mTOR) signaling. P70S6K is a downstream target of mTOR which is involved in translation of mRNA.
- FASN: Metformin inhibits fatty acid synthase, a key enzyme involved in fatty acid synthesis. Increased FASN expression has been correlated with decreased OvCa survival (54).
- IGF 1 and 2: Insulin like growth factors (IGF) are components of insulin signaling and have been associated with ovarian cancer prognosis (55, 56).
- Ki67: Since one of metformin's known actions impacts proliferation, tumor TMAs will be stained for Ki-67.
- TUNEL: Metformin's effect on apoptosis will be characterized by measuring Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL).

IHC staining of TMAs will be done by the University of Chicago Pathology core facility. Protein expression will be quantified on the stained slide using automated imaging with the Aperio Image Scope and software using algorithms to specifically identify tumor and surrounding stroma (57) and verified by pathologists at the University of Chicago.

One of metformin's primary targets is protein synthesis as a result of activation of AMPK and subsequent inhibition of mTOR (53). Therefore, for an unbiased approach we will also interrogate metformin's effect on the OvCa proteome. The OvCa proteome in the paired tumor samples from the neoadjuvant cohort will be profiled before and after chemotherapy/metformin. This will be done using quantitative proteomics in collaboration with the Max-Planck Institute.

Given the limited sample size in a phase 2 clinical trial, it is also possible that none of the targets measured will be differentially expressed in the biospecimens. Therefore, our approach is to use both candidate driven analysis of samples and unbiased methodologies (proteomics) to generate a focused list of potential markers for future testing in large prospective clinical trials. Given the exploratory status of biomarker development for metformin in cancer, we have made every effort to minimize risk to patients in biospecimen collection. Specifically, fasting serum and tumor

sample collection will be timed to correspond with routine clinical care. Subjects enrolled in the trial will not undergo any additional biopsies, surgeries, or blood draws outside of those indicated for routine ovarian cancer treatment and monitoring.

9.2 Laboratory Correlative Studies

PLEASE SEE LABORATORY MANUAL FOR HANDLING OF SPECIMENS AND COLLECTION OF BLOOD SAMPLES

9.3 Special Studies

9.3.1 *Special Correlative Study #1- proteomic profiling on paired tumor samples*

9.3.1.1 To understand the global effect of metformin plus chemotherapy on OvCa we will perform proteomic profiling of tumors from the neoadjuvant cohort before and after treatment. This analysis will be done using frozen tumor samples collected at time – T0 and T2.

9.3.1.2 Assessment

9.3.1.2.1 Method of Assessment: quantitative mass spectrometry (MS) using an easy nano-flow HPLC to perform high-resolution shot-gun proteomics

9.3.1.2.2 Timing of Assessment: Profiling will be performed on paired tumor samples collected before and after neoadjuvant chemotherapy plus metformin or placebo.

9.3.1.3 Data Recording

9.3.1.3.1 Method of Recording: Only anonymized patient samples will be sent for proteomic analysis. The proteomic profile for each sample will be recorded electronically identified by study ID number.

9.3.1.3.2 TIMING OF RECORDING: ALL PROTEOMIC ANALYSIS WILL BE DONE AFTER THE FINAL PATIENT IN THE NEOADJUVANT COHORT UNDERGOES CYTOREDUCTIVE SURGERY.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans and x-rays must be done ≤6 weeks prior to the start of therapy. 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. Figure 3 illustrates timing of tests and studies. Duration of **study treatment** is defined at 2 years from time of randomization. **Duration of study** will include standard clinical follow-up until patient progresses.

Primary debulking surgery	Pre-treatment	During cytotoxic chemotherapy and metformin/placebo treatment	Following cytotoxic chemotherapy , during metformin/placebo study treatment	Post-study treatment

Observations and Tests	Prior to initial study treatment	Wk 1-3	Wk 4	Prior to each course (Course 1-6 (up to 8))	Prior to initial course	Every 3 months	Month 6	Post-therapy monitoring every 6 months	Every 4-6 months
Informed consent	X								
Demographics	X								
Medical history	X					X		X	X
Survival status				X	X	X		X	X
Concurrent meds	X	X	X	X----------					
Physical exam	X[a]			X	X	X		X	X
Blood pressure, pulse, temperature	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[c]			X[g]					
Serum chemistry[b]	X[c]			X[g]					
Toxicity assessment	X		X[f]	X	X	X			
Tumor measurements	X				X				
Radiologic evaluation	X[c]				Radiologic measurements should be performed at 6 months after the completion of 6 cycles of chemotherapy, then every 6 months for the duration of the study treatment.[i]				
B-HCG	X[d]								
Serum CA-125 level	X[c]			X	X	X		X	X
Fasting blood sample in Purple Top Tube (x2) for: DNA and Plasma[e]	X			X[h]			X		
Fasting blood sample in Gold Top Tube (x1) for: glucose, insulin, C-reactive protein, lipids[e]	X			X[h]			X		
Archival formalin-fixed and paraffin-embedded primary tumor and/or metastatic tumor	X							X[j]	

a: Includes assessment of compliance (medication diary)
b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
c: Laboratory values within 14 days of initial protocol treatment. Obtain CT chest, abdomen, pelvis OR chest x-ray with MRI or CT abdomen, pelvis after primary debulking surgery to establish a post-surgical baseline for the extent of residual disease. This should be obtained within 4 weeks of registration.
d: Serum pregnancy test (women of childbearing potential).

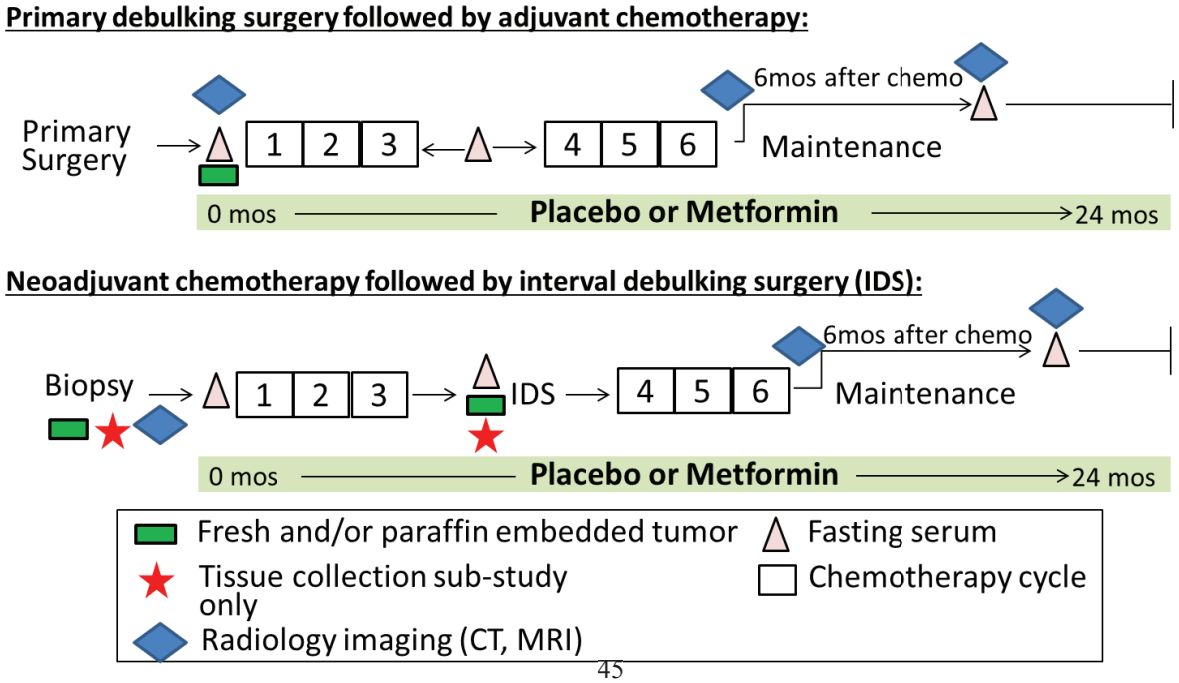
e: Study medication must be taken morning of collection
f: After week 1, if subject tolerates metformin, increase to 850 mg po BID. If intolerant, reassess for escalation at weeks, 2, 3 and 4
g: Within 4 days of protocol therapy
h: Between cycle 3-4
i: Follow-up radiographic assessment of disease: in the absence of disease progression as outlined in section 11.2.1, imaging using the same modality and encompassing the same field as in the initial pre-treatment evaluation should be repeated with the following schedule regardless of whether or not the patient had measurable disease on initial CT or MRI scan:
-at 6 months after the completion of 6 cycles of chemotherapy for all subjects whether they receive 6 or 8 cycles of chemotherapy
-every 6 months for the duration of the study treatment defined as 2 years from time of randomization
j: At time of recurrence if part of routine clinical care

Neoadjuvant chemotherapy with interval debulking surgery	Pre-treatment	During cytotoxic chemotherapy and metformin/placebo treatment		Interval debulking surgery	Following cytotoxic chemotherapy , during metformin/placebo only treatment				Post-study treatment
Observations and Tests	Prior to initial study treatment	Wk 1-3	Prior to each course (Course 1-6 (up to 8))	Day of Surgery	Prior to initial course	Every 3 months	Month 6	Post-therapy monitoring every 6 months	Every 4-6 months
Informed consent	X								
Demographics	X								
Medical history	X					X		X	X
Survival status			X		X	X		X	X
Concurrent meds	X	X	X----------						
Physical exam	X[a]		X		X	X		X	X
Blood pressure, pulse, temperature	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[c]		X[h]						
Serum chemistry[b]	X[c]		X[h]						
Toxicity assessment	X	X[g]	X		X	X			
Tumor measurements	X				X				
Radiologic evaluation	X[c]				Radiologic measurements should be performed at 6 months after the completion of 6 cycles of chemotherapy, then every 6 months for the duration of the study treatment.[i]				
B-HCG	X[d]								
Serum CA-125 level	X		X		X	X		X	X
Fasting blood sample in Purple Top Tube (x2) for: DNA and Plasma[e]	X			X			X		
Fasting blood sample in Gold Top Tube (x1) for: glucose, insulin, C-reactive protein, lipids[e]	X			X			X		
Fresh Frozen Tumor	X[f]			X[f]				X[j]	

Archival formalin-fixed and paraffin-embedded primary tumor and/or metastatic tumor	X							X[j]	

a: Includes assessment of compliance (medication diary)
b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
c: Laboratory values within 14 days of initial protocol treatment. Obtain CT chest, abdomen, pelvis OR chest x-ray with MRI or CT abdomen, pelvis within 4 weeks of registration. Imaging studies are not required at interval debulking surgery; however, if imaging studies are obtained before and/or after interval debulking surgery, results should be submitted.
d: Serum pregnancy test (women of childbearing potential).
e: Study medication must be taken morning of collection
f: Mandatory for participants in correlative tissue substudy.
g: After week 1, if subject tolerates metformin, increase to 850 mg po BID. If intolerant, reassess for escalation at weeks, 2, 3 and 4
h: Obtain within 4 days of protocol treatment
i. Follow-up radiographic assessment of disease: in the absence of disease progression as outlined in section 11.2.1, imaging using the same modality and encompassing the same field as in the initial pre-treatment evaluation should be repeated with the following schedule regardless of whether or not the patient had measurable disease on initial CT or MRI scan:
-at 6 months after the completion of 6 cycles of chemotherapy for all subjects whether they receive 6 or 8 cycles of chemotherapy
-every 6 months for the duration of the study treatment defined as 2 years from time of randomization
j: If available and collected as part of routine clinical cancer

Figure 3



11. MEASUREMENT OF EFFECT

Progression free survival as the primary endpoint and biochemical response and time to biochemical progression will be evaluated as secondary endpoints in this study.

11.1.1 Progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Patients will also be followed for CA125 response and progression using GCIG criteria. Progression by GCIG criteria may trigger a CT scan but in and of itself, will not constitute a progression event unless verified by progression of measurable lesions.

11.1.2 Disease Parameters

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 by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself

to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods 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 6 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (*e.g.*, skin nodules). 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. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at

follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

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. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.3 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with metformin.

Tumor markers. Specific guidelines for CA-125 response (in recurrent ovarian cancer) have been published [*JNCI* 96:487-488, 2004]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria [*JNCI* 92:1534-1535, 2000].

11.1.4 Progression-Free Survival

PFS is defined as the duration of time from randomization to time of progression or death, whichever occurs first.

11.2 Response Parameters

11.2.1 Evaluation of Target Lesions

11.2.11 Complete response (CR): Disappearance of all target lesions

11.2.12 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

11.2.13 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

11.2.14 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

11.2.2 Evaluation of non-target lesions

11.2.21 Complete response (CR): Disappearance of all non-target lesions and normalization of tumor marker level

Note: If serum CA125 levels are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response

11.2.22 Incomplete response

11.2.221 Stable disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

11.2.222 Progressive disease (PD): Appearance of one or more new lesions and/or unequivocal progression of 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 study chair

11.2.223 Progression Based on Serum CA-125

Progression can be based upon serum CA-125 if one of the three following conditions are met:

1. Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart.

   Or

2. Patients with elevated CA-125 pretreatment, which never normalizes must show evidence of CA-125 greater than or equal to two times the nadir value on two occasions at least one week apart

   Or

3. Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart.

   When disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pretreatment evaluation should be obtained within 2 weeks of the elevated CA-125 such that progression is documented

11.2.3 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).

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:

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

-In rare cases when there is evidence of disease on CT, MRI or physical examination, a discrepancy may exist between trends in CA-125 levels and data from either imaging or physical examination. If there is evidence of disease on CT, MRI or

physical examination, such disease is shrinking, AND there is no evidence of new disease, then rising CA-125 levels according to section 11.2.223 would be insufficient to determine disease progression

-Patients who are not evaluated for response will be classified as either: having no target lesions at the time of enrollment onto the study, not reassessed due to early death or unknown (not assessable or insufficient data)

11.2.4 Time to biochemical progression.

CA-125 will be monitored on this study but will not be a criteria for progression. If GCIG criteria for progression are met, a CT scan should be ordered by the treating physician within 2 weeks of CA-125 result. These criteria are:

- Patients with an elevated CA-125 pretreatment and normalization of CA-125 show evidence of CA-125 $\geq$ 2X the ULN on 2 occasions at least one week apart
- Patients with an elevated CA-125 pretreatment that never normalizes show evidence of CA-125 $\geq$ 2X the nadir value on 2 occasions at least one week apart
- Patients with CA-125 in the normal range pretreatment show evidence of CA-125 $\geq$ 2X ULN on 2 occasions at least one week apart

12. DATA REPORTING

Data reporting will be performed utilizing the eVelos electronic data capture system. The University of Chicago CRA will provide you with the applicable user registration information.

All required data must be recorded in the eVelos database at the completion of each cycle. AEs are to be entered in real time. SAEs are to be entered in eVelos on the Serious Event Reporting Form within 24 hours of the site's knowledge of the event. All case report forms must be completed by designated study personnel. Each screened (consented) patient is to be entered into eVelos within 48 hours of patient registration. In addition to direct data entry, you may be required to provide supporting source documentation. Source records are original documents, data, and records (e.g., medical records, raw data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. Each site will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical trial. Source records must be adequate to reconstruct all data transcribed onto the case report form.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Primary Endpoints and Analysis

This is a randomized, placebo-controlled trial that will enroll 160 patients (80 per treatment arm). Primary analysis will be by intent to treat, including all patients randomized into the study. The primary efficacy outcome variable is progression-free survival (PFS), defined as the time from randomization until disease progression or death from any cause. Surviving patients free of progression will be censored at the time of the last negative exam. Kaplan-Meier (58) curves will be generated and the metformin and placebo groups compared using a logrank test stratified by initial treatment (primary debulking surgery or neoadjuvant therapy) and chemotherapy regimen (R1/R2, R3, or R4/R5/R6). A one-sided alpha level of 0.15 will be used to determine statistical significance and declare metformin treatment worthy of phase III testing. Median PFS and associated 90% confidence interval will be estimated using the method described in Brookmeyer and Crowley (59). A Cox (60) regression model will also be fit to assess and adjust for the effects of the stratification factor (see section 13.3) and other baseline covariates (for example, age, ECOG performance status). Given that radiographic assessments will be performed at six months intervals, the discrete-time (proportional odds) form of the Cox model will be fit.

Adverse events will be analyzed as described in section 13.4 below.

13.2 Sample Size/Accrual Rate

Based on other large trials including patients with macroscopic residual disease or those receiving neoadjuvant therapy, a median PFS of 12 months is assumed for the control group (7, 11). Using a one-sided alpha level of 0.15 and 80% power, a total of 72 subjects in each arm (n=144) will be required to detect an increase in median PFS from 12 months to 17 months (HR =0.71) with metformin treatment. This assumes two years of accrual and two years of subsequent follow-up (four year study) and includes neoadjuvant and adjuvant subjects. We will increase the sample size by 10% to allow for the dropout rate (61, 62) reported in other trials using metformin for a total sample size of **160** patients. The targeted hazard ratio is consistent with the findings in OvCa retrospective cohort studies from the University of Chicago and the Mayo Clinic (32, 33). Diabetic patients on the MIMOSA trial of abagovomab who received metformin had a HR of progression of 0.419 [0.175-1.002] versus diabetic patients not receiving metformin and a HR of 0.575 [0.32-1.022] versus nondiabetic patients (no metformin) (35).

13.3 Stratification Factors and Randomization

Randomization will be stratified by initial treatment (primary debulking surgery or neoadjuvant therapy) and chemotherapy regimen (R1/R2, R3, or R4/R5/R6). Randomization lists will be created by the study biostatistician using computer-generated random numbers and the method of permuted blocks. The web-based randomization module in REDCap (63) will be employed to convey the treatment assignments to the participating sites. If there is an imbalance in chemotherapy regimen between groups, the analysis will be stratified first comparing the two treatment arms within each stratum, then getting an overall result by taking a weighted average of the within-stratum differences, weighted by the size of the strata.

13.4 Analysis of Secondary Endpoints

Time to biochemical (CA-125) progression, radiological progression, or death (whichever occurs first) and overall survival will be analyzed as described above for PFS using Kaplan-Meier curves, stratified logrank test, and Cox regression modeling. Biochemical progression is defined in section 11.2.4; surviving patients free of either type of progression will be censored at the time of the last negative exam. CA-125 response rates in the subgroup of patients with elevated CA-125 at entry (i.e., > institutional ULN) will be compared between the two treatment arms using a chi-square test. Adverse events will be summarized by type, grade, and attribution using CTCAE version 4.0 criteria; treatment group comparisons will be performed using chi-square or Fisher's exact test. Patients who receive any amount of study drug will be considered evaluable for toxicity.

13.4.1 Correlative endpoints

The goal of the correlative studies is to understand if changes in paired biospecimens are larger in samples from patients randomized to metformin compared to those on placebo. Sample size considerations are fixed by the clinical trial primary endpoint but we plan to analyze specimens from 30 patients per treatment arm in those undergoing neoadjuvant chemotherapy and participating in the tissue collection substudy.

Systemic effects.

Serum markers (e.g., insulin, C-reactive protein, glucose, HOMA score) will be measured on a continuous scale and log2 transformed for analysis as appropriate. Statistical blocking factors will be used to adjust for serum assay batch effects if needed. Linear mixed effects models will be used to test for changes from baseline to cycle 3 and 6 months post-treatment, and to test whether these changes differ between those with and without metformin. Assumptions will be verified and non-parametric tests used if needed.

Tumor effects.
Tissue microarrays. Analysis of IHC staining will begin with automated scoring via the Aperio system with an H-score (64, 56). The H-score is function of the strength of staining (0=negative, 1=weak, 2=moderate, 3=strong) multiplied by the percent of cells staining (0-100%) for that intensity, yielding a continuous 0-300 score for each sample: [1 x (% cells 1+) + 2 x (% cells 2+) + 3 x (% cells 3+)]. However, stain interpretation is partly hypothesis driven (i.e., is target in nucleus vs. cytoplasm). Thus the statisticians will work with the investigators and pathologists to review scientific aims in order to customize stain interpretation, scoring, and data acquisition to optimize analysis plans for each stain. Associations with stage and grade will be assessed via linear models. Associations with PFS and overall survival, and whether these associations are modified by metformin, will be assessed via Kaplan Meier and Cox regression methods in an exploratory fashion. Assumptions will be verified and non-parametric tests used if needed.

Proteomics. Our statisticians will collaborate with the statistical team at the Max Planck Institute regarding data processing and analysis for peptide and protein level analyses. Mixed effects models will be utilized to assess paired changes, and need for BMI as a covariate will be assessed. False discovery rates will be computed to assess significance (65). Model-based normalization strategies will be utilized if needed. Hierarchical cluster analysis will be used to

understand relationships in the data and pathway analysis will be performed using String Analysis (http://string-db.org/).

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with metformin.

13.5.2 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 possible exception of those who received no study medication) will be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration will not result in exclusion from the analysis of the response rate.

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

14. STUDY MANAGEMENT AND REGULATORY AFFAIRS

14.1 Multicenter Guidelines

The specific responsibilities of the Principal Investigator and the Coordinating Center are presented in Appendix B. Clinical studies coordinated by The University of Chicago must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements

The Study Lead PI/Coordinating Center is responsible for distributing all official protocols, amendments, and IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

14.2 Institutional Review Board (IRB) Approval and Consent

Unless otherwise specified, each participating institution must obtain its own IRB approval. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

14.3 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Cancer Clinical Trials Office (CCTO) at the University of Chicago Comprehensive Cancer Center.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Investigational drug accountability standard operating procedures
- Additionally, before the study can be initiated at any site, the required executed research contract/subcontract must be on file with the University of Chicago.

14.4 Data and Safety Monitoring

This study will be remotely monitored by the University of Chicago Clinical Research Associate (CRA) in accordance with the University of Chicago, Section of Hematology/Oncology standard operating procedure titled Monitoring of Multi-Institutional Investigator Initiated Clinical Trials.

Prior to subject recruitment, and unless otherwise specified, a participating site will undergo site initiation teleconference to be conducted by the designated University of Chicago research team.

The site's principal investigator and his or her study staff must attend the site initiation meeting.

Monitoring will be conducted to verify the following:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Compliance with regulations
- Submission of required source documents

Participating sites will also undergo a site close-out teleconference upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and to ensure that the site Investigator is aware of his/her ongoing responsibilities.

Unless otherwise specified, this protocol will undergo weekly review at the multi-institutional data and safety monitoring teleconference as per procedures specified by the UC CCC NCI-approved Data and Safety Monitoring Plan. The conference will review:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (Serious Adverse Event & Adverse Event reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

Protocol deviations are to be documented using the Protocol Deviation Form and sent via e-mail to PhaseIICRA@medicine.bsd.uchicago.edu. Deviations that are considered major because they impact subject safety or alter the risk/benefit ratio, compromise the integrity of the study data, and/or affect subjects' willingness to participate in the study must be reported within 7 calendar days of awareness of the event.

Monitoring Metformin Toxicity

As noted in Section 6.3 of the protocol the major side effects of metformin are gastrointestinal (nausea, abdominal bloating, diarrhea). Additional toxicities of concern are hepatic dysfunction, renal dysfunction, lactic acidosis, anemia, skin reactions, and Steven Johnson syndrome. Each of these types of adverse events will be specifically monitored. To ensure that the addition of metformin to chemotherapy does not exacerbate chemotherapy-related toxicities to an unacceptable degree, the occurrence of *any* serious adverse event (SAE) will also be monitored. The protocol allows for use of olaparib as maintenance therapy after chemotherapy for germline BRCA patients. Toxicities noted with olaparib include nausea, vomiting, abdominal pain, constipation, diarrhea, loss of appetite, indigestion. The occurrence of any SAE during the maintenance phase will also be monitored. The following safety monitoring plan will be used:

-A Toxicity Monitoring Report will be generated by the study statistician every 6 months
-The report will be circulated to a Safety Monitoring Committee consisting of key principal and

co-investigators
- Timing of these reports will correspond to increments of approximately 40 patients (i.e., after 40, 80, 120, and 160 patients have been randomized).
-Data will be broken out by treatment arm (metformin vs. placebo) and for each of the toxicities listed in Table 1 below
-The proportion of patients with grade 3 or higher toxicity per CTC 4.0 criteria will be compared between the two groups using a chisquare or Fisher's exact test.
-Tables will be generated based on all reported events, and separately based on events with an attribution of at least possibility related to the study drug(s), including adverse events designated as chemotherapy-related.
-Any differences statistically significant at the $p<0.05$ level will generate an "ALERT" signal and differences significant at $p<0.01$ will generate a "HIGH ALERT" signal.
- Consideration will be given to early termination of the trial if:
    - High alert signals are generated OR
    - Alert signals indicating a consistent pattern of increased toxicity in the metformin arm

Table 1. Monitored Toxicities

Nausea
Vomiting
Distention/bloating
Diarrhea
GI-other
Hepatic dysfunction (AST or ALT $\geq$ 1.8X ULN)
Renal dysfunction (Creatinine $\geq$ institutional ULN)
Acidosis (Lactate $\geq$ 5.0 mM, pH< 7.3)
Anemia (Hgb < 110 or MCV > 105)
Skin reactions (major-generalized urticarial, bullous rashes, exfoliative dermatitis)
Steven Johnson Syndrome
Any Serious Adverse Event (SAE)

Interim Futility Analysis (added June, 2019)
An interim futility analysis will be performed after one-half the expected number of primary events (disease progressions or deaths) are observed. The projected total number of primary events is 117 based on the sample size/power calculation. Therefore, this analysis will be conducted after 59 events are observed across the two treatment arms. If, at this point, the observed hazard ratio does not favor metformin, i.e., the HR (metformin/placebo) $\geq$ 1, we will consider stopping the trial early for futility. This empirical rule is associated with a minimal (<2%) power loss (66).

14.5 Auditing

In addition to the clinical monitoring procedures, the University of Chicago Comprehensive Cancer Center will perform routine Quality Assurance Audits of investigator-initiated clinical

trials as described in the NCI-approved UC CCC DSM Plan. Audits provide assurance that trials are conducted and study data are collected, documented and reported in compliance with the protocol. Further, the quality assurance audits ensure that study data are collected, documented and reported in compliance with Good Clinical Practices (GCP) Guidelines and regulatory requirements. The audit will review subjects enrolled at the University of Chicago in accordance with audit procedures specified in the UC CCC Data and safety Monitoring plan. For institutions who are formal members of the Personalized Cancer Care Consortium (PCCC), the UC CCC will conduct on site quality assurance audits on average every two years during the enrollment and treatment phase of the study.

Auditing procedures for participating sites that are not full members of the PCCC must be specified and approved by the UC CCC Clinical Research Advisory Committee. In general, for sites that are not full members of the PCCC, auditing responsibility will be delegated to the participating center, with the annual audit report forwarded to the University of Chicago for review.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the University of Chicago Cancer Clinical Trials Office and Regulatory Manager that such a request has been made.

14.6 Amendments to the Protocol

All modifications to the protocol, consent form, and/or questionnaires will be submitted to the University of Chicago IRB for review and approval. A list of the proposed modifications or amendments to the protocol and an explanation of the need of these modifications will be submitted, along with a revised protocol incorporating the modifications. Only the Study Lead PI can authorize any modifications, amendments, or termination of the protocol. Once a protocol amendment has been approved by the University of Chicago IRB, the Regulatory Manager will send the amended protocol and consent form to the affiliate institutions electronically. Upon receipt of the packet the affiliate institution is expected to do the following:

- The affiliate must reply to the email from the Regulatory Manager indicating that the amendment was received by the institution and that it will be submitted to the local IRB.

- The amendment should be submitted to the affiliate institution's IRB as soon as possible after receipt. The amendment **must** be IRB approved by the institution **within 3 months** from the date that it was received.

- **The University of Chicago version date and/or amendment number must appear on the affiliate consent form and on the affiliate IRB approval letter.** The version dates can be found on the header or footer of every page of the protocol and consent form. The amendment number can be found on the University of Chicago IRB amendment approval letter that is sent with the protocol/amendment mailing.

- The IRB approval for the amendment and the amended consent form (if amended consent is necessary) for the affiliate institution must be sent to the designated UC Regulatory Manager as soon as it is received.

14.7 Annual IRB Renewals, Continuing Review and Final Reports

A continuing review of the protocol will be completed by the University of Chicago IRB and the participating institutions' IRBs at least once a year for the duration of the study. The annual IRB renewals for participating institutions should be forwarded promptly to the Regulatory Manager. If the institution's IRB requires a new version of the consent form with the annual renewal, the consent form should be included with the renewal letter.

14.8 Record Retention

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

14.9 Obligations of Study Site Investigators

The Study Site Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Study Site Principal Investigator is responsible for personally overseeing the treatment of all study patients. He/she must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Study Site Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the CRFs. Periodically, monitoring visits or audits will be conducted and he/she must provide access to original records to permit verification of proper entry of data.

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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 Study Lead PI

- The Study Lead PI will be the single liaison with regulatory and data management staff, outside sponsor/s, FDA, and funding agencies The Study Lead PI 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 Study Lead PI. There will be only one version of the protocol, and each participating institution will use that document. The Study Lead PI is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Study Lead PI is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements are the responsibility of the Study Lead PI.
- The Study Lead PI is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Study Lead PI will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- The Coordinating Center is responsible for maintaining copies of IRB approvals from each participating site.
- 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 Study Lead PI.

- The Coordinating Center will maintain documentation of AE reports. The Coordinating Center will submit AE reports to the Study Lead PI for timely review.

APPENDIX C PILL CALENDAR

Subject Name: ________________________________Subject ID:______________________

This is a pill calendar on which you are to record the number of pills (metformin or placebo) you take each day for each cycle on this study. You will start a new calendar for each cycle.

- Begin the first cycle by taking **one pill (metformin or placebo) daily for about 1 week and then increase to 1 pill two times a day** for the rest of the study (approximately 2 years). The pills should be taken about 12 hours apart at approximately the same time every day.
- Pills should be taken with food and should not be crushed or split. Please take with about 8 ounces of water.
- If you develop any side effects, please contact your study nurse. Please make a note of any side effects or reasons you did not take metformin/placebo on the back of this diary
- Bring any unused pills, pill bottles and completed calendars to your next appointment.
- Please record the date the pill(s) are taken in each box. If you do not take metformin/placebo, please indicate this by marking an X or 0 on the # of pills line.

Cycle______________________________

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Date AM Time______ # of pills______ PM Time______ # of pills______	Date AM Time______ # of pills______ PM Time______ # of pills______	Date AM Time______ # of pills______ PM Time______ # of pills______	Date AM Time______ # of pills______ PM Time______ # of pills______	Date AM Time______ # of pills______ PM Time______ # of pills______	Date AM Time______ # of pills______ PM Time______ # of pills______	Date AM Time______ # of pills______ PM Time______ # of pills______
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Signature of subject____________________________________ Date_____________