Title: Phase I Clinical Trial of Combined Fostamatinib and Paclitaxel in Ovarian Cancer

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Phase I Clinical Trial of Combined Fostamatinib and Paclitaxel in Ovarian Cancer

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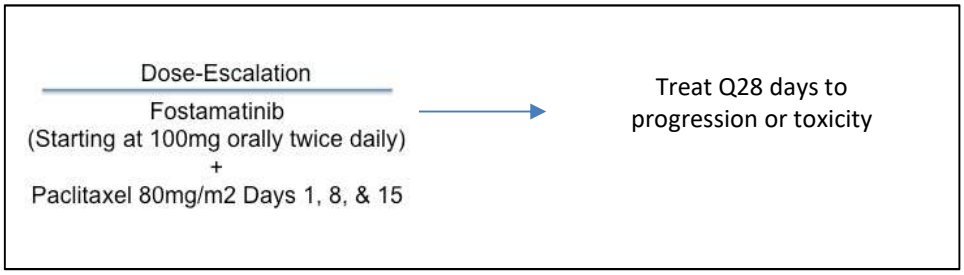
1. SUMMARY

This is a phase I, open-label, non-randomized multicenter dose-escalation study with the primary objective to determine the maximally tolerated dose (MTD) of fostamatinib when administered with weekly paclitaxel in women with recurrent platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer.

Between 8 and 18 adult female subjects will be enrolled and receive weekly paclitaxel in combination with increasing doses of fostamatinib. There will be three dosing regimens of fostamatinib (100 mg bid, 150 mg bid, and 200mg bid) selected based on the FDA approved doses and prior phase I studies of single agent fostamatinib. Dose-escalation will follow a modified toxicity probability interval (mTPI) design. In this study, up to 18 adult female subjects will be enrolled and receive weekly paclitaxel in combination with fostamatinib at the MTD of the combination; at least 6 patients will receive fostamatinib plus paclitaxel at the MTD. A total of up to 30 patients will be enrolled in this study.

2. SCHEMA



3. OBJECTIVES

3.1 Primary

3.1.1 To determine the safety, tolerability, and maximum tolerated dose (MTD) of fostamatinib when administered in combination with weekly paclitaxel

3.2 Secondary

3.2.1 To estimate the objective response rate in the study population treated with the combination of fostamatinib and paclitaxel

3.2.2 To estimate the progression-free survival in the study population treated with the combination of fostamatinib and paclitaxel

3.2.3 To assess the pharmacokinetic (PK) profile of fostamatinib when combined with weekly paclitaxel

3.3 Exploratory

3.3.1 To assess pharmacodynamic and predictive biomarkers of response from subject blood and tumor samples

3.3.2 To develop patient-derived xenografts (PDX) models to (1) assess response to the individual study drugs or the combination, (2) evaluate biomarkers of tumor response, and (3) identify mechanisms of therapeutic resistance to these agents.

4. BACKGROUND

4.1 Ovarian, Fallopian Tube, and Primary Peritoneal Carcinoma

Epithelial ovarian cancer is the most malignant of the gynecologic cancers, with a 5-year survival rate less than 50%. Each year an estimated 22,000 women will be diagnosed with and 14,000 women will die from the disease(1). Because of similarities in histology, clinical behavior, and possibly tissue of origin, the treatment paradigm for fallopian tube and primary peritoneal carcinomas parallels those for epithelial ovarian cancers. With aggressive therapy at diagnosis, including surgery and platinum based chemotherapy, more than 80% of women will have an initial complete response to therapy. Unfortunately these responses are infrequently durable and the majority of women with ovarian cancer develop recurrent, incurable disease. Responses to subsequent chemotherapeutic regimens shorten in duration over time because of progressive development of resistance to chemotherapy. Platinum-resistant disease is defined as disease recurrence or progression within 6 months of cessation of platinum-based therapy (i.e. cisplatin or carboplatin). For patients with platinum-resistant disease, platinum compounds are generally deemed to be ineffective. Subsequent therapy is generally with a single-agent, often with a taxane, pegylated liposomal doxorubicin, gemcitabine, or topotecan. Objective response rates to these agents are typically ~20% and median overall survival is less than 1 year(2-4). Thus developing new treatment strategies, including identifying novel therapeutic targets, is an urgent need.

4.2 Fostamatinib

4.2.1 Mechanism

Fostamatinib (R788) is an orally dosed pro-drug of the ATP-competitive spleen tyrosine kinase (SYK) inhibitor, R406. SYK is a non-receptor tyrosine kinase involved in immunoregulation and mediates diverse cellular responses including proliferation, differentiation, and cellular migration. Fostamatinib is in clinical development and has been (or is being) evaluated in clinical trials for the treatment of rheumatoid arthritis, immune thrombocytopenia, IgA nephropathy, hematologic malignancies, and solid tumors.

4.2.2 Pre-Clinical Studies

Fostamatinib and its active metabolite, R406, were shown to be effective in animal models of immune complex activation, arthritis, non-Hodgkin's lymphoma and chronic lymphocytic leukemia. In pre-clinical studies, R406/Fostamatinib was well tolerated; slight reduction in heart rate was noted at higher doses in a monkey cardiovascular study and mild behavioral hypoactivity was noted at higher doses in a rat CNS study(5). In toxicology studies, long term exposure (4-39 weeks) resulted in hematologic abnormalities, mild and fully reversible liver function test abnormalities, reproductive and/or developmental abnormalities. The developmental abnormalities consisted of bone growth plate effects and odontodysplasia. No mutagenic, clastogenic, or carcinogenic effects were identified.

Pre-clinical pharmacokinetic (PK) studies demonstrated conversion of fostamatinib to R406 pre-systemically, with little R788 detected in plasma(5). The conversion is likely facilitated by phosphatases in the intestinal mucosa and the bioavailability of R406 in systemic circulation is estimated to be 40-60%. The elimination half-life ranged from 0.6-3.4 hours and R406 is

extensively metabolized by oxidation and conjugation reactions. R406 is highly protein-bound in plasma and is preferentially and reversibly distributed to blood cells.

4.2.3 Clinical Studies

The clinical safety of fostamatinib has been established. Five phase 2 and three phase 3 trials have been conducted in patients with active rheumatoid arthritis(5). Over 3,400 patients received fostamatinib or placebo for 1.5-12 months. A statistically significant improvement in signs and symptoms as measured by the American College of Rheumatology 20 scale and functional improvement was found at doses of 100 and 150mg bid, however no benefit was found on bone erosion and joint destruction.

Three studies have evaluated fostamatinib in cancer patients. In a phase 1/2 study of patients with non-Hodgkin lymphoma and chronic lymphocytic leukemia, objective response rates were 22% (5 of 23) for diffuse large B cell lymphoma and 55% (6 of 11) for chronic lymphocytic leukemia(6). Toxicities were tolerable and primarily consisted of diarrhea, fatigue, cytopenias, hypertension, and nausea. Single-agent fostamatinib was evaluated in a small multi-cohort phase II trial for patients with selected solid tumors, predominantly colorectal cancer (22 of 37 patients)(7). No objective responses were observed although disease stabilization rate was 27% in colorectal cancer patients. Grade 3/4 toxicities included transaminitis, hyperbilirubinemia, and hypertension. Baseline liver function abnormalities and liver metastases influenced risk of developing toxicity. Studies of fostamatinib in subjects with impaired hepatic or renal function have shown that systemic exposure to R406 was not clinically significantly altered(5). Sixty-eight patients with relapsed or refractory DLBCL received fostamatinib in a two-arm, randomised, double-blinded manner at either 100 mg twice a day (BID) or 200 mg BID until disease progression or unacceptable toxicity. Grade 3/4 toxicities were infrequent and a 13% clinical benefit was observed(8). No study of fostamatinib in combination with chemotherapy has been performed to date.

4.2.3.1 Human PK and Drug Metabolism Studies

Similar to the animal studies, human PK studies have shown that R406 rapidly appeared in systemic circulation after administration of fostamatinib with a median tmax of 1 – 3 hours and a half-life of 12-19 hours(5). Oxidation and direct glucuronidation was the primary route of metabolism of R406. Renal elimination was low.

4.2.3.2 Metabolism, Drug Interactions, and Dietary Interactions

R406 is metabolized by CYP3A4. Inhibitors of CYP3A4 may slow the metabolism of R406, thus strong CYP3A4 inhibitors should not be co-administered with fostamatinib and moderate CYP3A4 inhibitors and inducers should be used with caution. Strong enzyme inducers should be administered with caution. Fostamatinib was determined to be a weak CYP3A4 inhibitor and clinically significant interactions with CYP3A4 substrates are thought to be unlikely. Fostamatinib is not expected to have effects on CYP2C8 substrates. The PK and PD of warfarin were not significantly affected by fostamatinib. There was no clinically relevant effect of ranitidine and statin medications on the PK of R406.

Fostamatinib increased the exposure to the following:

- Ethinyl estradiol to a modest degree, however no interaction was identified between fostamatinib and levonorgestrel;
- Rosuvastatin (2 fold by AUC) and simvastatin (1.7 fold by AUC); and
- Digoxin geometric mean AUC_{ss} and $C_{max,ss}$ were increased by 37% and 70%, respectively.

There was no clinically relevant effect of a high-fat/calorie meal. Fostamatinib should not be taken with grapefruit juice or other food/drink known to inhibit CYP3A4.

Fostamatinib inhibits UGT1A1, the sole enzyme responsible for bilirubin conjugation; this may increase unconjugated (indirect) bilirubin levels in some patients. The detection of elevated bilirubin, especially in the absence of any other LFT abnormalities, or signs or symptoms of liver impairment, suggests the (UGT1A1) effect of fostamatinib; in this case, continue the drug with regular LFT and fractionated bilirubin monitoring.

4.2.3.3 Safety Profile

The safety profile of fostamatinib has been studied in patients with rheumatoid arthritis and severely ill patients with lymphoma, chronically ill patients with ITP, and healthy subjects(5). The predominant effects consistently were on blood pressure, neutrophil counts, GI complaints (especially diarrhea) and hepatic transaminase elevations, all of which were reversible and manageable. Lymphoma patients experienced more cytopenias and infections, consistent with extensive prior therapy and underlying disease. In patients with solid tumors, baseline liver function abnormalities and liver metastases appeared to influence the development of hyperbilirubinemia and transaminitis(7). However, the overall pattern of adverse events was consistent with a population of heavily pretreated patients with relapsed solid tumors of varying histologies.

4.2.3.4 Rationale for Starting Dose and Dose Escalation Scheme

The majority of patients who have been treated with fostamatinib have received doses of 150 – 400 mg/day. The recommended phase 2 dose for lymphoma patients was 200 mg bid. In the solid tumor study, the MTD was 50 mg bid in patients with colorectal cancer, the majority of whom had liver involvement. The MTD was not reached for the other tumor cohorts and the maximum dose administered was 200 mg bid. Fostamatinib has not previously been combined with cytotoxic chemotherapy agents. Fostamatinib is available in 100 mg and 150 mg tablet formulations. For this phase I study, we plan to exclude patients with baseline liver function abnormalities. Thus, we plan to start dosing fostamatinib at 100 mg bid in combination with paclitaxel. If toxicities are acceptable in the first cohort we will increase the dose of fostamatinib by 50 mg bid per cohort until the maximum dose of 200 mg bid is reached. If toxicities in dose level 1 are not acceptable, we have allowed for a dose level -1 and dose level -2 which allow fostamatinib to be dose at 150mg daily and 100mg daily respectively.

4.3 Paclitaxel

Paclitaxel is a taxane that stabilizes microtubules, inhibiting disassembly, resulting in disruption of cell replication and proliferation. Although paclitaxel is typically given in front-line chemotherapy regimens for ovarian cancer, retreatment with paclitaxel, particularly on a weekly

schedule, is associated with response rates comparable to other chemotherapy agents used for platinum-resistant recurrent disease. Several studies have evaluated the efficacy of the weekly administration of paclitaxel in platinum-resistant ovarian cancer and shown response rates ranging between 10 and 29%(4, 9-14). In a Gynecologic Oncology Group (GOG) phase II study of weekly paclitaxel, 48 patients who had both platinum-resistant and paclitaxel-resistant disease were enrolled(15). Patients were treated with paclitaxel 80 mg/m2/week for 12 consecutive weeks followed by 80 mg/m2/week for 3 consecutive weekly doses during each 4-week cycle until disease progression. In this chemotherapy-resistant population, the objective response rate was 20.9% with two complete responses (4.2%) and 8 partial responses (16.7%). The median duration of response was 3.6 months with 2 durable responses >16 months. Serious adverse events were relatively uncommon, with 21% experiencing grade 2 neuropathy, 4% grade 3 neuropathy, and 8% grade 3 fatigue.

Subsequent trials have administered paclitaxel either weekly for 4 doses in each 4 week cycle or weekly for 3 consecutive doses during each 4-week cycle(16, 17). For this study, we have elected to administer paclitaxel 80mg/m2/week for 3 consecutive doses during each 4-week cycle while fostamatinib will be given continuously throughout each 4-week cycle.

4.4 Rationale for the Combination of Fostamatinib and Paclitaxel

We first identified a potential role for the spleen tyrosine kinase (SYK) in ovarian cancer when in a proteomic analysis we found SYK levels to be increased in recurrent high-grade serous ovarian tumors compared to the primary tumors from the same patients(18). SYK regulates adaptive immune receptor signaling, cell proliferation, differentiation, and survival of B-lymphocytes. SYK localizes to centrosomes(19) and several centrosome proteins are the substrates of SYK(20, 21). SYK has been reported as a candidate oncogene in B-cell leukemia, lymphomas, gastric carcinoma, and head and neck cancer(22-26). Expression levels of SYK are associated with increased cell motility and tumor progression in head and neck cancer(26), and peptides that block the substrate binding site of SYK induce apoptosis in B-precursor leukemia cells(27). Paradoxically, SYK expression may block tumor progression in breast cancer as loss of its expression is associated with poor prognosis and tumor metastasis(28). The evidence thus suggests that SYK can either negatively or positively regulate tumor development, depending on the biological context and tissue lineage.

Consistent with the proteomic data above, we found higher levels of SYK and phosphorylated-(activated-) SYK (p-SYK) are detectable in recurrent high-grade ovarian cancer tumors compared to patient-matched primary untreated tumors. In studies in ovarian cancer cell lines, we demonstrated that inactivating SYK, using small compound inhibitors, such as R406 (the active form of fostamatinib) or SYK knockdown, selectively sensitized cells to the cytotoxic effects of paclitaxel, overcoming paclitaxel resistance (unpublished results). This effect is likely a result of increased stabilization of microtubules with co-treatment of R406 and paclitaxel. Furthermore, we have shown that the combination of R406 and paclitaxel suppressed the growth of ovarian tumor xenografts in mice with no overt signs of toxicity.

Given the above data, we hypothesize that the addition of fostamatinib, the pro-drug of R406, to paclitaxel will have increased anti-tumor effects in patients with ovarian cancer. We propose to

investigate the toxicity profile and to define the maximum tolerated dose and recommended phase II dose of the combination of fostamatinib and paclitaxel. Following the determination of the MTD of the combination, we anticipate proposing a Phase 2 trial to evaluate the preliminary efficacy in participants with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancers.

4.5 Exploratory Correlative Studies Background

This trial will also include correlative analyses designed to evaluate whether therapy is associated with changes in SYK expression or activity and whether plasma levels of fostamatinib and paclitaxel at the MTD inhibit proliferation of ovarian cancer cell lines.

4.5.1 Immunohistochemistry of SYK, p-SYK, and Validated SYK Substrates

In a retrospective evaluation of patient-matched primary and post-treatment recurrent tumors, we found elevated expression of SYK and p-SYK. In ongoing work, we are identifying and validating SYK substrates in ovarian cancer cells. To evaluate the utility of SYK or its substrates as predictive biomarkers for fostamatinib response, we will obtain pre- and post-treatment tumor tissue from participants. Biopsy material will be obtained prior to treatment and at the end of cycle 1 by CT- or ultrasound-guidance if it is clinically and safely feasible. Expression levels of total SYK, p-SYK and other validated SYK substrates will be determined using immunohistochemistry and analyzed by digital imaging software. Expression levels will be correlated with response to therapy.

4.5.2 Inhibition Assays

Plasma samples will be collected from patients at the time of the biopsies outlined above (prior to initiation of treatment and at the end of cycle 1). For these assays, two index ovarian cancer cell lines (SKOV3TR and MPSC1TR) that express abundant SYK and p-SYK will be grown in 3-D cultures. The cells will be incubated with plasma samples collected from patients and cell cycle analysis or BrdU incorporation assays will be performed 12 hrs after incubation. Plasma collected at the end of the first cycle is expected to have a greater anti-proliferative effect than pre-treatment plasma. Inhibition of proliferation by plasma samples containing R406 would support the hypothesis that the MTD is effective in inhibiting ovarian cancer growth. Peripheral blood mononuclear cells (PBMCs) will also be analyzed for SYK activity in samples before and after fostamatinib treatment.

4.5.3 Development of PDX Models to Assess Response to and Identify Mechanisms of Resistance to Fostamatinib Therapy

Patient-derived xenografts (PDXs) have become an important platform to explore new biomarkers, treatments, and mechanisms of resistance to cancer therapy. Tumor tissue, from Johns Hopkins participants only who opt to participate via concurrent consent to this study and a companion protocol (IRB00184241/SKCCC#J18117), will be sent to Champions Oncology, Inc. for development of PDXs under the Champions TumorGraft™ program. The Champions TumorGraft™ program implants human tumor tissue into immune-deficient mice to produce patient-derived PDX. Successful PDX models will be sent back to the investigators for exploratory studies. The models will be used to (1) assess response to the individual study drugs or the

combination, (2) evaluate biomarkers of tumor response, and (3) identify mechanisms of therapeutic resistance to these agents.

5. PARTICIPANT SELECTION

5.1 Inclusion Criteria

5.1.1 Patients must have histologically or cytologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. Histologic documentation (via the pathology report) of the original primary tumor is required.

5.1.2 Patients must have measurable disease, according to RECIST v1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan, MRI, or calipers by clinical exam. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan or MRI (CT scan slice thickness recommended to be no greater than 5 mm). See Section 12 for the evaluation of measurable disease.

5.1.3 Patients must have recurrent, platinum-resistant disease (defined as having relapsed within 6 months of last platinum-containing regimen) or be unable to receive further platinum therapy. There is no limit on the number of prior treatment regimens; however, patients may not have previously received weekly paclitaxel in the recurrent setting. Previous dose dense paclitaxel as initial therapy is allowable.

5.1.4 Patients must have the ability to take oral medications.

5.1.5 Females, age ≥18 years. Because no dosing or adverse event data are currently available on the use of fostamatinib in combination with weekly paclitaxel in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

5.1.6 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

5.1.7 Life expectancy of greater than 3 months

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

Leukocytes	≥3,000/mcL
Absolute Neutrophil Count	≥1,000/mcL
Platelets	≥100,000/mcL
Total Bilirubin	≤ institutional upper limit of normal (ULN)
AST(SGOT) or ALT(SGPT)	≤3 × institutional ULN
Bilirubin	≤1.5 × institutional ULN
PT/INR	≤1.5 × institutional ULN (or an in-range INR, usually between 2 and 3 if a patient is on a stable dose of therapeutic warfarin)
Creatinine -OR- Glomerular Filtration Rate	≤1.5 x institutional ULN -OR- ≥60 mL/min/1.73 m^2 for patients with creatinine levels above 1.5 x institutional ULN

5.1.9 Patients with a diagnosis of hypertension are required to have adequate blood pressure control prior to enrollment, defined as blood pressure ≤ 140/90 mmHg.

5.1.10 The effects of fostamatinib on the developing human fetus are unknown. For this reason, women of childbearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation including for one month after last dose of fostamatinib. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately.

5.1.11 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial if the anti-retroviral therapy is not an excluded concurrent medication.

5.1.12 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated and the suppressive therapy is not an excluded concurrent medication.

5.1.13 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load and the HCV therapy is not an excluded concurrent medication.

5.1.14 Patients with **treated brain metastases** are eligible if follow-up brain imaging after central nervous system (CNS)-directed therapy shows no evidence of progression.

5.1.15 Patients who are willing and able to comply with the protocol and study procedures. Tumor biopsy or paracentesis for tumor cells before therapy (at baseline) and after initiation of treatment (before Cycle 2) for at least 75% of subjects if this is clinically and safely feasible to do so. For patients who have had tumor tissue sampled within 6 months

of enrollment and no intervening anti-neoplastic therapy, archived tissue may satisfy the requirement of the pre-treatment biopsy with permission of the protocol chair.

5.1.16 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial, with permission of the protocol chair.

5.1.17 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

5.1.18 The effects of fostamatinib on the developing human fetus are unknown. For this reason and because spleen tyrosine kinase inhibitors as well as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

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

5.2 Exclusion Criteria

5.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study. Hormonal therapy directed at the malignant tumor must be discontinued at least one week prior to registration.

5.2.2 Patients who have not recovered (CTCAE v4.03 grade ≤1) from adverse events due to agents administered more than 4 weeks earlier, unless those events are deemed to have returned to baseline, are irreversible, or are unlikely to develop into a life-threatening condition at the permission of the Protocol Chair (e.g., alopecia).

5.2.3 Patients who are currently receiving or have previously received any other investigational agents within 3 weeks prior to entering the study.

5.2.4 Patients with known, **untreated brain metastases**, as progressive neurologic dysfunction may develop that would confound the evaluation of neurologic and other adverse events.

5.2.5 Patients with Grade 2 or greater neuropathy.

5.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to fostamatinib or paclitaxel. Patients who are able to tolerate paclitaxel on a desensitization protocol will be allowed.

5.2.7 Strong CYP3A4 inhibitors or inducers should not be used within 3 days of Day 1 dosing

until the end of study. Moderate CYP3A4 inhibitors or inducers should be used with caution.

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

5.2.8 Uncontrolled intercurrent illness including, but not limited to, the following:

- ongoing or active infection, including latent tuberculosis infection,
- clinically significant GI disease (such as active Crohn's disease or ulcerative colitis),
- recent or significant cardiovascular disease (defined as any major CV event within the previous 6 months including myocardial infarction, unstable angina, cardiac arrhythmia, stroke, PE, or New York Heart Association Class III or IV heart failure),
- history of liver function abnormality requiring investigation, drug induced liver injury, chronic liver disease, excessive alcohol consumption or chronic alcohol-induced disease,
- psychiatric illness/social situations that would limit compliance with study requirements, or
- any other severe acute or chronic medical condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study

5.2.9 Pregnant women are excluded from this study because of the potential for teratogenic or abortifacient effects of fostamatinib. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with fostamatinib, breastfeeding should be discontinued if the mother is treated with fostamatinib. These potential risks may also apply to other agents used in this study.

5.3 Inclusion of Women and Minorities

Individuals of all races and ethnic groups are eligible for this trial. There is no bias towards age or race in the clinical trial outlined. This trial is open to the accrual of women only as ovarian cancer affects only females.

6. REGISTRATION PROCEDURES

6.1 Recruitment

Patients will be recruited through the gynecologic cancer clinics at each of the participating centers.

6.2 Registration

Subjects will be registered with the study coordinator at the coordinating center (Johns Hopkins) once an informed consent form is signed. After eligibility is established, the coordinating center study coordinator will assign a *study number*. Subjects will not begin protocol-specified treatment until eligibility is confirmed and the patient is assigned a study number.

After eligibility is established at the participating institution, the study staff will register patients with the Coordinating Center at Johns Hopkins. The following is required to be submitted for successful registration:

- Registration forms
- Copy of subject consent
- Copies of the following source documents:
    - Diagnostic pathology report(s), including receptor status
    - Laboratory reports, including hematology, chemistries as per the eligibility criteria and pregnancy test, if applicable
    - CT and/or MRI imaging confirming sites of disease, including measurable or evaluable disease
    - Other documents, if requested

Upon review of the registration documents, the Coordinating Center at Johns Hopkins will confirm successful registration by return email and/or fax to the local study team/designee.

Study treatment cannot begin until the patient is registered with the Coordinating Center.

Subjects who sign a consent form, but do not initiate protocol treatment for any reason (i.e., subjects who are screen failures), will be replaced and will not count towards our accrual goal.

6.2.1 Participating sites

The Protocol Chair at the Coordinating Center will maintain a list of the contact information for all participating sites. Each participating site will keep on file an Federalwide Assurance (FWA) with Office for Human Research Protections (OHRP).

6.3 General Guidelines

It is preferred that registration not occur more than 28 days prior to the planned day 1 of treatment; registration and confirmation of eligibility may occur outside this window in the event that required eligibility and baseline assessment windows will be maintained. In the event a

subject's day 1 is delayed for unforeseeable reasons and a baseline assessment(s) fall outside the intended window, it is expected that these be repeated and reviewed by the Coordinating Center prior to treatment unless explicit approval is given by the Protocol Chair or her designee.

7. TREATMENT PLAN

7.1 Overview

Treatment will be administered on an outpatient basis. Potential risks and appropriate dose modifications are described in Section 8. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Participants will receive paclitaxel on Days 1, 8 and 15 of each cycle and fostamatinib at a fixed oral dose twice daily throughout each 28-day cycle. The dose of fostamatinib will be determined by the enrollment dose level. Given the mTPI design, dose-escalation decisions will be made based on the three dosing intervals, where the underdosing interval corresponds to dose escalation (E), overdosing interval corresponds to dose de-escalation (D), and proper dosing corresponds to staying at the current dose (S). The initial dose level will be Level 1 of Table 1. Participants will be individually continually assessed for DLT. The associated dose-escalation decisions are presented in Table 2. For illustration, suppose a cohort of 3 patients is at the current dose.

- If 0 of 3 patients have a DLT, the decision is **E** (= escalate to the next dose);
- if 1 of 3 patients has a DLT, the decision is **S** (= stay at the current dose level with an additional 3 patients);
- if 2 of 3 patients have a DLT, the decision is **D** (= de-escalate to the next lower dose (or DL-1 if the current dose is DL1);
- if 3 of 3 patients experience a DLT, the decision is **DU** (= de-escalate to the next lower dose and never return to the current dose as it has been deemed unacceptably toxic).

The trial will terminate when the lowest dose is above the MTD or when 6 patients have been treated at the highest dose. A minimum of 6 patients will be treated at the MTD.

Dose Level	**Dose***	
	Paclitaxel (mg/m2) Days 1, 8, & 15 of 28 day cycle	**Fostamatinib (mg) continuous**
Level -2	80	100 QDay
Level -1	80	150 QDay
Level 1	80	100 BID
Level 2	80	150 BID
Level 3	80	200 BID

Table 1: Dose Levels. .

No. of patients experiencing a DLT	No. of Patients Treated at Current Dose Level					
	3	6	9	12	15	18
0	E	E	E	E	E	E
1	S	E	E	E	E	E
2	D	S	S	E	E	E
3	DU	S	S	S	S	E
4		DU	S	S	S	S
5		DU	DU	S	S	S
6		DU	DU	D	S	S
7			DU	DU	S	S
8			DU	DU	DU	S
9			DU	DU	DU	DU

Table 2: Dose-escalation decision rules based on the mTPI design with a cohort size of 3 for a maximum sample size of 18 patients and target DLT risk of 30%. **E** = Escalate to the next higher dose; **S** = Stay at the current dose; **D** = De-escalate to the next lower dose; **DU** = De-escalate and the current dose is unacceptably toxic; DLT = dose limiting toxicity.

7.2 Blinding and Randomization

This is a non-blinded, non-randomized study; dose levels will be assigned as above.

7.3 Regimen Description

7.3.1 Fostamatinib

Fostamatinib should be taken twice daily (approximately 12 hours apart) without interruption at approximately the same times each day. Participants are to be instructed to return all unused fostamatinib. A record of the number of tablets dispensed to and returned by each participant must be maintained. If a participant forgets to take a dose of fostamatinib, they should take the missed dose within four hours of that scheduled dose. If it is more than four hours from the time they were scheduled to take that dose, they should wait until the next dose. Participants must not make up the missed dose at the next dose.

If a participant vomits after taking a fostamatinib dose, the participant should be instructed not to retake the dose, but should instead resume dosing at the next scheduled dose. If vomiting persists, the participant should be instructed to contact the investigator.

The patient will be requested to maintain a medication diary of each dose of fostamatinib. The medication diary (see Appendix C) will be returned to clinic staff at the end of each cycle.

7.3.2 Paclitaxel

Intravenous paclitaxel should be administered according to the following schedule:

- 80 mg/m2 (60mg/m2 if dose is modified for toxicity), weekly, on Days 1, 8, and 15 (± 2 days) of a 28-day cycle, given as a one-hour intravenous infusion.

Prior to administration of the paclitaxel infusion, participants should be pre-medicated with a suggested regimen of (a) dexamethasone, (b) diphenhydramine, and (c) a H2 blocker according to local practice. Recommendations for pre-medication are as follows:

- 20 mg dexamethasone sodium phosphate orally, 12 and six hours prior to the paclitaxel infusion, OR dexamethasone 10 mg IV in 50 ml D5W over 15 min, 30 min prior to paclitaxel,
- 25-50 mg diphenhydramine orally OR by IV administration, 30 to 60 minutes prior to the beginning of the paclitaxel infusion, and
- 150 mg ranitidine orally OR 50 mg ranitidine by IV administration, 30 to 60 minutes prior to the beginning of the paclitaxel infusion

Additional information can be found in the prescribing information for paclitaxel [Taxol Package Insert, 2007]. NOTE: This is a suggested premedication regimen; established standard of care at each institution may be used as long as it is clearly documented in the medical record and reported with the research data.

With permission of the primary investigator, administration of paclitaxel through a local oncology infusion center will be allowed for cycles 2 and beyond, if in the best interest of the patient, and if the local oncology infusion center agrees to be in contact with the study investigators/staff, adhere to protocol measures, and provide information regarding infusion administration and any other study procedures performed.

Regimen Description					
Agent	**Premedications/Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Paclitaxel	Suggested premedications: dexamethasone, diphenhydramine, and a H2 blocker prior to Paclitaxel	** in 250 cc D5W	IV over 1 hour	Days 1, 8, and 15	28 days (4 weeks)
Fostamatinib	Take with water. Fostamatinib can be taken with or without food.	** tablet	PO twice daily approximately 12 hours apart	Daily throughout cycle	
**Doses as appropriate for assigned dose level.					

Table 3 Regimen Description.

7.4 Definition of Dose-Limiting Toxicity

Any grade 2 liver function toxicity (see criteria below), and clinically significant grade 3 or 4 toxicities, including any toxicity that requires delay of treatment for greater than 14 days, will be considered a DLT except for the following:

Hematologic Toxicities:

- Grade 3 or 4 neutropenia lasting less than 7 days (excluding febrile neutropenia)
- Grade 3 uncomplicated thrombocytopenia lasting less than 7 days with no evidence of bleeding
- Grade 3 or 4 decreased total WBC

Non-Hematologic Toxicities:

- Grade 3 fatigue persisting less than 7 days
- Grade 3 nausea, vomiting, or diarrhea that can be controlled by medication within 48 hours
- Grade 3 hyperglycemia, hypophosphatemia, hyponatremia, or hypocalcemia that is responsive to medical therapy within 24 hours
- Grade 3 dehydration that responds to medical intervention within 24 hours
- Grade 3 hypertension that is controlled within 1 week of diagnosis

Per FDA guidance for drug-induced liver injury (DILI), the following liver function toxicities based upon Hy's Law will be considered a DLT if:

- AST or ALT >8 x ULN; or
- AST or ALT >3 x ULN and total bilirubin >2 x ULN, with no elevation of alkaline phosphatase; or
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

AND

- No other reason(s) for these abnormalities or pre-existing liver disease.[32,33]

Any increase in bilirubin, with or without liver enzymes increases, should prompt an assessment of the fractionated bilirubin. Fostamatinib inhibits UGT1A1, the sole enzyme responsible for bilirubin conjugation; this may increase unconjugated (indirect) bilirubin levels in some patients. The detection of elevated bilirubin, especially in the absence of any other LFT abnormalities, or signs or symptoms of liver impairment, suggests the (UGT1A1) effect of fostamatinib; in this case, continue the drug with regular LFT and fractionated bilirubin monitoring.

The window for monitoring DLTs is the first 4 weeks (28 days) of protocol treatment.

Management and dose modifications associated with the above adverse events are outlined in Section 8.

Dose escalation will proceed within each cohort according to the dose-escalation decision rules in Table 2. Dose-limiting toxicity (DLT) is defined above.

7.5 General Concomitant Medication and Supportive Care Guidelines

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the participant are allowed, provided their use is documented in the subject records and on the appropriate case report form. If toxicity occurs, the appropriate treatment will be used to ameliorate signs and symptoms (including anti-emetics for nausea and vomiting, anti-diarrheals for diarrhea, and anti-pyretics and anti-histamines for drug fever). All supportive measures for optimal medical care will be given during the period of study.

Because there is a potential for interaction of Fostamatinib with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use

of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. Appendix B presents guidelines for identifying medications/substances that could potentially interact with the study agent(s).

7.6 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue 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.

NOTE: If a patient discontinues agent administration for any reason other than disease progression, ongoing radiologic evaluations to document progression are requested at least every 12 weeks after discontinuation of therapy.

7.7 Duration of Follow Up

Patients will be followed for 4 weeks after discontinuation of study treatment or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

7.8 Criteria for Removal from Study

Patients will be removed from study when toxicity monitoring is completed, as is described above, or one of the following:

- Subject withdraws consent.
- Subject is lost to follow-up.
- Study is canceled for any reason.

NOTE: The reason for removal from the study and date must be cleared documented in the records.

7.9 Additional Information

Subjects may be given parking vouchers (if applicable) to cover parking costs during the study, depending on the preferences of each participating site. No other subject remuneration is planned.

8. DOSE DELAYS/MODIFICATIONS

8.1 Summary

Treatment will be modified based on toxicity, defined per CTCAE v4.03, as described below for all participants receiving paclitaxel and fostamatinib. Dose adjustments will be made as outlined in Table 4. A maximum of two dose reductions is allowed for each patient, if feasible based upon the initially assigned dose level. Patients experiencing toxicity (hematologic or non-hematologic) that meets criteria for further dose reduction, after this maximum, will be removed from study therapy.

After 4 cycles, individualized modifications to the treatment plan, especially paclitaxel, may be considered to increase tolerability with permission of the primary investigator.

Study Drug	Initial Dose level	1 level reduction	2 level reduction
Paclitaxel	80mg/m2	60mg/m2	Remove from study*
Fostamatinib	100mg QDay	Consider decrease in paclitaxel only, or remove from study*	
	150mg QDay	100mg QDay	Consider decrease in paclitaxel only, or remove from study*
	100mg BID	150mg QDay	100mg QDay
	150mg BID	100mg BID	150mg QDay
	200mg BID	150mg BID	100mg BID

Table 4 Dose Reduction Parameters.

8.2 Dose Modifications for Hematologic Toxicity

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

- Patients will NOT receive prophylactic growth factors [filgrastim (G-CSF), sargramostim (GM-CSF), pegfilgrastim (Neulasta)] unless they experience recurrent neutropenic complications after treatment modifications specified below.

- Patients will NOT receive prophylactic thrombopoietic agents.

- Patients may receive erythropoietin (EPO), iron supplements, and/or transfusions as clinically indicated for management of anemia. Treating physicians should be aware of prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) which note that there is a potential risk of shortening the time to tumor progression or disease-free survival, and that these agents are administered only to avoid red blood cell transfusions. They do not alleviate fatigue or increase energy. They should not be used in patients with uncontrolled hypertension. They can cause an increased incidence of thrombotic events in cancer patients on chemotherapy. The updated package inserts should be consulted (http://www.fda.gov/Medwatch/safety/2007/safety07.htm).

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

8.2.3 Subsequent cycles of therapy will not begin (Day 1 of each cycle) until the ANC is ≥ 1000 cells/mcl and the platelet count is ≥ 100,000/mcl. Therapy will be delayed for a maximum of two weeks until these values are achieved. Patients who fail to recover adequate counts within a two-week delay will be removed from study therapy.

Day 8 and Day 15 paclitaxel treatment will not be given unless ANC is ≥ 1000 cells/mcl and the platelet count is ≥ 75,000/mcl. If Day 8 or Day 15 paclitaxel is held, it should not be made up.

8.2.4 Patients requiring greater than one dose reductions of paclitaxel during Cycle 1 for any cause will result in discontinuation of study treatment. If patients require more than two dose reductions of the fostamatinib, fostamatinib will be discontinued (with continuation of paclitaxel, if appropriate, until unacceptable toxicity or progression of disease).

8.2.5 Dose Modification Tables

For hematologic toxicity dose reduction of both drugs may be required. Please review both Tables 5 and 6 below.

8.2.5.1 Paclitaxel Dose Modification for Hematologic Toxicity:

	ANC[1]	PLT	ACTION FOR PACLITAXEL
Day 1	<1000	< 100,000	Delay. Monitor counts at least weekly until adequate for treatment. Restart when counts are adequate for treatment; reduce one dose level. If counts do not recover after 2 weeks delay, remove from study.
Day 8	< 1000	< 75,000	Hold dose
Day 15	< 1000	< 75,000	Hold dose
[1]For febrile neutropenia, and/or documented grade 4 neutropenia persisting greater than or equal to 7 days, reduce paclitaxel by one dose level on subsequent cycles.			

Table 5 Paclitaxel dose modification for hematologic toxicity.

8.2.5.2 Fostamatinib Dose Modification for Hematologic Toxicity:

	GRADE	ACTION FOR FOSTAMATINIB
Thrombocytopenia/ Neutropenia/ Anemia[1]	Grades 1 or 2	No interruption in treatment; maintain current dose.
	Grades 3 or 4	Interrupt treatment until toxicity is ≤grade 2; reduce one dose level. If no recovery to ≤grade 2 or recurrent grade 3 or 4, discontinue fostamatinib. Maximal interruption is 2 weeks.
[1]The dose delays and modifications for anemia apply only to anemia secondary to hemorrhage or bleeding. No specific dose delays or dose reductions are required for anemia due to other causes, but the investigator should dose delay and dose-decrease, if he/she feels it is necessary, in a manner consistent with good medical practice.		

Table 6 Fostamatinib dose modification for hematologic toxicity.

8.3 Dose Modifications for Non-Hematologic Toxicity

The following sections address the management of non-hematologic toxicities arising over the course of treatment on study.

8.3.1 Management of Hypertension

Toxicity	Grade	Paclitaxel	Fostamatinib
Hypertension	Grade 1 (sBP: 120-139 or dBP:80-89)	No change	No change; however for systolic between 130-139 or diastolic between 80-89 mmHg, anti-hypertensive therapy should be initiated for patients with increased cardiovascular risk
	Grade 2 (sBP: 140-159, dBP: 90-99, or symptomatic increase by >20mmHg diastolic)	No change	No change; however, initiate anti-hypertensive therapy, titrate as necessary. Monitoring per physician. If BP can not be controlled after an optimal trial of up to 2 antihypertensive medications, consider 1 dose reduction.
	Grade 3 (sBP ≥160, or dBP≥100)	No change	Hold Fostamatinib until ≤Grade 2. Monitoring per physician. If BP can not be controlled after an optimal trial of up to 2 antihypertensive medications, consider 1 dose reduction when sBP ≤159 and dBP≤99.
	Grade 4 (urgent intervention required, including hospitalization for symptomatic HTN)	No change	Permanently discontinue fostamatinib. Monitoring as recommended by physician.

Table 7.1 Dose Modifications for Hypertension

8.3.2 Management of Nausea, Vomiting, or Diarrhea

Toxicity	Grade	Paclitaxel	Fostamatinib
Nausea/Vomiting/ Diarrhea	Grade 1/2	No change	No change
	Persistent Grade 3 or Grade 4 (unresponsive to maximum medical management)	Hold until resolved to ≤ Grade 1 and reduce 1 dose level.	Hold until resolved to ≤ Grade 1 and reduce to next lower dose level.

Table 8.2 Dose Modifications for Nausea, Vomiting, or Diarrhea

8.3.3 Management of Elevated AST, ALT, or Bilirubin

Bilirubin/AST/ALT elevations	AST or ALT Grade 1 (≤3xULN), bilirubin Grade ≤1 (<1.5xULN)	No change	No change Consider stopping concomitant medications that may be contributing to LFT abnormalities (e.g. statins)
	AST or ALT Grade 2 (>3-5xULN), bilirubin Grade ≤1 (<1.5xULN) and asymptomatic	No change	Recheck q72hr until AST or ALT Grade 1 (≤3xULN), then follow weekly until stable. If worsens, follow guidance below. If remains elevated x 2 weeks, reduce to next lower dose level, recheck q72hr until AST or ALT Grade 1 (≤3xULN), then follow weekly until stable.
	AST or ALT Grade 2 (>3-5xULN), bilirubin Grade ≤1 (<1.5xULN) and symptomatic (e.g., nausea, vomiting, abdominal pain)	No change	Hold and recheck q72hr until AST or ALT Grade 1 (≤3xULN). Restart at next lower dose level and follow LFTs weekly until stable.
	AST or ALT Grade 3/4 (>5xULN), bilirubin Grade ≤1 (≤1.5xULN)	Hold, recheck q72hr until AST or ALT Grade 1 (≤1.5xULN). If resolves, restart same dose level. If persists >2wks, discontinue study treatment.	Hold, recheck q 72hr until AST or ALT Grade 1 (≤1.5xULN). If resolves, restart at next lower dose level. If persists >2wks, discontinue study treatment.
	AST or ALT Grade 2 (>3-5xULN), bilirubin Grade >1 (>1.5xULN)	Discontinue study treatment. Recheck q72hr until AST or ALT Grade 1 (≤3xULN) and bilirubin Grade ≤1 (≤1.5xULN).	
	Isolated elevated conjugated (direct) bilirubin >2xULN	Hold and evaluate for other potential causes. If unable to identify other potential cause, discontinue study treatment, recheck q72hr until <1.5xULN.	
	Isolated elevated unconjugated (indirect) bilirubin	No change	Continue fostamatinib with frequent monitoring since isolated increase in unconjugated (indirect) bilirubin may be due to UGT1A1 inhibition.

Table 9.3 Dose Modifications for Elevated AST, ALT, or Bilirubin

8.3.4 Management of Peripheral Neuropathy

Peripheral neuropathy	≥Grade 2	Hold until resolved to ≤ Grade 1 and reduce 1 dose level for next cycle.	No change

Table 10.4 Dose Modifications for Peripheral Neuropathy

8.3.5 Management of other clinically significant toxicities not-specifically addressed above

Other clinically significant adverse events not mentioned elsewhere[1]	Grade 1/2	No change	No change
	Grade 3/4	Hold until resolved to ≤ Grade 1 and reduce by one dose level for next cycle	Hold until resolved to ≤ Grade 1 and reduce to next lower dose level for next cycle
[1]If treatment is held for a non-hematologic grade 3/4 adverse event not described above both drugs should be dose-reduced unless the toxicity can be clearly attributed to paclitaxel or fostamatinib specifically.			

Table 11 Dose Modifications for Other Clinically Significant Toxicities

8.4 Dose Interruption for Surgery

8.4.1 Fostamatinib

It is recommended that fostamatinib is stopped 5 days prior to elective surgery and restarted when the surgical wound has healed. If emergency surgery is performed fostamatinib should be withheld until the wound has healed.

8.4.2 Paclitaxel

It is recommended that paclitaxel be held for at least 4 weeks after any major surgery (e.g. laparotomy, laparoscopy, thoracotomy, video assisted thorascopic surgery). There is no restriction on minor procedures (e.g. central venous access catheter placement, ureteral stent placement or exchange, paracentesis, thoracentesis).

8.5 Special Considerations

Any consideration to modification of the above dose modification guidelines may be permitted after discussion/approval with the Protocol Chair/designee.

9. PHARMACEUTICAL INFORMATION

9.1 Fostamatinib

9.1.1 Classification

Fostamatinib is an investigational agent supplied to investigators by Rigel Pharmaceuticals, Inc.

9.1.2 Formulation

Fostamatinib will be supplied as 100 and 150 milligram (mg) tablets.

9.1.3 Storage and Stability

Fostamatinib is stored at room temperature, protected from light.

9.1.4 Supply

Rigel Pharmaceuticals, Inc. will supply Fostamatinib for use in this clinical trial. A study-specific supply will be given to all subjects.

9.1.5 Adverse Effects

The most common side effects of Fostamatinib include the following:

Incidence of Common (≥5%) Adverse Reactions from Double-Blind Clinical Studies (C788-047 and C788-048)[5]	
Preferred Term	**All Grades (%)**
Diarrhea[a]	31
Hypertension[b]	28
Nausea	19
Dizziness	11
ALT Increased	11
AST Increased	9
Respiratory Infection[c]	11
Rash[d]	9
Abdominal Pain[e]	6
Fatigue	6
Chest Pain	6
Neutropenia[f]	6

ALT = Alanine Aminotransferase; AST= Aspartate Aminotransferase
a. Includes diarrhea and frequent bowel movement.
b. Includes hypertension, blood pressure (BP) increased, BP diastolic abnormal, and BP diastolic increased.
c. Includes upper respiratory tract infection, respiratory tract infection, lower respiratory tract infection, and viral upper respiratory tract infection.
d. Includes rash, rash erythematous, and rash macular.
e. Includes abdominal pain and abdominal pain upper.
f. Includes neutropenia and neutrophil count decreased.

9.2 Paclitaxel

9.2.1 Classification

Paclitaxel is an antimicrotubule agent. It promotes microtubule assembly and stabilizes tubulin polymers by preventing their depolarization, resulting in the formation of extremely stable and nonfunctional microtubules, and consequently inhibition of many cell functions.

9.2.2 Formulation

Paclitaxel is supplied as 30mg (5ml), 100mg (16.7ml), and 300mg (50ml) multidose vials. Each ml of sterile nonpyrogenic solution contains 6mg paclitaxel, 527mg of purified Cremophor EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

9.2.3 Storage and Stability

Please refer to the package insert for standard preparation instructions

9.2.4 Supply

Paclitaxel is commercially available.

9.2.5 Adverse Effects

The most common (> 10% frequency) adverse events associated with weekly paclitaxel are anemia, nausea, fatigue, and peripheral neuropathy (4). Please refer to the package insert for common adverse effects.

9.3 Drug Accountability

The research pharmacy will keep records for Fostamatinib receipts, dispensation, and destruction as per standard practice at each institution for supplied agents.

10. CORRELATIVE STUDIES

10.1 Fostamatinib Pharmacokinetics

To measure the pharmacokinetics of fostmatinib, blood will be collected in a sodium heparin vacutainer on days 1, 8, and 15 of the first cycle. Blood draws will occur pre-treatment and at the following times after administration:

Timing of Pharmacokinetic Analyses During Cycle 1 of Treatment		
Cycle 1 Day 1	**Cycle 1 Day 8**	**Cycle 1 Day 15**
Prior to administration 1 hour post administration 3 hours post administration 6 hours post administration	Prior to administration	Prior to administration

Samples will be frozen at -80ºC and sent in batches to Rigel Pharmaceuticals for analysis.

10.2 Pharmacodynamic Analyses

10.2.1 Immunohistochemistry of SYK, p-SYK, and Validated SYK Substrates

In a retrospective evaluation of patient-matched primary and post-treatment recurrent tumors, we found elevated expression of SYK and p-SYK. In ongoing work, we are identifying and validating SYK substrates in ovarian cancer cells. To evaluate the utility of SYK or its substrates as predictive biomarkers for fostamatinib response, we will obtain pre- and post-treatment tumor tissue from at least 75% of participants. Biopsy material will be obtained prior to treatment and at the end of cycle 1 by CT- or ultrasound-guidance if it is clinically and safely feasible. For patients who have had tumor tissue sampled within 6 months of enrollment and no intervening anti-neoplastic therapy, archived tissue may satisfy the requirement of the pre-treatment biopsy with permission of the protocol chair. Expression levels of total SYK, p-SYK and other validated SYK substrates will be determined using immunohistochemistry and analyzed by digital imaging software. Expression levels will be correlated with response to therapy.

10.2.2 Inhibition Assays

Plasma samples will be collected from patients at the time of the biopsies outlined above (prior to initiation of treatment and at the end of cycle 1). For these assays, two index ovarian cancer cell lines (SKOV3TR and MPSC1TR) that express abundant SYK and p-SYK will be grown in 3-D cultures. The cells will be incubated with plasma samples collected from patients and cell cycle analysis or BrdU incorporation assays will be performed 12 hrs after incubation. Plasma collected at the end of the first cycle is expected to have a greater anti-proliferative effect than pre-treatment plasma. Inhibition of proliferation by plasma samples containing R406 would support the hypothesis that the MTD is effective in inhibiting ovarian cancer growth. Peripheral blood mononuclear cells will be analyzed for SYK activity in samples before and after fostamatinib treatment.

10.2.3 Modeling Tumor Response to Fostamatinib +/- Paclitaxel in PDX Models

Tumor tissue, from participants who opt to participate, will be sent to Champions Oncology, Inc. for development of PDXs under the Champions TumorGraft™ program. The Champions TumorGraft™ program implants human tumor tissue into immune-deficient mice to produce patient-derived PDX. Successful PDX models will be used by the study investigators to (1) assess response to the individual study drugs or the combination, (2) evaluate biomarkers of tumor response, and (3) identify mechanisms of therapeutic resistance to these agents.

The procedural protocols pertaining to the above correlative studies are being optimized, thus **explicit instructions for handling, preserving, and shipping the specimens will be provided in the laboratory manual once finalized**.

10.3 Additional Information

Submission of data for Genome Wide Association Studies (GWAS) is not currently planned; however, subjects will be asked for permission in the informed consent process. A revision to the protocol and/or any regulatory approvals will be secured prior to any GWAS submission or inclusions in the future, if applicable.

11. STUDY CALENDAR

Pre-study evaluations are to be conducted within 4 weeks prior to start of protocol therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of therapy.

Timing of on-treatment evaluations:

- Labs for Day 1 of each cycle may be performed up to 3 days prior to the cycle.
- Radiologic evaluations should be done every 8 weeks (+/- 3 days). If stable disease or response to therapy is documented after Cycle 4, imaging can then continue every three (3) cycles thereafter. Imaging can be done at a shorter interval per provider discretion.

Procedure	Pre-Study	Cycle 1				Cycle 2-Beyond[i]				Off Study[c]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	
Fostamatinib		A: twice daily continuously				A: twice daily continuously				
Paclitaxel		B	B	B		B	B	B		
Informed Consent	X									
Demographics	X									
Medical History	X									
Physical Exam	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]				X[h]
Vital Signs, Height (Baseline Only)	X	X	X	X	X	X	X	X		X
Weight	X	X				X				X
Performance Status	X	X				X				X
CBC w/Diff, Plts	X	X[f]	X	X	X	X	X	X		X
Serum Chemistry[a]	X	X[f]	X	X	X	X				X
CA125[g]		X[f]				X				
B-HCG	X[b]									
PT/INR	X									
EKG	X									
Concurrent Medications	X	X X								
Adverse Event Evaluation		X X								X
Radiologic Evaluation/ Tumor Measurements	X	Radiologic measurements should be performed every 8 weeks. See Section 12.2 for additional information.								X
Biopsy[j]	X				X[d]					
Plasma	X				X[e]					
PK Analyses		X[e]	X	X						
PBMC Collection		X[e]	X[e]							

A: Fostamatinib: Dose as assigned; administered orally BID continuously throughout the 28 day cycle. A Study Drug Diary (Appendix C) must be completed by subjects with each dose/cycle and collected by the study staff.
B: Paclitaxel: Dose as assigned; administered IV on Days 1, 8, and 15 of each 28 day cycles
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b: Serum pregnancy test (women of childbearing potential only).
c: Off-study evaluation; subjects who discontinue therapy for a reason other than disease progression should continue to be followed for radiologic evaluation/tumor measurements about every 12 weeks until disease progression.

d: Biopsy should be obtained during week 4 of cycle 1.
e: Plasma to be obtained at the time of biopsy. PK analyses are pre- and post-dosing on C1D1. PBMC Collection performed pre-dose.
f: If C1D1 labs are performed within 7 days prior to start of therapy, they do not need to be repeated. CA125 does not need to be repeated if performed within 28 days.
g: Per standard of care
h: In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.
i: Administration of paclitaxel through a local oncology infusion center will be allowed for cycles 2 and beyond, if in the best interest of the patient, and if the local oncology infusion center agrees to be in contact with the study investigators/staff, adhere to protocol measures, and provide information regarding infusion administration and any other study procedures performed.
j: Biopsies (prior to treatment and prior to C2) are required from at least 75% of participants.

12. MEASUREMENT OF EFFECT

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline. The Protocol Chair (or designee) may choose to review cases at Johns Hopkins.

In addition, if a formal re-read for RECIST measurements is performed, but the results are not available prior to the scheduled start of the next cycle, treatment should continue based upon review of the routine/clinical radiologist report of the status of disease (i.e., response, stability or progression). In the event that a RECIST re-read would have changed the treatment decision for the subject, if known prior, the Protocol Chair/designee should be consulted and course of action clearly documented in the medical record. If it is in the best interests of the subject to continue on study, this is permissible. These cases will be reviewed in detail at the time of study analyses.

The schedule of evaluations will occur per the Study Calendar.

12.1 Definitions

12.1.1 Measurable Disease

- A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.
- A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

NOTE: Tumor lesions in a previously irradiated area are only considered measurable disease in the event that there is evidence of post-radiation progression.

12.1.2 Non-Measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] 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" 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 subject, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

12.2 Guidelines for Evaluation of Disease

12.2.1 Measurement Methods

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For subjects having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

12.2.2 Modalities for Measurable Disease

- 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. CT is preferred; MRI is also acceptable in certain situations (e.g., for body scans).

  Diagnostic quality CT is expected (with oral and IV contrast); any deviations from this must be approved by the Protocol Chair/designee in advance. (See note below regarding contrast allergy).

  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.

NOTE: If prior to enrollment it is known a subject is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the subject at baseline and follow-up should be guided by the anatomic location(s) of the disease. For subjects who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist and Protocol Chair/designee to determine if substitution of these other approaches is possible and, if not, the subject may be considered not evaluable from that point forward.

- 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 scans are preferable.

- Clinical Lesions: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) 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.

- 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.

- PET-CT: 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 with approval from the Protocol Chair/designee.

- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A ‘positive’ FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that

of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered 'negative.' New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- 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.
- 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.

12.2.3 Additional Considerations

- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
- 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.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

12.3 Lesion Documentation

12.3.1 Target Lesions

- Measurable lesions: up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined), where no more than 2 lesions are from the

same organ and no more than 2 malignant nodal lesions are selected.

NOTE: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

- Baseline Sum of Diameters (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Sum of the Diameters (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

- The minimum sum of the diameters (MSD) is the minimum of the BSD and the PBSD.

12.3.2 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions or non-target lymph nodes 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.

12.4 Response Criteria

12.4.1 Overview

All target lesions, as well as non-target lesions must be measured on re-evaluation at evaluation time points. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

NOTE: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to

be repeated only when complete response is identified in target disease or when progression in bone is suspected.

12.4.2 Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (NOTE: The appearance of one or more new lesions is also considered progression.)
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.4.3 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

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

- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

- Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

  NOTE: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at

baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described above for target lesions for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

12.4.4 Symptomatic Deterioration

Subjects with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A subject is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

- Weight loss >10% of body weight
- Worsening of tumor-related symptoms
- Decline in performance status of >1 level on ECOG scale

12.4.5 Evaluation of Best Overall Response

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

- For Subjects with Measurable Disease at Baseline:

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD	Yes	PD

	Not All Evaluated*		

- For Subjects with Non-Measurable/Evaluable Disease Only at Baseline:

Non-Target Lesions	New Lesions	Overall Objective Status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
UNK/Not All Evaluated*	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

* NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the NCCTG protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

12.4.6 Duration of Response

12.4.6.1 Duration of Overall Response

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

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

12.4.6.2 Duration of Stable Disease

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

12.4.7 Progression-Free Survival

Progression-free survival (PFS) is defined as the time from the initiation of the study treatment until the date of objective disease progression or death (by any cause in the absence of progression).

12.4.8 Response Review

There is no independent or central review of the radiology assessments planned for this trial. It is the responsibility of each Principal Investigator to ensure that tumor assessments are reported per the RECIST 1.1 criteria outlined above. The Protocol Chair (or her designee) may choose to review select cases.

13. ADVERSE EVENTS

13.1 General

This study will use the descriptions and grading scales found in the revised National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 for adverse event reporting that can be found at http://ctep.cancer.gov/reporting/ctc.html.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded, and followed as appropriate.

All adverse events experienced by subjects will be collected from the time of first dose of study medication, throughout the study and until the final study visit. Subjects continuing to experience toxicity believed to be related to fostamatinib after discontinuation of the study may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

The Coordinating Center may periodically request that de-identified AE logs and deviation logs from participating site be submitted via email to the Coordinating Center, such as for annual continuing review.

13.2 Definitions

13.2.1 Adverse Event (AE): An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (or therapy) even if the event is not considered to be related to the study.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol).

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy.

13.2.2 Serious Adverse Event (SAE): A serious adverse event is an untoward sign, symptom, or medical condition which:

- results in death;
- is immediately life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- jeopardizes the subject and requires medical or surgical intervention to prevent; or one of the outcomes listed above.

The definition of serious adverse event (experience) also includes *important medical event*. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

A hospitalization planned before the start of the study agent(s) and/or for a preexisting condition that has not worsened does not constitute a serious adverse event (e.g., elective hospitalization). A hospitalization for a social reason in the absence of an adverse event also does not meet the criteria for a serious adverse event.

13.2.3 Expectedness

- Unexpected Adverse Event: An adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk

- Expected (Known) Adverse Event: Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

13.2.4 Attribution

The relationship of all adverse events and serious adverse events to study medication will be assessed by an investigator and assigned as follows:

- Definite: The AE is clearly related to the study treatment. An adverse event which has a timely relationship to the administration of the investigational agent, follows a known pattern of response, for which no alternative cause is present.
- Probable: The AE is likely related to the study treatment. An adverse event, which has a timely relationship to the administration of the investigational agent, follows a known

pattern of response, but for which a potential alternative cause may be present.

- Possible: The AE may be related to the study treatment An adverse event, which has a timely relationship to the administration of the investigational agent, follows no known pattern of response, but a potential alternative cause does not exist.
- Unlikely: The AE is doubtfully related to the study treatment. An adverse event which does not have a timely relationship to the administration of the investigational agent, follows no known pattern of response, does not reappear or worsen after re-administration of the investigational drug/agent (if applicable), and for which there is evidence that it is related to a cause other than the investigational agent.
- Unrelated: The AE is clearly NOT related to the study treatment. An adverse event, for which there is evidence that it is definitely related to a cause other than the investigational agent. In general, there is no timely relationship to the administration of the investigational agent, or if there is a timely relationship, the event does not follow a known pattern of response, and there is an alternative cause.

13.3 Reporting Procedures

13.3.1 General

All adverse events will be captured on the appropriate study-specific case report forms (CRFs).

13.3.2 Serious Adverse Events

13.3.2.1 General

All serious adverse events, regardless of causality to study drug, will be reported to the Principal Investigator and/or the Study Coordinator at each institution, and also to the Coordinating Center.

All serious adverse events must be reported to the Coordinating Center within 1 business day after the investigator becomes aware of the event. Events should be reported using a MedWatch form (3500) as available on the FDA website (see link below).

Follow-up information must also be reported within 1 business day of receipt of the information by the investigator.

The Coordinating Center will disseminate information regarding serious adverse events to the participating sites within 5 days of review of the information by the Protocol Chair (or her designee in the event of extended absence) only in the case that the event(s) is believed to be related (i.e., possibly, probably, or definitely) related to the study medication. The Coordinating Center will be responsible for reporting of events to the FDA and supporters, as appropriate (outlined below).

13.3.2.2 Pregnancy

If a female subject becomes pregnant while receiving investigational therapy, the pregnancy must also be reported in the same time frame as a serious adverse event. In addition, any occurrence of pregnancy within 6 months after the last dose of investigational drug must also be reported. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should additionally always be classified as serious, and expeditiously

reported.

13.3.3 Institutional Review Board

All adverse events and serious adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse event. If an adverse event requires modification to the study protocol, these modifications will be provided to the IRB as soon as is possible.

13.3.4 Food and Drug Administration (FDA)

In this trial, unexpected adverse events believed to be definitely, probably, or possibly related to the medications will be reported to the Food and Drug Administration via MedWatch (using the online form available at https://www.accessdata.fda.gov/scripts/medwatch/; by telephone 1-800-FDA-1088; or by fax 1-800-FDA-0178 using form available at http://www.fda.gov/medwatch/report/hcp.htm). The Coordinating Center will be responsible for correspondence regarding adverse events with the FDA for all participating sites.

13.3.5 Rigel Pharmaceuticals, Inc.

All adverse events and serious adverse events will be reported to Rigel Pharmaceuticals, Inc., as required.

14. DATA AND SAFETY MONITORING

14.1 Data Management

All information will be collected on study-specific case report forms by the study staff at each institution. The necessary forms will be provided to each site by the Coordinating Center.

The completed forms will be forwarded to the Coordinating Center for central review and inclusion in the study dataset with relevant source documentation as outlined in the case report forms. The data submission schedule is as follows:

At the time of registration:

- Registration Form
- Informed Consent Form (signed by the subject)
- Eligibility Checklist
- Source documents related to eligibility and registration

Within 2 weeks after registration:

- Baseline study case report forms
- Pertinent source documents

Within 2 weeks after completion of each cycle:

- On study case report forms by cycle
- Pertinent source documents

Within 2 weeks after 30 day follow-up:

- On study case report forms
- Pertinent source documents

Every 3-6 months during follow-up:

- Follow-up case report forms
- Pertinent source documents (if necessary)

All study data will be reviewed for completeness and accuracy by the Protocol Chair. The Principal Investigator (or his/her designee) at each respective institution is responsible for review, and ensuring the completeness and accuracy, of the data generated by his/her institution. The study data will also be periodically reviewed by the Sidney Kimmel Comprehensive Cancer Center Clinical Research Office.

14.2 Meetings

Scheduled meetings will take place as needed with the medical oncology co-investigators and The Coordinating Center will schedule teleconferences to take place approximately every three (3) months, or more frequently depending on the rate of accrual, and will include the Protocol Chair

and Principal Investigators from each site. The following study team members involved with the conduct of the trial will be included as appropriate: study coordinators, data managers, research nurses, sub-investigators, collaborators (if applicable), and statistician.

During these meetings matters related to the following will be discussed: enrollment rate relative to expectation, characteristics of subjects, retention of subjects, adherence to protocol (potential or real protocol violations), validity and integrity of the data, shipment of research/blood samples, and progress of data for objectives.

A summary of the items discussed at each teleconference will be prepared by the Coordinating Center and forwarded to each participating site.

14.3 Monitoring and Auditing

This study is being reviewed by the United States Food and Drug Administration (FDA) and will require an IND; sponsored by a Johns Hopkins investigator (Dr. Stephanie Gaillard).

This study will be monitored per the SKCCC Data Safety Monitoring Plan with monitoring completed by the SKCCC Clinical Research Office Quality Assurance (CRO QA) group. The study conduct will additionally be reviewed at least annually by the SKCCC's Clinical Research Review Committee (CRC) and Data and Safety Monitoring Committee (DSMC); with continual oversight by the Johns Hopkins Medicine Institutional Review Board (JHM-IRB).

As above, all data will be sent to the Coordinating Center for central collation and review. There are no formal on-site evaluations planned by the Coordinating Center; however, these may occur depending on site accrual rate, identified problems or concerns, or other reasons, as appropriate.

15. ADMINISTRATIVE PROCEDURES

15.1 Protocol Amendments

Any changes to the protocol or consent document will be made in the form of an amendment and must be approved by the IRB before implementation. Any modifications to the protocol or consent will also be reviewed and approved by sponsoring agencies, as required. Amendments will be distributed by the coordinating center of the lead institution (Johns Hopkins) to all affiliate sites upon approval by the Johns Hopkins IRB.

15.2 Informed Consent

An investigator will explain to each subject the nature of the study, its purpose, procedures involved, expected duration, potential risks and benefits. Each subject will be informed that participation in the study is voluntary and that she may withdraw from the study at any time, and that withdrawal of consent will not affect her subsequent medical treatment. This informed consent will be given by means of a standard written statement and will be submitted for IRB approval prior to use. No patient will enter the study before her informed consent has been obtained. In accordance with the Health Insurance Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

15.3 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

15.4 Regulatory Authorities

15.4.1 Institutional Review Board

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per the current institutional standards of each participating center.

15.4.1.1 JHM Single IRB

Johns Hopkins Medicine is serving as the single IRB for this study. It is the preference of Johns Hopkins Medicine IRB to use the SMART IRB reliance agreement as the basis of reliance. The SMART IRB master reliance agreement was created in 2016 to harmonize and streamline the IRB review process for multisite studies. It enables reliance on a study-by-study basis, clearly defines roles and responsibilities of relying institutions and reviewing IRBs, and eliminates the need to sign reliance agreements for each study [e.g., a non-SMART IRB agreement]. 900+ institutions have already signed onto this agreement and are actively using it as the basis of reliance for multisite projects. Sites that will rely on JHM IRB are still responsible for conducting a local context review prior to the start of research at their site and for following any local and institutionally required policies as it applies to research at their site [e.g., reporting of unanticipated problems].

15.4.2 Food and Drug Administration (FDA)

This trial does not involve an Investigational New Drug (IND) application and no reporting is required with regards to the clinical trial outlined at this time.

16. COORDINATING CENTER & SITE RESPONSIBILITIES

16.1 Protocol Chair

The Protocol Chair is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments.
- Assuring that all participating institutions are using the correct version of the protocol.
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Reviewing and ensuring reporting of Serious Adverse Events (SAE).
- Reviewing data from all sites.

16.2 Coordinating Center

The Coordinating Center is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals from each site.
- Managing central patient registration.
- Collecting and compiling data from each site.
- Establishing procedures for documentation, reporting, and submitting of AE's and SAE's to the Protocol Chair, and all applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

16.3 Participating Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).
- Submitting data to the Coordinating Center.
- Registering all patients with the Coordinating Center by submitting patient registration form, and signed informed consent promptly.
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.
- Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.
- Collecting and submitting data according to the schedule specified by the protocol.

Additional information for participating sites:

16.3.1 Staffing

The participating sites will provide experienced staff, and adequate equipment and facilities to support this clinical trial. The participating sites will also be responsible for research staff training in computer applications, human subjects research, and HIPAA compliance, as well as the

continuing education in these areas as required by local institutional standards.

16.3.2 Documentation

Each participating site is responsible for submitting copies of all relevant regulatory documentation to the Coordinating Center. The required documents include, but are not limited to the following: local IRB approvals (i.e., protocol, consent form, amendments, participant brochures and recruitment material, etc.), IRB membership rosters, summary of unanticipated problems or protocol deviations, and documentation of expertise of the investigators. The Coordinating Center will provide each participating site with a comprehensive list of the necessary documents. It is the responsibility of the participating sites to maintain copies of all documentation submitted to the Coordinating Center.

The requirements for data management, submissions, and monitoring are outlined below.

16.3.3 Confidentiality

All unpublished information that the Coordinating Center gives to the investigator shall be kept confidential and shall not be published or disclosed to a third party without the prior written consent of the Protocol Chair (or her designee).

16.3.4 Record Retention

Following closure of the study, each participating center will maintain a copy of all site study records in a safe and secure location. The Coordinating Center will inform the investigator at each site at such time that the records may be destroyed.

16.3.5 Publication

It is understood that any manuscript or releases resulting from the collaborative research will be circulated to all participating sites prior to submission for publication or presentation. The Protocol Chair will be the final arbiter of the manuscript content.

16.3.6 Additional Information

Each participating site is responsible for submitting additional information as requested by the Protocol Chair (or her designee). The Coordinating Center may terminate the study at a participating site in the event that these conditions are not followed.

17. STATISTICAL CONSIDERATIONS

17.1 Study Design and Endpoints

This is a phase I, open-label, multicenter dose-escalation study with the primary objective to determine the maximally tolerated dose (MTD) of fostamatinib when administered with weekly paclitaxel in women with recurrent platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer. The dose-escalation part of the study will enroll a maximum of 18 subjects who will be administered a combination of fostamatinib and paclitaxel. Three dose levels of fostamatinib have been identified with a fixed dosage of paclitaxel (Section 7.1). Dose escalation will follow a modified toxicity probability interval (mTPI) design(29, 30). This design uses a Bayesian statistical framework with a beta-binomial model to guide dose escalation to the highest dose level for which the risk of dose-limiting toxicity (DLT) lies within an acceptable range. The range is effectively a window around a pre-specified target risk. The decision rule for dose escalation leads to escalation if the probability is high that the current dose level is below the acceptable range. If the study data suggest that the risk of DLT with the current dose is above the acceptable range, the rule calls for de-escalation. If the data suggest that the current dose's risk of DLT is most likely in the acceptable range, the rule calls for staying at this dose. The probability a dose level's risk of DLT is in each of the three intervals is updated as information from treated patients accrues. Essentially, the Bayesian calculations compute the posterior probabilities that the risk of DLT lies in each of three intervals, and the procedure leads to choosing the dose level with the highest probability of having a risk of DLT near the target. Effectively, the chosen dose level (MTD) will also have the highest probability of having a risk of DLT in the acceptable region. Depending on the number of patients needed to identify the MTD (see Section 17.1.5), an expansion cohort of patients will be enrolled to receive weekly paclitaxel in combination with fostamatinib at the MTD to ensure the safety of the combination and to further explore clinical and biological effects of the therapy.

17.1.1 Primary Endpoint

Definition of the dose limiting toxicities of the combination of fostamatinib and weekly paclitaxel graded based on CTCAE 4.03 and determination of the MTD of fostamatinib when administered in combination with paclitaxel. The risk and severity of toxicities of the combination will be recorded.

17.1.2 Secondary Endpoints

- The objective response rate in the study population treated with the combination of fostamatinib and paclitaxel.
- The progression-free survival in the study population treated with the combination of fostamatinib and paclitaxel.
- The pharmacokinetic (PK) profile of fostamatinib when combined with weekly paclitaxel

17.1.3 Exploratory Endpoints

- Pharmacodynamic and predictive biomarkers of response from subject blood and tumor samples.

17.1.4 Dose Escalation

Given the mTPI design, dose-escalation decisions will be made based on the three dosing intervals, where the underdosing interval corresponds to dose escalation (E), overdosing interval corresponds to dose de-escalation (D), and proper dosing corresponds to staying at the current dose (S). For this study, we consider

1) cohorts of size 3,
2) dose escalation starts at dose-level 1 (DL1),
3) the target DLT risk is 30%,
4) an associated range of DLT risks believed to be acceptable (essentially equivalent to the target of 30%) is 25-35% (i.e., target DLT risk ± 5%) and,
5) a dose would be excluded if the posterior probability of risk of DLT being larger than 30% is 95% or higher;
6) the maximum number of patients in the dose-escalation part is 18.

The associated dose-escalation decisions are presented below.

No. of patients experiencing a DLT	**No. of Patients Treated at Current Dose Level**					
	3	6	9	12	15	18
0	**E**	**E**	**E**	**E**	**E**	**E**
1	**S**	**E**	**E**	**E**	**E**	**E**
2	**D**	**S**	**S**	**E**	**E**	**E**
3	**DU**	**S**	**S**	**S**	**S**	**E**
4		**DU**	**S**	**S**	**S**	**S**
5		**DU**	**DU**	**S**	**S**	**S**
6		**DU**	**DU**	**D**	**S**	**S**
7			**DU**	**DU**	**S**	**S**
8			**DU**	**DU**	**DU**	**S**
9			**DU**	**DU**	**DU**	**DU**

Dose-escalation decision rules based on the mTPI design with a cohort size of 3 for a maximum sample size of 18 patients and target DLT risk of 30%. **E** = Escalate to the next higher dose; **S** = Stay at the current dose; **D** = De-escalate to the next lower dose; **DU** = De-escalate and the current dose is unacceptably toxic; DLT = dose limiting toxicity

For illustration, suppose a cohort of 3 patients are at the current dose.

- If 0 of 3 patients have a DLT, the decision is **E** (= escalate to the next dose);
- if 1 of 3 patients has a DLT, the decision is **S** (= stay at the current dose level with an additional 3 patients);
- if 2 of 3 patients have a DLT, the decision is **D** (= de-escalate to the next lower dose (or DL-1 if the current dose is DL1);
- if 3 of 3 patients experience a DLT, the decision is **DU** (= de-escalate to the next lower dose and never return to the current dose as it has been deemed unacceptably toxic).

The trial will terminate when the lowest dose is above the MTD, the last dose is much lower than the MTD or a pre-specified maximum sample size is reached. If the MTD is established as one of the 3 dose levels, a minimum of 6 patients will be treated at the MTD. The table below presents

the operating characteristics of the proposed design for this trial under different scenarios of hypothetical risks of DLT based on 2000 simulations.

Operating Characteristics of the Design

Target DLT Risk = 0.30	Dose				Avg. Fraction Experiencing a DLT	Avg. Total Sample Size
	1	2	3	None		
Scenario 1					0.202	16.4
True DLT risk	0.05	0.15	0.35			
Selection probability	0.015	0.349	0.380	0.257		
Avg. # of patients treated	3.9	6.5	6.0			
Scenario 2					0.269	17.5
True DLT risk	0.10	0.30	0.50			
Selection probability	0.152	0.640	0.141	0.0675		
Avg. # of patients treated	5.8	8.7	3.0			
Scenario 3					0.238	17.1
True DLT risk	0.10	0.25	0.40			
Selection probability	0.097	0.537	0.228	0.139		
Avg. # of patients treated	5.4	7.9	3.9			
Scenario 4					0.110	13.5
True DLT risk	0.05	0.10	0.15			
Selection probability	0.008	0.099	0.186	0.707		
Avg. # of patients treated	3.7	4.7	5.0			
Scenario 5						
True DLT risk	0.01	0.20	0.35		0.211	16.4
Selection probability	0.004	0.439	0.323	0.234		
Avg. # of patients treated	3.5	7.4	5.5			

17.1.5 Expansion Cohort

An expansion cohort will be enrolled only if the MTD is established as one of the 3 dose levels. The sample size of the expansion cohort is planned to be up to 15. A maximum of 18 patients may be treated at the MTD. Monitoring the safety of fostamatinib at the MTD in combination with weekly paclitaxel will continue with this expansion cohort (see table above regarding dose decision making) to ensure that the DLT risk of the combination therapy does not convincingly exceed 30%. Clinical activity and correlative outcomes will also be explored.

17.2 Sample Size/Accrual Rate

17.2.1 Summary

The accrual rate for this study is expected to be 1-2 patient per month. The study will enroll up to 18 patients who will be administered the combination of fostamatinib and paclitaxel. The maximum sample size in the dose-escalation part of the study is expected to be up to 18 patients. Once the MTD is established, accrual may continue as a dose expansion at this dose with the objective of studying additional patients at the MTD as long as the total study accrual does not exceed 30.

17.2.2 Early Stopping Guidelines for Safety in an Expansion Cohort

For dose expansion at the MTD to a maximum of accrual of 18, toxicity will be monitored continually in the expansion cohort. If the risk of DLT convincingly exceeds 35%, the upper bound

of the acceptable risk range, we will temporarily halt the study pending dose modification. Specifically, a Bayesian toxicity monitoring rule will suggest suspending enrollment to the expansion cohort if the posterior probability of risk being larger than 0.35 is 70% or higher. The prior for this monitoring rule is beta (1.5, 3.5), representing the risk of DLT has mean of 30%, which falls in the acceptable risk range, and there is 90% probability that this risk is between 4.6% and 65%. The stopping rules for safety and the operating characteristics under different scenarios of hypothetical actual sample sizes based on 5000 simulations are as below.

No. patients	4	5	6	7	8
experiencing a DLT Out of	7	8-10	11-13	14-15	16-18

Actual sample size	True risk of DLT	Prob. declaring regimen too toxic	Avg. sample size
12	0.25	10.8%	11.6
	0.30	19.7%	11.2
	0.35	31.1%	10.8
	0.40	43.4%	10.3
	0.45	58.5%	9.7
	0.50	70.8%	9.1
15	0.25	13.4%	14.2
	0.30	23.6%	13.6
	0.35	36.5%	12.8
	0.40	52.9%	11.8
	0.45	66.8%	10.8
	0.50	79.5%	9.9
18	0.25	14.6%	16.8
	0.30	26.2%	15.8
	0.35	41.2%	14.6
	0.40	56.8%	13.3
	0.45	72.1%	11.8
	0.50	84.4%	10.5

17.3 Analysis of Objectives

17.3.1 Analysis of Primary Objective

The MTD will be determined as the dose level with the highest probability of having a risk of DLT in the acceptable region based on the mTPI dose-escalation design. The proportion of dose limiting toxicities at each dose level will be reported with exact binomial proportions and 95% confidence intervals. All toxicities will be reported by type and grade using NCI CTCAE version 4.03.

17.3.2 Analysis of Secondary Objectives

Objective response rate will be estimated with an exact 95% confidence interval. Progression-free survival (PFS) will be described by the method of Kaplan and Meier. Median PFS will be estimated

along with its 95% confidence interval. Descriptive statistics will be used to summarize pharmacokinetic marker profile.

17.3.3 Analysis of Exploratory Objectives

Immunostaining intensities of SYK, p-SYK, and other substrate markers from biopsy samples before and after fostamatinib and paclitaxel treatment will be compared using paired t-tests after proper data transformation. Linear dose-response modeling will be performed using a mixed effects model for change in immunostaining intensity using dose as a continuous explanatory variable with biopsy time, dose, and time-by-dose interaction as fixed effects.

PDX mice will be randomized into 4 groups and treated with either vehicle, R406, paclitaxel, or R406 + paclitaxel according to previously published protocol (31). Tumor size and percent Tumor Growth Inhibition (%TGI) in response to treatment will be reported as a mean ± SE. ANOVA will be used to compare %TGI among four groups. If the null hypothesis of no difference is rejected at significance level alpha=0.05, pairwise comparison will be conducted to identify different pairs. Mean differences will be estimated along with 95% CI, and response rates will be reported along with their respective confidence intervals. Using growth inhibition of more than 60% as definitive response, a secondary analysis will use logistic regression to evaluate differences in definitive response rates between treatment groups. P-values < 0.05 will be considered statistically significant. Both continuous (%TGI) and binary (%TGI >60%) measures will be used as response variables in linear and logistic regression models, and covariates will include phosphorylation levels of expressions from SYK, pSYK, and candidate substrates, clinical and pathological features of the tumors from which the xenografts were derived. For each PDX model, the target effect size is f=1.35 which was observed from over 67% of preliminary cell line essays. To control false discovery rate of 10%, we need n=6 mice/group to reach 80% power to detect difference between combination therapy and single agent. This sample size also gives over 90% power to reject the null hypothesis in ANOVA at a two-sided significance level of 0.05.

17.4 Reporting and Exclusions

17.4.1 Evaluable for Toxicity

All subjects will be evaluable for toxicity from the time of their first dose of fostamatinib.

17.4.2 Evaluable for Objective Response

Only those subjects who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below.

NOTE: Subjects who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.

17.4.3 Evaluable for Non-Target Disease Response

Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-

evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

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APPENDICES

A Performance Status Scale
B Information on Possible Drug Interactions
C Study Drug Diary – Fostamatinib

APPENDIX A: PERFORMANCE STATUS SCALE

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: INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

Fostamatinib interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

Fostamatinib interacts with (a) certain specific enzyme(s) in your liver.

- The enzyme(s) in question is CYP3A4 which is an enzyme that metabolizes drugs in order to be cleared from your system.
- Fostamatinib must be used very carefully with other medicines that need these liver enzymes to be effective or to be cleared from your system.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP3A4**."
- Your prescribers should look at this web site http://medicine.iupui.edu/clinpharm/ddis/table.aspx or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.
- Be careful:
    - If you take acetaminophen regularly: You should not take more than 4 grams a day if you are an adult or 2.4 grams a day if you are older than 65 years of age. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.
    - If you drink grapefruit juice or eat grapefruit: Avoid these until the study is over.
    - If you take herbal medicine regularly: You should not take St. John's wort while you are taking Fostamatinib.
    - Other medications or foods that should not be taken while on this study include:

CYP3A4 Inhibitors	CYP3A4 Inducers
Amiodarone	Barbiturates
Erythromycin	Efavirenz
Isoniazid	Nevaripine
Norfloxacin	Pioglitazone
Troleandomycin	Rifampin
Chloramphenicol	Carbamazepine
Fluconazole	Modafinil
Itraconazole	Phenytoin
Norfluoxetine	Rifabutin
Verapamil	St. John's Wort
Cimetidine	
Fluvoxaimine	
Ketoconazole	
Ritonavir	
Ciprofloxacin	
Grapefruit Juice	
Mifepristone	
Rotonavir	
Clarithromycin	
Imatinib	
Nefazodone	
Seville Oranges	
Diltiazem	
Indinavir	
Nelfinavir	
Star Fruit	

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is

_____

and he or she can be contacted at

_____

INFORMATION ON POSSIBLE DRUG INTERACTIONS

You are enrolled on a clinical trial using the experimental agent **Fostamatinib. Fostamatinib** interacts with drugs that are processed by your liver. Because of this, it is very important to:

- Tell your doctors if you stop taking regular medicine or if you start taking a new medicine.
- Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

Fostamatinib interacts with a specific liver enzyme called **CYP3A4**, and must be used very carefully with other medicines that interact with this enzyme.

- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP3A4**."
- Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis/table.aspx for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.

APPENDIX C: STUDY DRUG DIARY – FOSTAMATINIB

This is a medication diary on which you are to record the number of fostamatinib tablet(s) you take each day. The instructions on how to take the fostamatinib are below.

Use the calendar to record date, time and number of tablet(s) taken each day. You will start taking ____ tablets of fostamatinib twice a day for 28 days. (It is possible your doctor may reduce the amount of fostamatinib you take while participating in this study. Your doctor will discuss the new treatment plan with you at that time.) A 28-day period of time is called a cycle. These cycles will be repeated as long as your tumor is not growing and you are not experiencing any unacceptable side effects. Each medication diary sheet should last you 4 weeks (one cycle). Medication should be taken as instructed without skipping any days. If you have missed a dose please mark "0" in the slot for that dose. If your doctor changes the amount of fostamatinib you take, please be sure to write down the correct number of pills and correct amount taken in the columns below.

How to take Fostamatinib:
Tablet(s) should be taken twice daily at approximately the same time each day. Tablets should be taken with approximately 1 cup (240mL) of water. Tablets should be swallowed whole and should not be crushed or broken.

What to do if you forget a dose:
If you forget to take a dose of fostamatinib, you can take the missed dose within four hours of the scheduled dose. If it is more than four hours from the time you were scheduled to take that dose, you should wait until the next day to take the next dose. You should not take two doses at one time to make up for a missed dose. If you vomit after taking a fostamatinib dose, you should not to retake the dose, but should instead resume dosing at the next scheduled dose. If vomiting persists, please contact the study physician or research nurse.

If you develop any side effects, please write side effects the day they occurred and anything else you would like to tell the doctor in the comments section.

Please note: You must not take Grapefruit juice or St. John's Wort while on this study.

Bring any unused tablets, empty medication containers, and your completed diary to your next appointment.

Note to staff: Please give patient a medication diary at initial enrollment and at the start of every cycle. Instruct patient how to complete the medication diary. If they are taking the first pill at a visit complete the log with them. Remind them they must bring the log back at each visit along with pill bottles even if empty.

Medication Diary – Fostamatinib

Participant Initials: _____ Study ID: _____ Cycle Number: ____ Day 1 Date: _____

Dose/Number of tablets to take at each dose: _____

INSTRUCTIONS:
1. Complete one form per cycle of therapy.
2. Record the date, the number of tablets of you took, and when you took them.
3. Please record comments or side effects in the Comments section.
4. Please return the forms to your physician/research nurse prior to the next cycle of therapy.

Day	Date	Time of AM dose	# of tablets	Time of PM dose	# of tablets	Comments
1						
2						
3						
4						
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Reviewed by: _____ Date: _____