Philip J. DiSaia, M.D.
President

Administrative Office
Four Penn Center
1600 John F. Kennedy Boulevard, Suite 1020
Philadelphia, Pennsylvania 19103
Phone: 215-854-0770 Fax: 215-854-0716

Laura L. Reese
Executive Director of Operations

GOG® FOUNDATION, INC.

Larry J. Copeland, M.D.
Vice President

Finance/Development Office
2127 Espey Court
Suite 100
Crofton, Maryland 21114
Phone: 410-721-7126 Fax: 301-261-3972

Mary C. Sharp
Chief Financial Officer

SUMMARY OF CHANGES

For Protocol Amendment #5

NCI Protocol #: GOG-0283
Local Protocol #: GOG-0283

NCI Version Date: May 18, 2016
Protocol Date: May 18, 2016

#	Section	Page(s)	Comments
1.	Title Page	**1-3**	**The NCI Version Date has been updated.** **Includes Amendments 1-5 has been added.** **Revised has been added to the footer**
2.	3.11	**18**	**Pathology eligibility has been updated.**
3.	App VI	**75**	**Contact information for distributing specimens for translational research has been updated**
4.	ICD		**NCI Version Date has been updated.**

PROTOCOL GOG-0283

A PHASE II TRIAL OF DCTD-SPONSORED DASATINIB (NSC #732517 IND #120636) IN RECURRENT /PERSISTENT OVARY, FALLOPIAN TUBE, PRIMARY PERITONEAL, AND ENDOMETRIAL CLEAR CELL CARCINOMA CHARACTERIZED FOR THE RETENTION OR LOSS OF BAF250a EXPRESSION

NCI Version: May 18, 2016

Includes Amendments 1-5

POINTS:

PER CAPITA -10

MEMBERSHIP -3

Suggested TR Per Capita – Award based on specimen submission with 1 point for each FFPE and whole blood (MAX = 5 points).

Lead Organization: NRG/NRG Oncology

STUDY CHAIR DAVID HYMAN, M.D. MEMORIAL SLOAN-KETTERING CANCER CENTER 300 E 66th Street, Rm 1353 New York, NY 10065 PHONE: (646) 889-4544 FAX: (646) 888-4586 EMAIL: hymand@mskcc.org	STUDY CO-CHAIR CAROL AGHAJANIAN, M.D. MEMORIAL SLOAN-KETTERING CANCER CENTER 1275 York Avenue New York NY 10021 PHONE: (212) 639-2252 FAX: (212) 639-8865 EMAIL: aghajanc@mskcc.org
NURSE CONTACT KATHLEEN O'CONNOR, B.S.N. MEMORIAL SLOAN-KETTERING CANCER CENTER 300 E 66th Street, Room 1353 New York, NY 10065 PHONE: (646) 888-4544 FAX: (212) 639-2283 EMAIL: oconnork@mskcc.org	STUDY PATHOLOGIST ROBERT SOSLOW, M.D. (SEE GOG WEBSITE DIRECTORY)
TRANSLATIONAL RESEARCH CO-CHAIR DOUGLAS A. LEVINE, M.D. (SEE GOG WEBSITE DIRECTORY)	TRANSLATION RES. SCIENTIST HEATHER A. LANKES, PhD, MPH (SEE GOG WEBSITE DIRECTORY)
STUDY STATISTICIAN WILLIAM BRADY, PhD (SEE GOG WEBSITE DIRECTORY)	

OPEN TO PATIENT ENTRY FEBRUARY 3, 2014;
TEMPORARILY CLOSED TO PATIENT ENTRY DECEMBER 19, 2014; REVISED NOVEMBER 2, 2015; REOPENED TO PATIENT ENTRY NOVEMBER 9, 2015; REVISED JANUARY 27, 2016; REVISED

SCHEMA (11/2/15)

Patients with recurrent or persistent ovarian, fallopian tube, peritoneum, endometrial, or endometriosis-associated clear cell carcinoma.

Must be ≥ 50% clear cell histomorphology and be negative for expression of the WT-1 antigen and estrogen reception (ER) antigen by immunohistochemistry (IHC)

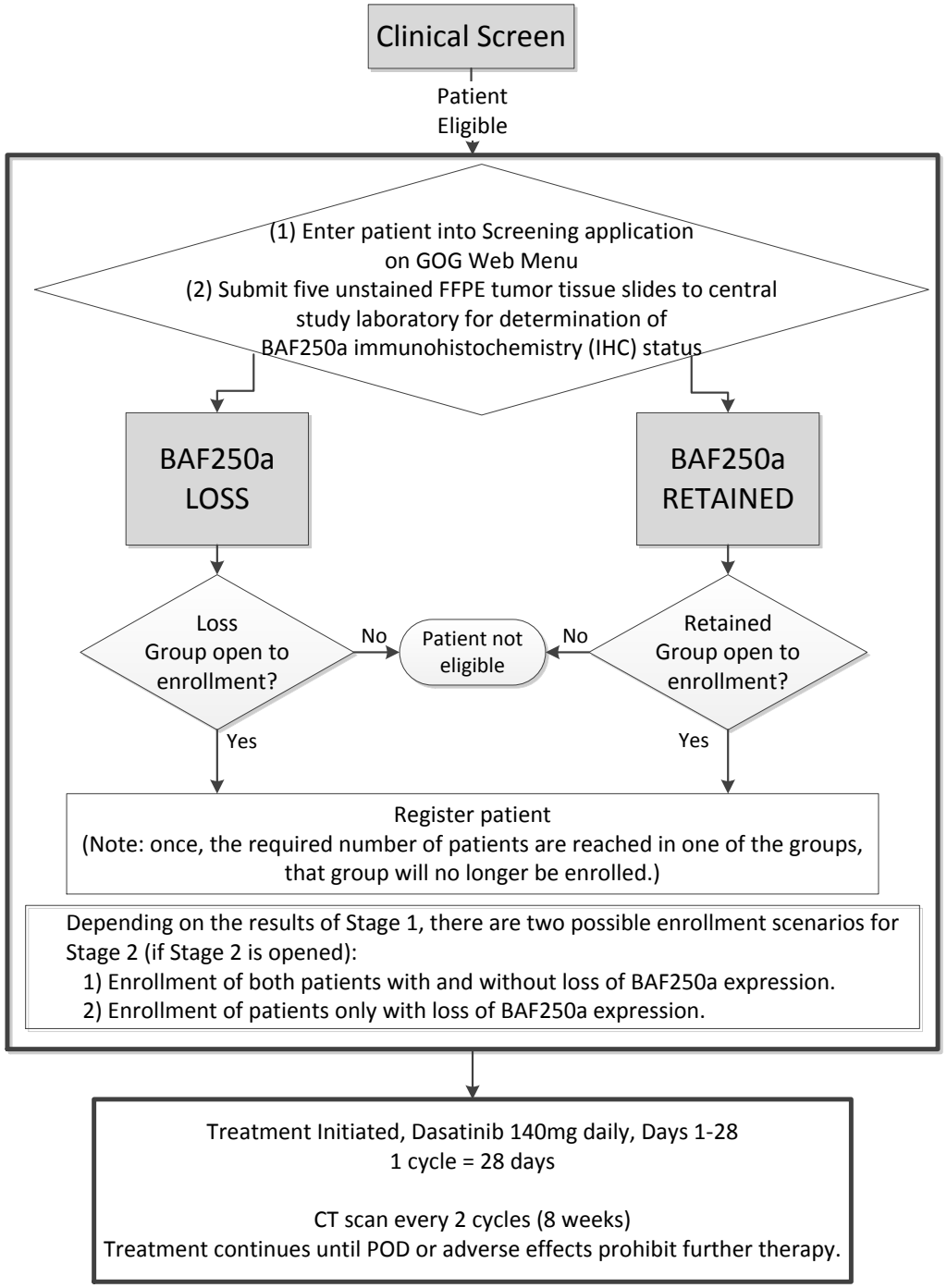


TABLE OF CONTENTS

PAGE

1.0 OBJECTIVES

1.1 Primary Objectives:

To assess the clinical activity of dasatinib in patients with recurrent or persistent ovarian, fallopian tube, primary peritoneal, and endometrial clear cell carcinoma using objective tumor response (complete and partial):

- in patients without loss of BAF250a expression, and
- in patients with loss of BAF250a expression

1.2 Secondary Objectives

1.21 To examine the nature and degree of toxicity in this patient population treated with this regimen in patients with and without loss of BAF250a expression.

1.22 To examine the progression-free survival and overall survival for this patient population receiving dasatinib in patients with and without loss of BAF250a expression.

1.3 Translational Research Objectives

1.31 To examine the agreement between BAF250a immunohistochemistry and ARID1A mutation status using next generation sequencing performed in formalin-fixed, paraffin-embedded tumor tissue.

2.0 BACKGROUND AND RATIONALE

2.1 Rationale for a Clear Cell Carcinoma Specific Trial

Approximately 22,000 cases of ovarian cancer and 46,000 cases of endometrial are diagnosed in the United States annually.[1] The majority (≥80%) of these cases are of the serous (ovarian) or endometrioid (endometrial) histologies. Although the precise frequency of clear cell carcinoma of the ovary and endometrium varies by continent, this orphan disease represents only 3-5% of cases in the first-line clinical trials for ovarian cancer.[2] Several meta-analyses have evaluated the outcome of large numbers of patients treated in first-line ovarian cancer clinical trials and have found that clear cell histology is an independent poor-prognostic feature.[2, 3] Matched by stage, clear cell cancers have a lower-response rate to standard platinum-based chemotherapy, a higher recurrence rate, and inferior survival when compared to serous ovarian cancers.[4] Consensus panels of gynecologic cancer experts have called on researchers to acknowledge these differences and design clear cell specific clinical trials moving forward.[5]

2.2 Rationale for Inclusion of Ovarian and Endometrial Clear Cell Carcinoma

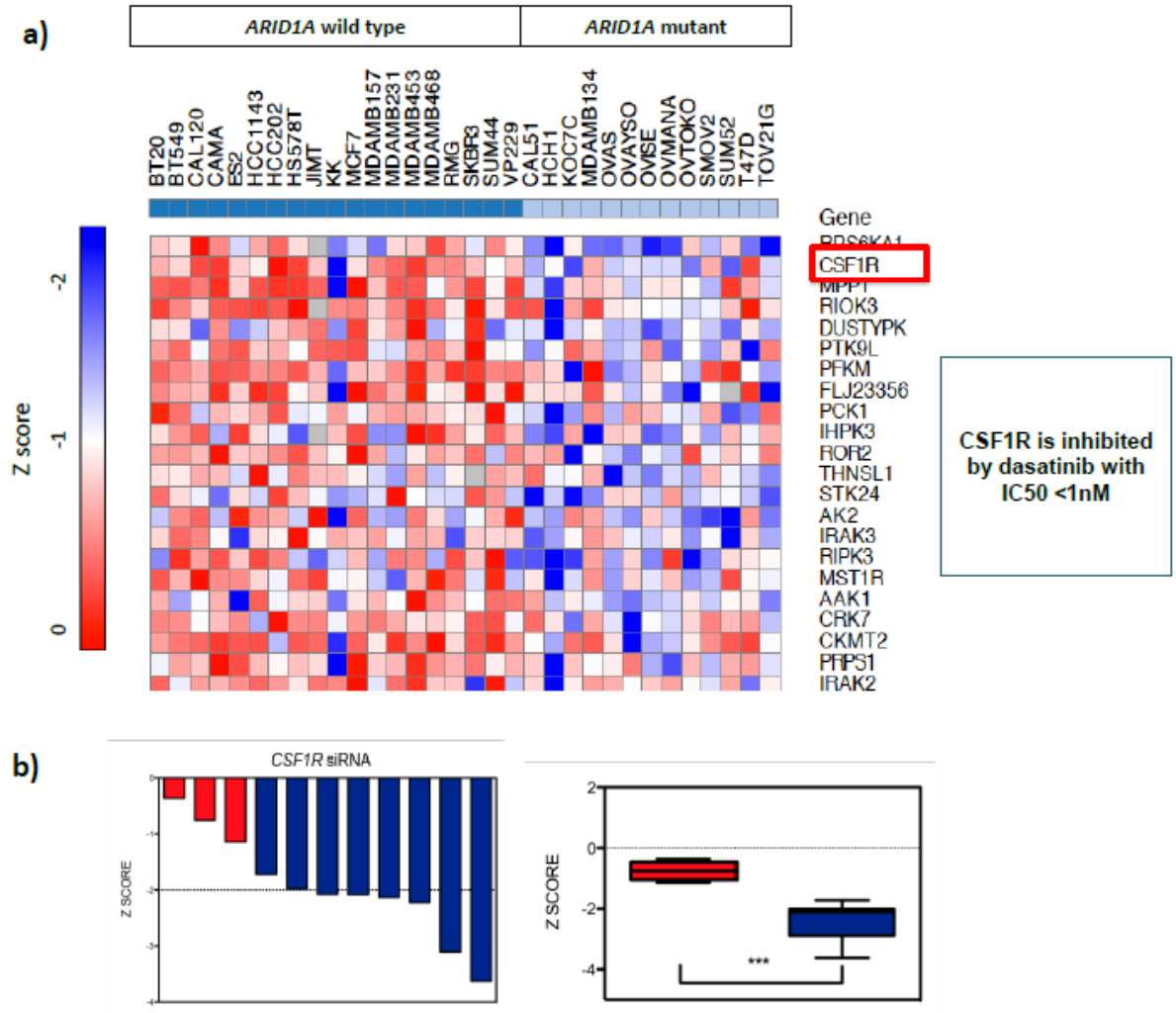
Historically, distinctions have been made between clear cell carcinomas of the gynecologic tract arising from the ovary and endometrium. Recently, however, molecular profiling has demonstrated that both clear cell carcinomas are patho-physiologically linked to—and represent malignant transformation of—endometriosis.[6, 7] Clear cell ovarian carcinomas of the ovary, arising from endometriosis, and clear cell endometrial carcinomas arising de novo in the endometrium and are therefore increasingly viewed as a single disease entity with a shared genetic lineage.

2.3 Rationale for Dasatinib in Gynecologic Clear Cell Carcinoma

As described above, we now understand that endometrial and gynecologic clear cell carcinomas are associated with endometriosis.[7] In 2010, a report in the NEJM identified that ARID1A mutations are present in approximately 50% of endometriosis-associated clear cell carcinomas.[8] ARID1A is a putative tumor suppressor gene that encodes a protein BAF250a.[9] BAF250a is involved in chromatin remodeling and it is believed that dysregulation of this protein may alter the accessibility of transcription factors to chromatin. The central importance of ARID1A mutations to the genetic events associated with transformation of endometriosis into clear cell carcinoma is supported by the recent reports that ARID1A mutations are almost universally present in the precursor lesions adjacent to ARID1A-deficient gynecologic clear cell carcinomas including non-atypical endometriosis, atypical endometriosis, and borderline clear-cell adenofibromas.[10] Furthermore, the loss of ARID1A expression has been linked to shorter progression free survival and chemoresistance of endometriosis associated

clear cell carcinomas.[11] A functional profiling of endometriosis associated clear cell carcinomas was recently presented at the 2012 ASCO meeting.[12] An siRNA kinome screen identified colony stimulating factor-1 receptor (CSF1R) as a synthetically lethal target of ARID1A-deficient but not ARID1A-intact endometriosis associated clear cell carcinoma cell lines (**Figure 1**). The synthetic lethality of CSF1R inhibitor in ARID1A-deficient clear cell carcinomas was maintained across multiple cell lines. CSF1R is a member of the type II receptor tyrosine kinase family characterized by five immunoglobulin-like extracellular domains and a kinase insert. CSF1R has been correlated with tumor invasiveness and poor prognosis in breast cancer.[13] Dasatinib, a small molecule inhibitor of BRC-ABL, is also known to inhibit CSF1 at single-digit nanomolar concentrations.[14] The ability of dasatinib to selectively inhibit ARID1A-deficient endometriosis associated clear cell lines at physiologically achievable levels (1-10nM) in a series of confirmatory experiments (**Figure 2**).[12] Finally, to demonstrate that CSF1R was the therapeutic target of dasatinib, ARID1A mutant and wild-type cell lines were treated with the selective CSF1R inhibitor, GW2580, again demonstrating selective inhibition (**Figure 3**).

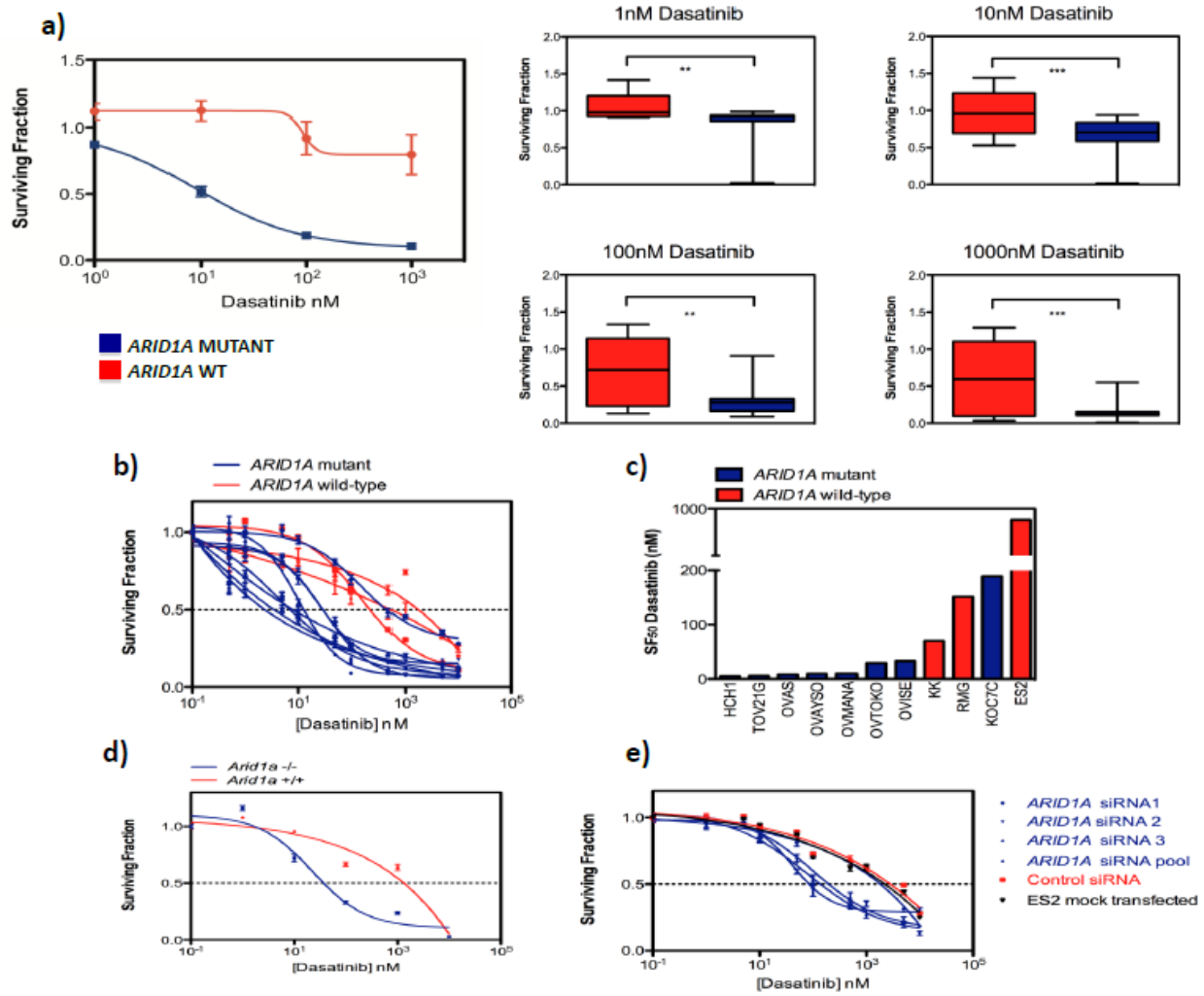
Figure 1: *ARID1A* mutant cell lines are addicted to *CSF1R*



(a). Heat map showing the results of a supervised clustering of siRNA Z scores. OCCC cell lines were clustered according to *ARID1A* gene mutation status and differential effects between *ARID1A* mutant and wild type groups identified using the median permutation test. Statistically significant effects ($p<0.05$) are shown. CSF1R is the only dasatinib target which is selective for *ARID1A* mutant cell lines. (b) Waterfall and box/whiskers plots of *CSF1R* siRNA Z scores across the panel of OCCC cell lines. Student's T=test *** $p = 0.0009$ between *ARID1A* mutant and wild-type groups.

REF: Miller, ASCO Abstract 5035, 2012

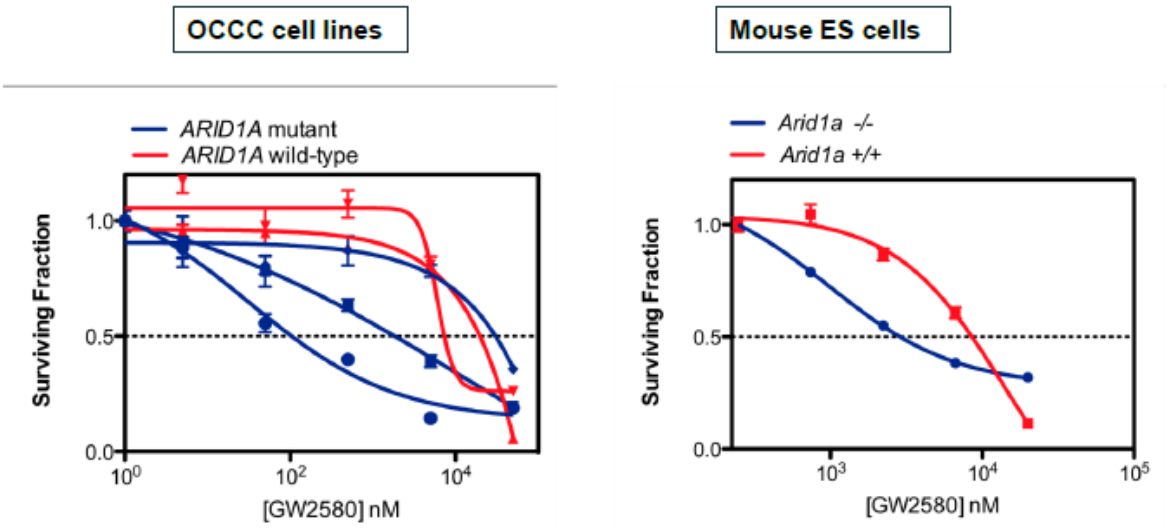
Figure 2: Dasatinib is selective for *ARID1A* mutant cell lines



(a) Surviving fraction from *ARID1A* mutant versus wild-type cell line cohorts from chemical screen are shown. p values were calculated using Student's t-test ** p = 0.0015, *** p<0.0001. (b) Cells were plated in 96 well plates and exposed to dasatinib for 5 days after which SF were calculated. (c) Box-plot showing the dasatinib SF_{50} for each cell line (nM). (d) Dasatinib is selective for *Arid1a* null mouse embryonic stem cells. 2000 cells were plates on gelatin coated plates and exposed to dasatinib for 14 days after which colonies were counted and SF calculated. (e) Transfection with *ARID1A* siRNA but not control siRNA shifts the dose response curve to the left.

REF: Miller, ASCO Abstract 5035, 2012

Figure 3: *ARID1A* mutant cell lines are sensitive to CSF1R inhibitor, GW2580



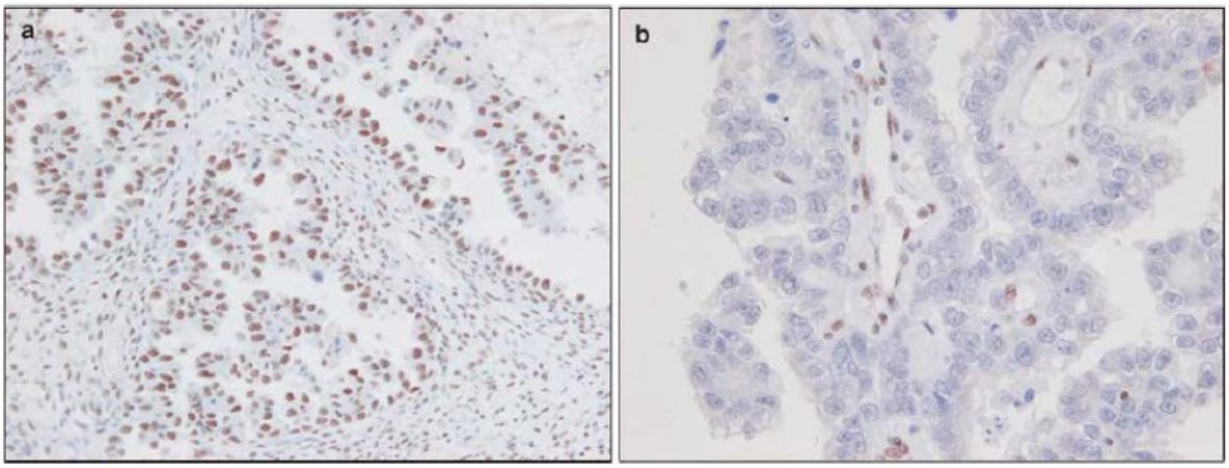
Long term drug assay in OCCC cell lines and (d) mouse ES cells demonstrate increased sensitivity in the *ARID1A* mutant OCCC cell lines and the *Arid1a* null mouse ES cells.

REF: Miller, ASCO Abstract 5035, 2012

2.4 Rationale for Using BAF250a Expression as a Marker for ARID1A Mutation Status

ARID1A is a large gene with over 80,000 base pairs and 20 exons. As is typical for large tumor suppressor genes, nonsense, missence, insertion and deletion mutations of ARID1A have been described across the entire length of the gene, the majority of which are protein truncating. The lack of a small number of "hot-spot" mutations, as well as the overall size of the gene, make tumor selection by prospective sequencing challenging. Moreover, mutation data alone does not necessary provide information on the functional impact on BAF250a expression. Fortunately, loss of BAF250a expression as detected by immunohistochemistry (IHC) correlates well with presence ARID1A mutation with an estimated sensitivity and specificity of 73% and 89%, respectively.[8, 10] **Figure 4** demonstrates representative BAF250a IHC in ovarian clear cell carcinoma samples. It is therefore reasonable to use BAF250a expression as a surrogate for ARID1A-difficient clear cell carcinomas. Because ARID1A mutations are an early event in the development of endometriosis associated clear cell carcinomas, BAF250a IHC status in archival tissue from the time of diagnosis should be reflective of the status in recurrent or persistent metastatic lesions.

Figure 4: BAF250a staining in OCCC



(a) *ARID1A*-intact OCCC showing diffuse nuclear BAF250a staining, **(b)** *ARID1A*-deficient OCCC showing undetectable BAF250a(stromal cells act as positive controls)

REF: Yamamoto S, Mod Path (2012) 25, 615-624

2.5 Dasatinib

Dasatinib (BMS-354825), an aminothiazole analogue, is an orally administered (PO) protein tyrosine kinase (PTK) inhibitor with specificity for five kinases/kinase families that have been strongly linked to multiple forms of human malignancies[17- 19]. These targets include: BCR-ABL, c-SRc, c-KIT, PDGFβ receptor, and EPHA2. *In vivo* and *in vitro* studies have established that dasatinib demonstrates potent antiproliferative activity in a wide spectrum of cancer cell lines/types, and clinical results suggest anticancer activity of dasatinib in chronic myelogenous leukemia (CML) and solid tumor patients[20-23].

Dasatinib potently and selectively inhibits the five oncogenic PTKs/kinase families by competing with ATP for the ATP-binding sites in the kinases: SRC family kinases (IC_{50}: SRC = 0.55 nM, LCK = 1.1 nM, YES = 0.41 nM, FYN = 0.2 nM); BCR-ABL (<3 nM); c-KIT (13 nM); EPHA2 (17 nM) and PDGFβ receptor (28 nM) [17]. The agent was found to be less potent against unrelated PTKs and several serine/threonine kinases. Dasatinib also demonstrates potent inhibition of VEGF- and bFGF-driven proliferation of human umbilical vein endothelial cells (HUVECs), with IC_{50} values of 43 and 248 nM, respectively.

BCR-ABL, a constitutively active cytoplasmic tyrosine kinase, is present in >90% of all patients with CML and in 15-30% of adult patients with acute lymphoblastic leukemia (ALL). The inhibition of BCR-ABL by imatinib, another PTK inhibitor, is effective in the management of CML thus providing proof-of-concept for targeting PTKs. However, resistance to imatinib therapy associated with BCR-ABL gene mutation/over-expression and activation of selected SRC kinases has been increasingly encountered[24]. Dasatinib has activity in a number of imatinib-resistant tumors[25-27, 29, 30] in addition to being 500-fold more potent than imatinib in inhibiting BCR-ABL. The ability of dasatinib to inhibit imatinib-resistant forms of BCR-ABL is presumed to be due to its relaxed binding requirements because, unlike imatinib which binds only to the inactive conformation of the BCR-ABL kinase, dasatinib binds to both the active and inactive conformations[31].

2.51 Nonclinical Studies

Efficacy

Dasatinib inhibits growth of multiple BCR-ABL-dependent leukemic cell lines and also shows activity against 14 of 15 imatinib-resistant BCR-ABL kinase mutants[29]. Inhibition of CML cell lines established from patients who were resistant to imatinib therapy has also been reported[23]. Dasatinib potently inhibits wild-type (IC_{50}: 1-10 nM) and mutant (IC_{50}: 10-100 nM) KIT kinases in M07E cells and human mast cell leukemia cell lines, respectively[22]. Also of note, dasatinib selectively killed primary neoplastic bone marrow mast cells from patients with systemic mastocytosis while sparing other hematopoietic cells[28].

Dasatinib demonstrated antiproliferative activity in a wide-spectrum of solid tumor types, including mastocytoma, prostate, and breast cell lines with IC_{50} values ranging from 5.4-103 Nm[18]. The agent also inhibited stem cell factor-driven proliferation of three small cell lung cancer (SCLC) cell lines with IC_{50} values in the range of 114-220 nM and showed activity in head and neck squamous cell carcinoma and non-small cell lung cancer cell lines[32].

When dasatinib was administered twice daily (BID) on a 5-days-on/2-days-off schedule for a total of 14 to 25 days at doses of 10-50 mg/kg/dose, *in vivo* antitumor activity of dasatinib was seen in prostate, colon, breast, and pancreatic xenograft models[18]. Similarly, dasatinib was effective against K562 and imatinib-resistant K562-R human CML xenografts in SCID mice at doses as low as 2.5-5 mg/kg/day[26]. In combination with docetaxel, dasatinib produced antitumor effects against PC3 human prostate carcinoma xenografts that were substantially better than the effects of either single agent alone[18].

Dasatinib at 20 or 50 mg/kg inhibited the T-cell proliferation response in mice following the transfer of lymphocytes from allogeneic donor mice[17]. In addition, treatment of mice with dasatinib 25 mg/kg BID inhibited the graft-versus-host response in a non-vascularized model of murine heart transplant. The 5-days-on/2-days-off regimen almost completely eliminated immunosuppressive activity in this model.

SRC kinase is known to play a major role in osteoclast function. In short-term studies, dasatinib acted as a potent inhibitor of bone resorption as measured by its ability to reduce the release of ^{45}calcium into the culture medium by fetal rat long bones *in vitro* (IC_{50} = 2 nM). Dasatinib also inhibited parathyroid hormone (PTH)-stimulated release of ^{45}calcium in a dose-dependent manner with an apparent IC_{50} of 2 nM. At 5 nM, dasatinib completely blocked PTH-stimulated bone resorption in thyro-parathyroidectomized rats. The therapeutic utility of dasatinib in the treatment of cancer-related hypercalcemic syndromes has not been fully explored, and the long-term effects of dasatinib on bone physiology are also unknown.

Nonclinical Pharmacokinetic and Pharmacodynamic Studies

Nonclinical metabolic and pharmacokinetic (PK) studies were conducted with dasatinib in several species including mouse, rat, dog, and monkeys to assess the absorption, distribution, metabolism, and excretion of the compound in animals. These studies showed that dasatinib has varying degrees of oral bioavailability, ranging from 15% in monkeys to 34% in dogs. The permeability of dasatinib in the Caco-2 cell model is 102 nm/sec at pH 7.4, suggesting that it has the potential for good (>50%) oral absorption in humans. The agent is highly bound to serum proteins (>91%) and has extensive extravascular distribution. Dasatinib is principally eliminated by hepatic metabolism and excreted in feces. The agent is primarily metabolized by the CYP3A4 enzyme to produce multiple metabolites.

The value of phospho-SRC as a biomarker of dasatinib efficacy has been explored in nonclinical studies[33]. In nude mice bearing subcutaneous PC-3 tumors (human prostate), measurement of phospho-SRC by western blot in tumor and peripheral blood mononuclear cells (PBMCs) following treatment with a single dose of dasatinib (15 or 50 mg/kg) produced similar results in both tissues. Levels of phospho-SRC were maximally inhibited at 3 hours post dose, then recovered partially between 7 and 17 hours and returned to the basal level by 24 hours after agent administration. These results were quantitated by image scanning and compared to efficacy results when the agent was administered PO BID at

15-50 mg/kg/dose for 14 days on a 5-days-on/2-days-off schedule. Efficacy and phospho-SRC inhibition appeared to correlate, and this pharmacodynamic model permitted the authors to predict that the plasma concentration of dasatinib required to produce 90% inhibition of phospho-SRC would be 164 nM and 91 nM in PC-3 tumor and PBMCs, respectively. Studies to evaluate the clinical utility of phospho-SRC as a biomarker are ongoing.

Toxicology

A range of toxicology studies have been conducted to support the oral administration of dasatinib in humans. The oral studies indicated that dasatinib induced reversible toxicities of the gastrointestinal (GI) and lymphoid systems in rats and monkeys, and of the hematopoietic system in rats. Embryo fetal development studies in rats and rabbits indicated that dasatinib caused embryo lethality or skeletal malformations at doses that did not cause maternal toxicity, suggesting that it is a selective developmental toxicant. An *in vitro* cytogenetics study in CHO cells indicated that it was clastogenic at concentrations ≥5 μg/mL, a level not achievable *in vivo*. The agent is nongenotoxic and did not show significant potential for undesirable functional activity in *in vitro* receptor/ion channel binding and enzyme assays. *In vitro* potassium channel current (HERG/IKr) and Purkinje fiber assays suggested that dasatinib could potentially prolong cardiac ventricular repolarization (QT interval), and a single-dose cardiovascular study in monkeys demonstrated that the agent at a dose of 10 mg/kg caused a minimal increase in blood pressure for approximately 2 hours post dose. There were no drug-related neurologic observations in rats or monkeys. Dasatinib was found to be phototoxic in an *in vitro* assay in mouse fibroblasts.

2.52 Clinical Experience

Over 2000 subjects have received dasatinib, the majority with CML refractory or intolerant to imatinib[18]. Studies conducted in healthy volunteers include the following: PK; formulation comparisons; the effect of food; drug interactions; and supportive care. Data are available from 11 phase 1 and phase 2 studies in patients with CML, Philadelphia chromosome-positive (Ph+) ALL, or solid tumors using different dosage regimens and designed to determine PK, pharmacodynamic, safety, and efficacy in these populations.

Pharmacokinetics

Pharmacokinetic (PK) studies were conducted using a single 100 mg dose of dasatinib administered to healthy volunteers in four different formulations: 50 mg clinical tablets x 2, 5 mg clinical tablets x 20, 20 mg commercial tablets x 5, and 50 mg commercial tablets x 2. The PK profile

of the agent was similar in all four formulations. The PK profile of dasatinib was also assessed in CML and Ph+ ALL patients providing data which showed that the PK parameters in the patient population appear to be similar to that in the healthy volunteers. The agent was absorbed rapidly following oral administration; peak plasma concentrations were achieved in 0.5-3 hours and dose-related increases in plasma concentrations were observed. The mean terminal half-life ($t_{1/2}$) of dasatinib was 4 hours. Dosing interval exposures and $t_{1/2}$ values were comparable regardless of whether the agent was administered on a once daily or twice daily (BID) 5-day-on/2-day-off schedule, or BID continuously.
A phase 1 study has been initiated in solid tumor patients to determine the effect of the CYP3A4 inhibitor ketoconazole on dasatinib PK. In a study of 18 patients with solid tumors, 20 mg of dasatinib once daily co-administered with 200 mg of ketoconazole twice daily increased the dasatinib Cmax and AUC by four- and five-fold, respectively.

Efficacy
A phase I study treated patients with CML in chronic phase (CP) or advanced disease (accelerated phase or blast crisis) or Ph+ ALL who were intolerant or resistant to imatinib[34, 30]. Dasatinib was administered once daily at doses ranging from 15 to180 mg/day or BID at doses ranging from 25 to 50 mg for 5-7 consecutive days each week. Complete hematologic response was documented in 37 of 40 CP patients (92%) and the rate was similar with both schedules (once daily or BID). Fourteen CP patients (35%) achieved a complete cytogenetic response and four (10%) experienced partial responses. In 44 patients with advanced CML or Ph+ ALL, 31 major hematologic responses were documented (70%). Cytogenetic responses were documented in 25 advanced CML or ALL patients, including complete responses in 11 patients.

A phase 1 study has been conducted in patients with refractory solid tumors in order to evaluate the safety, tolerability, and the pharmacologic profile of dasatinib[20]. Patients received escalating doses (25 to 120 mg) of dasatinib without food administered BID for 5 consecutive days every week followed by 2 days of rest (5D2 schedule), or on a continuous daily dosing (CDD) schedule. There were no objective responses on CT scans, but stable disease (SD) was observed in 11 patients (16%), including three gastrointestinal stromal tumor (GIST) patients. These 11 were comprised of seven (21%) of 33 patients on the 5D2 schedule and four (12%) of 34 patients on the CDD schedule. The median duration of SD was 3.6 months (range 1.7 – 23.6 months). The investigators noted that the clinical benefits of the agent in a subset of imatinib-resistant GIST patients have been encouraging.

In solid tumors, the recommended phase 2 dose for dasatinib was found to be 120 mg BID on the 5D2 schedule, or 70 mg BID on the CDD regimen[20]. In October 2010, dasatinib was approved by the FDA for treatment of chronic, accelerated, and blast phase CML and Ph+ ALL with resistance or intolerance to imatinib. Results from two phase 3 dose-optimization studies supported starting doses of 100 mg once/day for CP CML and 140 mg once/day for imatinib-resistant accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL. A randomized phase 3 trial comparing dasatinib to imatinib led to FDA approval of dasatinib (100 mg once/day) for first-line therapy of newly diagnosed CML.

Safety

Myelosuppression, probably attributable to suppression of the Ph+ clone, was the most frequent adverse event (AE) in the phase 1 study in CML or Ph+ ALL, while the most significant AE was grade 3/4 thrombocytopenia (28%) [18]. Severe myelosuppression was reversible and easily managed with a short dose interruption; about 60% of patients required interruption of treatment, and the myelosuppression generally resolved within 3 months, often in association with a cytogenetic response[30]. Twenty-five percent of leukemia patients required a dose reduction. In the phase 1 study in solid tumor patients, hematologic AEs were uncommon: two patients on the 5D2 schedule with grade 1 or 2 anemia developed grade 3 anemia while on study drug, whereas on the CDD schedule one patient developed grade 4 neutropenia and another grade 3 anemia[20].

Non-hematologic AEs from the two phase 1 trials include GI intolerance (primarily diarrhea, nausea, and vomiting), GI hemorrhage, fatigue, dyspnea, anorexia, dehydration, fluid retention, pleural and pericardial effusion, a moderate increase in QTc F (with no QTc F >500 msec), elevated creatinine, depression, and tumor lyses syndrome. In addition to these AEs, dasatinib treatment has the potential to produce skin rashes, other respiratory events, and CNS hemorrhage. While neither immunosuppression nor osteoclast function abnormalities (*e.g.*, osteoporosis) were observed in these short-term studies, SRC kinase inhibitors have the potential to cause these types of events.

As of September 2010 in the overall population of 2840 subjects, a total of 740 (26%) deaths were reported in adult dasatinib-treated subjects with CML or Ph+ ALL. Of these 740 deaths, 296 occurred within 30 days of the last dose of study therapy. Of the 740 deaths, 380 (51%) were due to disease progression and 11 (1.5%) have been positively attributed to study drug toxicity.

2.53 Potential Drug Interactions

Dasatinib is primarily metabolized by CYP3A4 and therefore, potent inhibitors of this enzyme are contraindicated (Investigator's Brochure, 2010). Dasatinib is also a significant inhibitor of this hepatic enzyme but a weak inhibitor of other cytochrome enzymes, and the agent does not induce CYP3A4. Thus, dasatinib may decrease the clearance of drugs that are significantly metabolized by the CYP3A4 enzyme, and caution should be used with concurrent use of such drugs or substances. In a study in cancer patients, concomitant use of a potent CYP3A4 inhibitor (ketoconazole) produced >5-fold increase in exposure to dasatinib, while healthy subjects treated concurrently with dasatinib and a potent CYP3A4 inducer experienced a 5-fold decrease in dasatinib exposure. When the CYP3A4 substrate simvastatin was studied in combination with dasatinib, increased simvastatin exposure resulted, indicating the necessity of caution when dasatinib is administered with CYP3A4 substrates with a narrow therapeutic margin (*e.g.,* cyclosporine).

2.6 Rationale for Examining Dasatinib in Patients based on BAF250 Expression

Based on the above results showing that dasatinib selectively inhibits ARID1A-deficient endometriosis associated clear cell lines at physiologically achievable levels (1-10nM), we expect dasatinib to be active in the histologic patient population under study here—if they have ARID1A mutations. Moreover, we use BAF250 expression as a marker for ARID1A status as noted above.

However, we investigate the efficacy of dasatinib in both patients with and without loss of BAF250 expression in the event that the agent works in an unselected patient population.

2.7 Inclusion of Women and Minorities

The Gynecologic Oncology Group and GOG participating institutions will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire clear cell ovarian, fallopian tube, peritoneal and endometrial cancer population treated by participating institutions.

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Eligible Patients

3.11 Patients must have recurrent or persistent ovarian, fallopian tube, peritoneum, and endometrial clear cell carcinoma. Primary tumors must be at least 50% clear cell histomorphology in order to be eligible or have a histologically documented recurrence with at least 50% clear cell histomorphology. In addition, the tumors should be negative for expression of WT-1 antigen (with the exception of endometrial cancers where WT-1 stains are not required) and Estrogen Receptor (ER) antigen by immunohistochemistry. Focal, weak, ER staining of tumor cells (<5%) is permitted. Appropriate tissue sections must be available for histologic evaluation for central pathology review by GOG. Immunohistochemical stained slides for ER and WT-1 antigen must be available for review by GOG. (XX/XX/XX)

- If the primary tumor had at least 50% clear cell histomorphology, a biopsy of the recurrent or persistent tumor is not required. However, immunohistochemical studies of the primary tumor for ER and WT-1 antigens should be performed and the slides submitted to the GOG for review. The percentage of clear cell histomorphology must be documented in the pathology report or in an addendum to the original report. If slides of the primary tumor are not available for review due to disposal of slides by the histology laboratory (typically 10 years after diagnosis), biopsy of recurrent or persistent disease is required.

- If the primary tumor had less than 50% clear cell histomorphology (or if slides of the primary tumor are not available for review), a biopsy of the recurrent or persistent tumor is required to confirm at least 50% clear cell histomorphology and lack of immuno-reactivity for ER and WT-1 antigens by immunohistochemistry. The percentage of involvement must be documented in the pathology report or in an addendum to the original report.

3.12 Patients must have results from the determination of BAF250a immunohistochemistry (IHC) status (see Section 5.1 and Appendix IV) and must have a BAF250a expression status that is currently open to enrollment. (11/2/15)

3.13 All patients must have measurable disease. Measurable disease is defined by RECIST (version 1.1). Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by CT, MRI or caliper measurement by clinical exam; or ≥ 20 mm when

measured by chest x-ray. Lymph nodes must be > 15 mm in short axis when measured by CT or MRI (See section 8).

3.14 Patients must have had one prior platinum-based chemotherapeutic regimen for management of primary disease. Patients are allowed to receive, but are not required to receive, two additional cytotoxic regimens for management of recurrent or persistent disease.

3.15 Patients must be ≥ 3 weeks from last chemotherapy or radiation (6 weeks for nitrosoureas or mitomycin).

3.16 Patients must have progressed on, be ineligible for, or have declined participation in GOG-0254 provided that protocol is actively accruing patients.

3.17 Patients must have adequate organ function defined as follows:

Bone Marrow:

- Leukocytes ≥3,000/mcL
- Absolute Neutrophil Count ≥1,500/mcL
- Platelets ≥100,000/mcL

Renal:

- Creatinine ≤ 1.5 times the ULN

  OR
- Creatinine Clearance ≥ 60 mL/min/1.73 m^2

Hepatic:

- Bilirubin ≤1.5 ULN
- AST (SGOT) and ALT (SGPT) ≤ 3x ULN

3.18 Patients who are on concomitant medications that are STRONG inducers or inhibitors of the CYP3A4 enzyme should stop 2 weeks prior to first dose of dasatinib, if all other eligibility has been confirmed. An updated list of STRONG CYP3A4 inducers and inhibitors can be found at: http://www.medicine.iupui.edu/clinpharm/ddis/

3.19 QTc interval on electrocardiogram must be ≤ 480 msec (Fridericia correction).

3.110 Patients who have received one prior regimen must have a GOG Performance Status of 0, 1 or 2. Patients who have received two or more prior regimens must have GOG performance status of 0 or 1.

3.111 Patients who have met the pre-entry requirements specified in Section 7.0.

3.112 Patients must have signed an approved informed consent and authorization permitting release of personal health information.

3.2 Ineligible Patients

3.21 Prior treatment with dasatinib, imatinib or nilotinib.

3.22 As dasatinib can cause fluid shifts, patients with symptomatic effusions (pleural, pericardial, or peritoneal) and/or those who have required a procedure for symptomatic effusions within 4 weeks of start of dasatinib are ineligible.

3.23 Patients with a history of cardiac disease including: (1) uncontrolled angina, congestive heart failure, or myocardial infarction within six months prior to study entry, (2) congenital long QT syndrome, (3) clinical significant ventricular arrhythmias.

3.24 The concomitant use of H2 blockers and proton pump inhibitors (PPIs) with dasatinib is not recommended. The use of antacids should be considered in place of H2 blockers or proton pump inhibitors in patients receiving dasatinib therapy. If antacid therapy is needed, the antacid dose should be administered two hours before or after the dose of dasatinib. Patients who cannot tolerate discontinuation of H2 blockers or PPIs are ineligible.

3.25 Therapeutic anticoagulation is not contraindicated, but for those patients on therapeutic anticoagulation, alteration in coagulation parameters is expected following initiation of dasatinib. For patients on therapeutic anticoagulation, coagulation parameters should be assessed weekly for the first cycle following initiation of dasatinib, weekly for the first cycle following a dose reduction, and weekly for a minimum of two weeks after stopping dasatinib.

3.26 Patients whose circumstances do not permit completion of the study or the required follow-up.

3.27 Patients who are pregnant or nursing. The effects of dasatinib on the developing human fetus are unknown. For this reason and because protein thyrosine kinase inhibitors 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 and for 3 months after completion of therapy. 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. A negative serum pregnancy test within 72 hours of starting drug is required.

3.28 Patients under the age of 18.

3.29 Patients who have a major surgical procedure, or significant traumatic injury within 28 days prior to the first date of treatment on this study, or anticipation of need for major surgical procedure during the course of the study; patients with placement of vascular access device or core biopsy within 7 days prior to the first date of treatment on this study**.**

3.210 Patients with other invasive malignancies, with the exception of non melanoma skin cancer, who had (or have) any evidence of other cancer present within the last 5 years or whose previous cancer treatment contraindicates this protocol therapy.

3.211 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with dasatinib. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy.

3.212 Patients who are unable to swallow pills.

4.0 STUDY MODALITIES

4.1 Dasatinib (BMS-354825) NSC# 732517

4.11 **Chemical Name**: *N*-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate

4.12 **Mechanism of Action***:* Dasatinib is a potent, broad spectrum ATP-competitive inhibitor of 5 critical oncogenic tyrosine kinase families: BCR-ABL, SRC family kinases, c-KIT, ephrin (EP) receptor kinases, and PDGFβ receptor. Overexpression or activation of these kinases plays critical roles in the etiology of various cancer types

4.13 **Molecular formula**: $C_{22}H_{26}ClN_7O_2S \cdot H_20$ **MW:** Dasatinib monohydrate: 506.02 daltons

4.14 **Approximate Solubility:** Dasatinib's solubility ranged from 18.42 mg/mL at pH 2.6 to < 0.001 mg/mL at pH 7.

4.15 **How Supplied:** BMS supplies and CTEP, NCI, DCTD distributes dasatinib. Dasatinib is available in the following tablet/bottle sizes:

- 5 mg round, plain white film-coated tablets containing 30 tablets per bottle.
- 20 mg biconvex round, white to off-white film-coated tablets containing 30 tablets per bottle. The tablet is debossed with "20" on one side and "527" on the other side.
- 50 mg biconvex oval, white to off-white film-coated tablets containing 30 tablets per bottle. The tablet is debossed with "50" on one side and "528" on the other side.

Inactive ingredients include lactose, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate. The film-coating contains hypromellulose, titanium dioxide, glycerol triacetate (in the 5 mg), and polyethylene glycol (in the 20 mg tablets and 50 mg tablets).

Note: The 5 mg tablets are restricted to pediatric trials.

4.14 **Storage:** Store the intact bottles at controlled room temperature (15°C-25°C) and protect from light.

4.18 **Stability:** Stability studies are ongoing.

4.19 **Route of Administration:** Oral. Tablets may be taken with or without food. They should be swallowed whole and not crushed or broken.

4.20 **Potential Drug Interactions:** Dasatinib is primarily metabolized by the human CYP3A4 enzyme; therefore, potent CYP3A4 inducers and inhibitors are prohibited on dasatinib trials.

Concomitant use of dasatinib and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate. Therefore, caution is warranted when dasatinib is co-administered with CYP3A4 substrates of narrow therapeutic index.

Systemic antacids (both H_2 receptor antagonists and proton pump inhibitors) are **prohibited** on dasatinib trials. Locally acting antacids can be given up to two hours prior or two hours following dasatinib administration.

Dasatinib may prolong the QT/QTc interval. Use caution when administering dasatinib with other potential QTc-prolonging medications.

Due to the possibility of CNS, gastrointestinal, cardiac, and cutaneous hemorrhage, use caution in patients who require medications that inhibit platelet function or anticoagulants.

4.21 **Special Handling:** Dasatinib tablets consist of a core tablet (containing the active drug) surrounded by a film coating to prevent exposure to the active drug substance. If tablets are accidentally crushed or broken, caregivers should wear disposable chemotherapy gloves. Pregnant women should avoid exposure to crushed and/or broken tablets.

4.22 Reported Adverse Events and Potential Risks: (01/27/16)

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Dasatinib (BMS-354825, Sprycel, NSC 732517)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2937 patients.* Below is the CAEPR for Dasatinib (BMS-354825, Sprycel).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational

agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.6, September 1, 2015[1]

Adverse Events with Possible Relationship to Dasatinib (BMS-354825, Sprycel) (CTCAE 4.0 Term) [n= 2937]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
	Febrile neutropenia		
CARDIAC DISORDERS			
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Pericardial effusion		
GASTROINTESTINAL DISORDERS			
	Abdominal distension		
	Abdominal pain		***Abdominal pain (Gr 2)***
	Anal mucositis		
	Constipation		
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		
	Gastrointestinal hemorrhage[2]		
	Mucositis oral		
Nausea			***Nausea (Gr 3)***
	Rectal mucositis		
	Small intestinal mucositis		
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	General disorders and administration site conditions - Other (generalized edema)		
	General disorders and administration site conditions - Other (superficial edema)		***General disorders and administration site conditions - Other (superficial edema) (Gr 2)***
	Non-cardiac chest pain		
	Pain		
INFECTIONS AND INFESTATIONS			
	Infection[3]		***Infection[3] (Gr 3)***
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
		Electrocardiogram QT corrected interval prolonged	

Adverse Events with Possible Relationship to Dasatinib (BMS-354825, Sprycel) (CTCAE 4.0 Term) [n= 2937]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Neutrophil count decreased			***Neutrophil count decreased (Gr 3)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight gain		
	Weight loss		
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Hypocalcemia		
	Hypokalemia		
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
Myalgia			***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Headache			***Headache (Gr 3)***
		Intracranial hemorrhage	
		Leukoencephalopathy	
		Reversible posterior leukoencephalopathy syndrome	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
Dyspnea			***Dyspnea (Gr 3)***
	Laryngeal mucositis		
	Pharyngeal mucositis		
Pleural effusion			***Pleural effusion (Gr 3)***
	Pneumonitis		
		Pulmonary hypertension	
	Tracheal mucositis		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
		Erythema multiforme	
	Pruritus		
	Rash acneiform		
Rash maculo-papular			***Rash maculo-papular (Gr 2)***
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
VASCULAR DISORDERS			
	Flushing		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[3]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[4]Gastrointestinal ulcer includes Anal ulcer, Colonic ulcer, Duodenal ulcer, Esophageal ulcer, Gastric ulcer, Ileal ulcer, Jejunal ulcer, Rectal ulcer, and Small intestine ulcer under the GASTROINTESTINAL DISORDERS SOC.

Adverse events reported on Dasatinib (BMS-354825, Sprycel) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Dasatinib (BMS-354825, Sprycel) caused the adverse event:

CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Cardiac disorders - Other (cardiomegaly); Cardiac disorders - Other (heart rate increased); Chest pain - cardiac; Myocarditis; Palpitations; Pericarditis; Sinus tachycardia; Ventricular tachycardia
CONGENITAL, FAMILIAL AND GENETIC DISORDERS - Congenital, familial and genetic disorders - Other (Keratosis follicular)
EAR AND LABYRINTH DISORDERS - Ear pain; Middle ear inflammation; Tinnitus; Vertigo
EYE DISORDERS - Blurred vision; Conjunctivitis; Dry eye; Eye disorders - Other (optic nerve neuritis)
GASTROINTESTINAL DISORDERS - Ascites; Colitis; Dry mouth; Dysphagia; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastrointestinal disorders - Other (anal fissure); Gastrointestinal disorders - Other (hematemesis); Gastrointestinal disorders - Other (mouth ulceration); Gastrointestinal disorders - Other (oral soft tissue disorder); Gastrointestinal disorders - Other (oropharyngeal pain); Gastrointestinal disorders - Other (tongue eruption); Gastrointestinal ulcer[4]; Ileus; Oral pain; Pancreatitis; Periodontal disease; Stomach pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Edema trunk; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (temperature intolerance); Localized edema; Malaise
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatobiliary disorders - Other (cholestasis)
IMMUNE SYSTEM DISORDERS - Anaphylaxis
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (herpes virus infection)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Cardiac troponin T increased; CD4 lymphocytes decreased; CPK increased; Creatinine increased; GGT increased; Investigations - Other (bone densitometry); Investigations - Other (EKG T-wave inversion); Investigations - Other (pancytopenia); Investigations - Other (thermometry abnormal); Lymphocyte count decreased; Lymphocyte count increased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Bone pain; Chest wall pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (epiphyses delayed fusion); Musculoskeletal and connective tissue disorder - Other (muscle spasm); Musculoskeletal and connective tissue disorder - Other (muscle stiffness); Musculoskeletal and connective tissue disorder - Other (nuchal rigidity); Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis); Musculoskeletal and connective tissue disorder - Other (tendonitis); Myositis; Osteoporosis; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (hemangiomatosis)
NERVOUS SYSTEM DISORDERS - Acoustic nerve disorder NOS; Amnesia; Cognitive disturbance; Concentration impairment; Dysarthria; Dysgeusia; Ischemia cerebrovascular; Lethargy; Peripheral motor

neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Syncope; Transient ischemic attacks; Tremor
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia; Libido decreased; Suicidal ideation
RENAL AND URINARY DISORDERS - Acute kidney injury; Proteinuria; Urinary frequency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Gynecomastia; Irregular menstruation
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Bronchospasm; Epistaxis; Hypoxia; Pulmonary edema; Sore throat
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Dry skin; Hyperhidrosis; Nail loss; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Periorbital edema; Photosensitivity; Purpura; Skin and subcutaneous tissue disorders - Other (acute febrile neutrophilic dermatosis); Skin and subcutaneous tissue disorders - Other (hair color changes); Skin and subcutaneous tissue disorders - Other (panniculitis); Skin ulceration; Urticaria
VASCULAR DISORDERS - Hematoma; Hot flashes; Hypertension; Hypotension; Phlebitis; Superficial thrombophlebitis; Thromboembolic event; Vasculitis

Note: Dasatinib (BMS-354825, Sprycel) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

4.23 Drug Ordering and Accountability: NCI supplied agents may be requested by the Principal Investigator or their authorized designee at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is being treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD, through an annual submission of FDA Form 1572, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form. If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application < https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx >. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account < https://eapps-ctep.nci.nih.gov/iam/ > and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

The Investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from the PMB using the NCI Drug Accountability Record Form (DARF). See the CTEP web site for Policy and Guidelines for Accountability and Storage of Investigational Drugs at http://ctep.cancer.gov/requisition/

Requests for Investigator's Brochures (IB) should be e-mailed to ibcoordinator@mail.nih.gov or you may call the IB coordinator at 240-276-6570.

4.24 Drug Returns: Only unreconstituted drug supplies should be returned to the PMB. When it is necessary to return study drug, investigators should return the study drug to the PMB using the NCI Return Drug List available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575.

.

5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE

Sites must submit, all IRB approvals (initial and continuing) on NCI sponsored adult Cooperative Group phase I, II & III prevention and treatment studies to the CTSU Regulatory Office, at the Coalition of Cancer Cooperative Groups in Philadelphia. A CTSU IRB/Regulatory Approval Transmittal Sheet should be submitted along with the CTSU IRB Certification Form or its equivalent. (CTSU forms can be downloaded at https://www.ctsu.org/public/rss2_page.aspx). IRB submissions can be faxed or e mailed (preferred methods) or mailed to:

Cancer Trials Support Unit (CTSU)
ATTN: Coalition of Cancer Cooperative Groups (CCCG)
Suite1100
1818 Market Street
Philadelphia, PA 19103
FAX: 1-215-569-0206
CTSURegulatory@ctsu.coccg.org

5.1 Patient Screening and Registration (11/2/15)

When a suitable candidate has been obtained for protocol entry, the following steps should be taken:

Screening

When a suitable candidate has been identified for protocol entry, the following steps should be taken:

- An approved informed consent form and authorization permitting the release of personal health information must be signed by the patient or guardian. Current FDA, NCI and institutional regulations concerning informed consent will be followed.

- All eligibility requirements indicated in Section 3.0 must be satisfied, with the exception of 3.12 (BAF250a expression results).

- Log onto the GOG website, go to the Web Menu page and open the link to Screening to obtain a Screening Patient Identifier.

- Obtain five (minimum four) unstained sections (charged, 4-6µm). Label each individual slide with the Screening Patient Identifier. Slides may also be labeled with the pathology accession and block number, but these identifiers are not required. Do not label slides with any personal identifying information (e.g., patient name, patient initials, date of birth). **See Appendix IV for further details**.

- Complete the GOG-0283 BAF250a Immunohistochemistry Requisition (Appendix V). Ensure the Screening Patient Identifier on the slides matches the Screening Patient Identifier on the requisition.

- Ship the slides along with a de-identified copy of the corresponding pathology report (labelled with the Screening Patient Identifier) to:

  ATTN: Jessica Menzel
  Memorial Sloan-Kettering Cancer Center
  Department of Pathology
  1275 York Ave
  New York, NY 10065
  Phone: 212-639-7297
  Fax: 646-422-2070
  Email: menzelj@mskcc.org

- Receive the results of the central pathology review on the Screening web application.

- If the patient's BAF250a expression status is one to which the trial is open, proceed to patient registration in GOG-0283.

Registration

5.11 The eligibility check list data must be gathered.

5.12 All site staff will use OPEN to enroll patients to this study. OPEN can be accessed at on the GOG web menu page and clicking on the OPEN link.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the GOG or CTSU roster.

- To perform registrations you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

5.13 The institution must enter the patient's name, and GOG patient study ID, in the appropriate place in their Log Book to verify the patient's entry.

NOTE: If this protocol switches to selective enrollment (see Section 11) of only patients with loss of BAF250a expression, the protocol accrual will briefly halt and the protocol will undergo an amendment to reflect new screening and registration procedures. (11/2/15)

5.2 Treatment Plan

5.21 Treatment will be administered on an outpatient basis. Patients will receive dasatinib 140mg by mouth, once daily, on days 1-28. One cycle is 4 weeks long (28 days). Dasatinib tablets may be taken with or without food as desired, but should be swallowed with at least 8 ounces (240 mL) of water. A light meal is not required, but may improve gastric tolerance for dasatinib. Tablets must be swallowed whole and may not be broken. If vomiting occurs within 30 minutes of swallowing the tablet(s), the dose may be replaced if the tablets can be seen and counted. Four weeks (28 days) constitutes one cycle of treatment.

Patients will be provided with a Medication Diary for dasatinib (Appendix III), instructed in its use, and asked to bring the diary along with all pill bottles with them to each appointment.

Treatment interruptions of up to one cycle (4 weeks) are permitted for resolution of treatment-related toxicities. Failure of resolution of treatment-related toxicity within 4 weeks will require discontinuation of study treatment.

Laboratory parameters for cycle 1 day 1 are detailed in the Eligibility Criteria, Section 3.17.

Laboratory parameters for all subsequent visits are as follows:

-Absolute neutrophil count ≥1,000/mcL

-Platelets ≥75,000/mcL

-Creatinine ≤ 1.5 times the ULN -OR- creatinine clearance (calculated or measured) ≥ 60 mL/min/1.73 m^2

-Bilirubin ≤1.5 ULN

-AST (SGOT)/ ALT (SGPT) ≤ 3x ULN

Dose modification for toxicity will be made as specified in Section 6.0.

See the NRG Oncology General Therapy Guidelines for appropriate treatment windows (Appendix II).

Treatment may continue until patient demonstrates objective progression of disease or experiences unacceptable treatment-related toxicity (attributed as possibly related or greater). (11/2/15)

5.3 Criteria for removal from treatment

5.31 Inability to tolerate toxicity.

5.32 Patients may withdraw from the study at any time for any reason. Patients with evidence of disease progression or significant side effects will be removed from study.

5.33 Patients with substantial non-compliance with study protocols which, in the opinion of the investigator, compromises the patient's participation in the protocol.

5.34 The reason for removal from treatment must be documented in the case report form.

6.0 TREATMENT MODIFICATIONS

6.1 Dose Modifications

Patients requiring dose modification of dasatinib will be managed as follows. Patients that require more than a two dose level reduction due to drug related adverse events will be removed from study.

Dose Level	Dasatinib Dose
Starting Dose	140 mg once daily (Two 50mg tablets, Two 20mg tablets)
-1	100 mg once daily (Two 50mg tablets)
-2	70 mg once daily (One 50mg tablet, One 20mg tablet)

6.2 Selected Agent-Related Hematologic and Non-Hematologic Adverse Events

Event	AE Grade or Observation	Dose modification
Neutropenia	Grade 1 or 2	Maintain dose
	Grade 3 or 4 [1]	Hold dasatinib until ≤ grade 2, then reduce 1 dose level and resume treatment
Thrombocytopenia	Grade 1 or 2	Maintain dose
	Grade 3 or 4 [1]	Hold dasatinib until ≤ grade 2, then reduce 1 dose level and resume treatment
Hemorrhage/Bleeding/ Coagulopathy (without thrombocytopenia)	Grade 1	No interruption in treatment; maintain current dose. Monitor as clinically indicated
	Grade 2	Hold dasatinib until AE resolved to ≤ grade 1. Discontinue treatment and withdraw subject from study.[3] Follow up per protocol (see Section 5.3)
	Grade 3 or 4	Discontinue treatment and withdraw subject from study. Follow up per protocol (see Section 5.3).
Hemorrhage/Bleeding/Coagulopathy (with thrombocytopenia[2])	Grade 1	Hold dasatinib until thrombocytopenia resolved to ≤ Grade 1, then reduce 1 dose level and resume treatment. Monitor as clinically indicated.
	Grade 2	Hold dasatinib until AE resolved to ≤ grade 1 and thrombocytopenia resolved to ≤ Grade 1. Discontinue treatment and withdraw subject from study.[3] Follow up per protocol (see Section 5.3)
	Grade 3 or 4	Discontinue treatment and withdraw subject from study. Follow up per protocol (see Section 5.3)
QTc Prolongation	Grade 1 or 2	Maintain dose.
	Grade 3 (> 500 ms)	Hold dasatinib. Correct electrolyte abnormalities and discontinue any contributory concomitant medications. When AE resolved to ≤ Grade 2,

		then resume treatment. First recurrence: Management as above, then reduce 1 dose level and resume treatment. Second recurrence: Stop dasatinib and remove patient from study. Follow up per protocol (see Section 5.3)
	Grade 4 (>500 ms AND Torsade de pointes OR Ventricular arrhythmia)	Discontinue treatment and withdraw subject from study. Follow up per protocol (see Section 5.3).
Pleural Effusion, Pericardial Effusion, or Ascites	Grade 1	Continue dasatinib.
	Grade 2 or 3	Hold dasatinib until AE resolved to ≤ grade 1 and institute support measures (drainage and/or diuretics as clinically indicated). Reduce dasatinib by 1 dose level. Recurrent grade 3 events require study removal.
	Grade 4	Discontinue treatment and withdraw subject from study. Follow up per protocol (see Section 5.3).

1 These recurrent grade 3 events require a 2nd dose reduction; recurrent grade 4 events require study removal.
2. Dose modification instructions for thrombocytopenia must also be followed.
3. Under very limited circumstances, it may be appropriate to resume treatment following a Grade 2 hemorrhage/bleeding/coagulopathy AE. These includes circumstances where the intervention required to address bleeding was minimal such as holding pressure on a superficial bleeding wound or nasal packing. Investigators much first seek permission from the Study Chair prior to resuming treatment following Grade 2 hemorrhage/bleeding/coagulopathy. Under these circumstances, dasatinib will be reduced by 1 dose level. If grade 2 hemorrhage/bleeding/coagulopathy resumes following dose reduction, stop dasatinib and remove patient from study.

6.3 General Management Guidelines for Agent-Related Non-Hematologic Toxicity

Severity	Management	
Grade 2	1st event:	Institute supportive therapy. May hold dasatinib, or continue without dose reduction, or reduce by one dose level
	2nd event:	Hold dasatinib and maximize supportive therapy. Decrease dose by one dose level
	3rd event:	Hold dasatinib. May discontinue if AE poorly controlled.
Grade 3	1st event:	Hold dasatinib. Institute supportive therapy. Restart dasatinib with reduction by one dose level allowed.
	2nd event:	Hold dasatinib. Maximize supportive therapy. Dasatinib may be restarted or discontinued if dose already reduced.
Grade 4	1st event:	Hold dasatinib. Maximize supportive therapy. Dasatinib may be restarted with dose reduction by one dose level or discontinued.

In general, dose will not be re-escalated after a dose reduction. If, however, the investigator feels the patient would benefit from re-escalation and this could be

accomplished safely, it will be permissible with the explicit permission of the Study Chair or Co-Study Chair.

7.0 STUDY PARAMETERS

7.1 Observations and Tests (11/2/15)

The following observations and tests are to be performed and recorded on the appropriate form(s):

PARAMETER	Pre-Therapy	Prior to Each Treatment Cycle	After Cycle 2, then every other cycle	Follow up[7] Every 3 months x 2 years; then every 6 months x 3 years
History & Physical	1	X		X
Performance Status	1	X		X
Height	1			
Weight	1	6		X
Vital Signs (blood pressure, heart rate and temperature)	1	X		X
Toxicity Assessment	1	X		X
CBC, differential, hemoglobin, platelets, Electrolytes, BUN, Creatinine, Ca, Mg, PO4, Bilirubin, AST/SGOT, ALT/SGPT, Alkaline Phosphatase	2	6		X
PT, INR	2, 5	5		
Pregnancy test	3			
CA125	2	X		X
Chest Imaging (CT of Chest)	1		9	9†
Radiographic disease assessment	1		4	4†
Electrocardiogram	1	8		
Patient diary documenting dasatinib dosing		X		
Central Confirmation of BAF250a IHC Expression Loss (Section 5.1 and Appendix V)	X			

† Until disease progression or death or until patient is put on non-protocol cancer therapy

1. Must be obtained within 28 days prior to initiating protocol therapy.

2. Must be obtained within 14 days prior to initiating protocol therapy.
3. If in the investigator's opinion the patient is of child-bearing potential. Must be obtained within 72 hours prior to initiating protocol therapy.
4. CT scan or MRI if used to follow lesion for measurable disease every other cycle for the first 6 months; then every 3 months x 2; then every 6 months thereafter until disease progression; and at any other time if clinically indicated based on symptoms or physical signs suggestive of progressive disease or rising serum tumor marker levels. Note that radiology must be done to confirm response per Section 8.135 for CR and PR cases.
5. PT/INR for patients on therapeutic anticoagulation. INR should be between 2 and 3 on a stable dose of warfarin (or other anticoagulant) or on stable dose of heparin prior to restarting treatment. Coagulation parameters should be assessed weekly for the first cycle following initiation of drug.
6. Must be obtained within 4 days before treatment or re-treatment with protocol therapy. CBC/Differential/Platelets, creatinine and LFTs (bilirubin, AST, ALT) and phosphate must be result prior to initiating treatment with dasatinib at the start of each cycle.
7. Performed at time patient officially goes off-treatment due to disease progression or toxicity.
8. Should be performed on Cycle 2, Day 1. If QTc interval is ≤ 480 msec, ECGs are not required to be repeated in subsequent cycles except as clinically indicated. If the QTc interval is >480 msec, follow guidelines in Section 6.0.
9. Repeat chest imaging is required regardless of whether patient had chest involvement by tumor at baseline. Performed on same schedule as radiographic disease assessment.

7.2 CENTRAL PATHOLOGY REVIEW

Pathology slides are required for central review by the GOG Pathology Committee. Central pathology review by a panel of three pathologists will take place after registration and initiation of treatment. At least one representative stained slide (or slides) documenting the primary tumor must be submitted (unless slides have been disposed of by the pathology laboratory). In addition, representative immunohistochemical studies of ER and WT-1 must be submitted to document lack of immuno-reactivity (unless slides/blocks have been disposed of by the pathology laboratory). If the primary tumor had less than 50% clear cell histomorphology (or if slides of the primary tumor are not available for review), at least one representative stained histology slide to document recurrent or persistent disease must be submitted along with the negative immunohistochemical slides for ER and WT-1 performed on the recurrent/persistent biopsy specimen. A biopsy of the recurrent or persistent tumor is required to confirm at least 50% clear cell histomorphology. The percentage of involvement must be documented in the pathology report or in an addendum to the original report. When submitting pathology material to the GOG SDC, individual slides must be labeled with GOG Patient ID, patient initials, accession number and cut (i.e. A1, 2b, 34 etc.), and packed in plastic slide cassettes. Tape plastic slide cassettes shut and wrap in bubble wrap or another type of padded material prior to shipping. Please include the GOG Patient ID, patient initials, and protocol number on all pages of the pathology report and black out the patient's name. Ship pathology slides and two copies of the official pathology report directly to:

Pathology Materials Coordinator
GOG Statistical and Data Center

Roswell Park Cancer Institute
Research Studies Center
Elm and Carlton Streets
Buffalo, New York 14263
Phone: (716) 845-570

7.3 Translational Research

7.31 Specimen Requirements (11/2/15)

If the patient gives permission for her specimens to be collected and used for this optional translational research component, then participating institutions are required to submit the patient's specimens as outlined below (unless otherwise specified).

A detailed description of the translational research specimen requirements and procedures can be found in Appendix VI.

Required Specimen (Specimen Code)	**Collection Time Point**	**Ship To**
FFPE Primary Tumor (FP01)* 1st Choice: block 2nd Choice: 25 unstained slides (10 charged, 5µm & 15 uncharged, 10µm)	Prior to any treatment *Preferred FFPE*	GOG Tissue Bank within **1 week** of registration[1]
FFPE Metastatic Tumor (FM01)* 1st Choice: block 2nd Choice: 25 unstained slides (10 charged, 5µm & 15 uncharged, 10µm)	Prior to any treatment *Optional if FP01, FRP01, FRM01, FPP01, or FPM01 is submitted*	
FFPE **Recurrent Primary** Tumor (**FRP01**)* 1st Choice: block 2nd Choice: 25 unstained slides (10 charged, 5µm & 15 uncharged, 10µm)	Prior to study treatment *Optional if FP01, FM01, FRM01, FPP01, or FPM01 is submitted*	
FFPE **Recurrent Metastatic** Tumor (**FRM01**)* 1st Choice: block 2nd Choice: 25 unstained slides (10 charged, 5µm & 15 uncharged, 10µm)	Prior to study treatment *Optional if FP01, FM01, FRP01, FPP01 , or FPM01 is submitted*	
FFPE Persistent Primary Tumor (FPP01)* 1st Choice: block 2nd Choice: 25 unstained slides (10 charged, 5µm & 15 uncharged, 10µm)	Prior to study treatment *Optional if FP01, FM01, FRP01, FRM01, or FPM01is submitted*	
FFPE Persistent Metastatic Tumor (FPM01)* 1st Choice: block 2nd Choice: 25 unstained slides (10 charged, 5µm & 15 uncharged, 10µm)	Prior to study treatment *Optional if FP01, FM01, FRP01, FRM01, or FPP01 is submitted*	
Whole Blood (WB01) 7-10mL drawn into purple top (EDTA) tube(s)	Prior to or after starting study treatment	GOG Tissue Bank the day the specimen is collected[1]

* A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the GOG tissue Bank

1 GOG Tissue Bank / Protocol GOG-0283, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, email: GOGBank@nationwidechildrens.org

7.32 Laboratory Testing

7.321 ARID1A Mutation Analysis

FFPE and DNA isolated from whole blood will be used for next generation sequencing with a focus on ARID1A mutation status, clear cell ovarian and endometrial cancer "hotspots" (e.g., PIK3CA, KRAS, CTNNB1, PPP2R1A0), and targets of dasatinib (e.g., CSF-1R, SRC, FMS, EPHA1, PDGFβ). Because these tests will be done in a research laboratory, the results will not be returned to patients.

7.33 Future Research

Details regarding the banking and use of specimens for future research can be found in Appendix VI.

8.0 EVALUATION CRITERIA

8.1 Antitumor Effect – Solid Tumors

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) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

8.11 *Definitions*

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

Evaluable for objective response. Only those patients 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 patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable 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.

8.12 *Disease Parameters*

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy. Thus, a confirmed biopsy in an irradiated area at a date longer than 90 days post-completion of radiation can be considered a target lesion to assess progression and response.

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

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

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

8.13 *Methods for Evaluation of Measurable Disease*

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

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans), but NOT lung.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if

possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. PET-CT scans are not always done with oral and IV contrast. In addition, the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed. For these reasons, the GOG will not allow PET-CT use for RECIST 1.1 response criteria.

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.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

CA125 (Ovarian, fallopian tube and primary peritoneal cancer trials): CA125 alone cannot be used to assess response. If CA125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response. Specific guidelines for CA-125 response (in recurrent ovarian cancer) have been published [*JNCI* 96:487-488, 2004]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

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

8.14 Response Criteria

8.141 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.

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. (Note: the appearance of one or more new lesions is also considered progressions).

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.

8.142 Evaluation of Non-Target Lesions

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 short axis).

Note: If CA125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of CA125 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.

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

8.143 Progression Based on Serum CA-125

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

OR

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

OR

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

When disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pretreatment evaluation should be obtained within 2 weeks that such progression is documented. The patient should continue therapy, as per protocol, until progressive disease is documented by imaging.

8.144 Evaluation of Best Overall Response

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

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	

PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

8.15 Duration of Response

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.

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.

8.16 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

8.17 Survival

Survival is defined as the duration of time from start of treatment to time of death or the date of last contact.

9.0 DURATION OF STUDY

9.1 Patients will continue on study until disease progression or adverse effects prohibit further treatment. The patient can refuse the study treatment at any time.

9.2 All patients will be treated (with completion of all required case report forms) until disease progression or study withdrawal. Patients will then be followed (with physical exams and histories) every three months for the first two years and then every six months for the next three years. Patients will be monitored for delayed toxicity and survival for this 5-year period with follow-up forms submitted via Medidata Rave unless consent is withdrawn.

9.3 A patient is considered off study therapy when the patient has progressed or died, a subsequent drug or therapy (directed at the disease) is initiated or all study therapy is discontinued. Report all treatment received on Cycle Drug Information Forms and adverse events on Toxicity forms until the patient qualifies as being off study therapy

10.0 STUDY MONITORING AND REPORTING PROCEDURES

10.1 ADVERSE EVENT REPORTING FOR AN INVESTIGATIONAL AGENT

10.11 Definition of Adverse Events (AE)

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that occurs in a patient administered a medical treatment, whether the event is considered related or unrelated to the medical treatment.

CTCAE term (AE description) and grade: The descriptions and grading scales found in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

The CTCAE Manual is also available on the GOG member web site (http://www.gog.org under MANUALS).

10.12 Reporting Expedited Adverse Events

Depending on the phase of the study, use of investigational agents, and role of the pharmaceutical sponsor, an expedited AE report may need to reach multiple destinations. For patients participating on a GOG trial, all expedited AE reports should be submitted by using the CTEP automated system for expedited reporting (AdEERS). All AdEERS submissions are reviewed by GOG before final submission to CTEP. Submitting a report through AdEERS serves as notification to GOG, and satisfies the GOG requirements for expedited AE reporting. All adverse reactions will be immediately directed to the Study Chair for further action.

The requirement for timely reporting of AEs to the study sponsor is specified in the Statement of Investigator, Form FDA-1572. In signing the FDA-1572, the investigator assumes the responsibility for reporting AEs to the NCI. In compliance with FDA regulations, as contained in 21 CFR 312.64, AEs should be reported by the investigator.

10.13 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 3 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 3 calendar days of the initial 24-hour report.
  - "7 calendar days" - A complete AdEERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.

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

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP-IND:

- Grades 2-4 myelosuppression (including neutropenia, anemia, and thrombocytopenia) that do not require hospitalization are exempt from expedited reporting

10.14 Procedures for Expedited Adverse Event Reporting

10.141 AdEERS Expedited Reports: Expedited reports are to be submitted using AdEERS available at http://ctep.cancer.gov. The CTEP, NCI Guidelines: Adverse Event Reporting Requirements for expedited adverse event reporting requirements are also available at this site.

AML/MDS events must be reported via AdEERS (in addition to your routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment related secondary malignancy.

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP website and will NO LONGER be accepted.

For the purposes of expedited reporting of adverse events to CTEP, unexpected events are those not listed in the Agent Specific Adverse Event List (ASAEL). The ASAEL is a subset of AEs within the Comprehensive Adverse Event and Potential Risks List (CAEPR). This list of events is based on CTEP's clinical

experience with this agent and defines "expected" Grade 2 and 3 AEs not requiring hospitalization as exempt from expedited reporting. The CAEPR is a complete list of reported and/or potential AEs associated with an agent under a CTEP IND. For questions or comments regarding the ASAEL or CAEPR, please contact the AdEERS MD Help Desk at adeersmd@tech-res.com.

10.15 Routine Adverse Event Reporting

For studies using investigational agents, the GOG Statistical and Data Center (SDC) routinely reports adverse events electronically to the CTEP Clinical Data Update System (CDUS Version 3.0). The SDC submits this data quarterly. The AEs reported through AdEERS will also be included with the quarterly CDUS data submissions.

10.2 GOG DATA MANAGEMENT FORMS

The following forms must be completed for all patients registered and submitted according to the schedule below. Protocol forms with the exception F forms and Pathology Reports must be submitted via the Medidata Rave Electronic Data Entry System which is available through the GOG Web Menu page (www.gogstats.org). All amendments to forms submitted through Medidata Rave must also be submitted through Medidata Rave. **Note: Pathology material (path report and slides) may be submitted together via postal mail. Pathology report can also be submitted by using the upload feature of SEDES (stained slides must be submitted via postal mail).**

Form[±]	**Due within**		**Copies***	**Comments**
	Weeks	**Event**		
Specimen Consent Application	1	Registration	N/A	Online
Registration Form	2	Registration	N/A	Mandatory Submission via Medidata Rave
Visit Information – Baseline Form Pre-Study History: - History Information Form - Primary Surgery Form♦ - Chemotherapy Information Form♦	2	Registration	N/A	Mandatory submission via Medidata Rave
Pre-Treatment Summary Form	4	Registration	N/A	Mandatory submission via Medidata Rave

Solid Tumor Evaluation: - Target Lesions Form♦ - Non-Target Lesions Form♦	2	Registration	N/A	Mandatory Submission via Medidata Rave
Primary disease: Pathology Report Stained Slides Recurrent or Persistent Disease: Pathology Report Stained Slides	6 6 6 6	Registration Registration Registration Registration	2 ** 2 **	Submit together to SDC via postal mail Submit together to SDC via postal mail
Visit Information Form - Cycle Patient Information Form - Cycle Drug Information Form - Labs and Chemistries Form - Vital signs Assessment Form	2	Completion of each cycle of therapy	N/A	Mandatory submission via Medidata Rave
Solid Tumor Evaluation: - Target Lesions Form♦ - Non-Target Form♦ - New Target Lesions Form♦ - Status and Response Form♦	2	Clinical response assessment	N/A	Mandatory submission via Medidata Rave
Toxicity Report - Section 1 Form - NADIRS Form - Adverse Event Form - Adverse Event Grades	2	Beginning of each subsequent cycle	N/A	Mandatory submission via Medidata Rave
Treatment Completion Form	2	Completion of study Rx and change in Rx	N/A	Mandatory submission via Medidata Rave
Visit Information Follow-Up Form - Follow-Up Form Follow-Up Period Adverse Event: - Reporting Form – Part 1♦ - Reporting Form – Part 2♦	2	Disease progression; death; normal follow-up	N/A	Mandatory submission via Medidata Rave quarterly for 2 years, semi-annually for 3 more years
Form TR-FP01- 0283*** FFPE primary tumor	1	Registration	N/A	Mandatory submission via Medidata Rave

Form TR-FM01- 0283*** FFPE metastatic tumor (optional)	1	Registration	N/A	Mandatory submission via Medidata Rave
Form TR-**FRP01**- 0283*** FFPE **recurrent primary** tumor (optional)	1	Registration	N/A	Mandatory submission via Medidata Rave
Form TR-**FRM01**- 0283*** FFPE **recurrent metastatic** tumor (optional)	1	Registration	N/A	Mandatory submission via Medidata Rave
Form TR-FPP01-0283*** FFPE persistent primary tumor (optional)	1	Registration	N/A	Mandatory submission via Medidata Rave
Form TR-FPM01-0283*** FFPE persistent metastatic tumor (optional)	1	Registration	N/A	Mandatory submission via Medidata Rave
Form TR-WB01- 0283 whole blood	1	Registration	N/A	Mandatory submission via Medidata Rave

* The number of required copies including the original form which must be sent to the Statistical and Data Center.

** At least one representative stained slide (or slides) documenting the primary. For recurrent or persistent disease submit Pathology Report, and slides only if histologically documented (See Section 7.2 for additional requirements). If the primary tumor had less than 50% clear cell histomorphology, a biopsy of the recurrent or persistent tumor is required to confirm at least 50% clear cell histomorphology. The percentage of involvement must be documented in the pathology report or in an addendum to the original report.

*** A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the GOG Tissue Bank

♦Appropriate forms will be loaded based on answers reported on corresponding Visit Information Forms.

This study will be monitored by the **Complete** Clinical Data System (CDUS) Version 3.0 CDUS data will be submitted quarterly to CTEP by electronic means.

11.0 STATISTICAL CONSIDERATIONS

The primary objective of this study is to assess the efficacy of dasatinib in patients with recurrent or persistent ovarian, fallopian tube, primary peritoneal, or endometrial clear cell carcinoma. The trial will examine the effect in patients with and without loss of BAF250a expression.

11.1 Design Summary:

This is a two-group, single arm, Phase II clinical trial that will examine the efficacy of the study regimen in patients with and without loss of BAF250a expression. No randomization is involved. All patients will be registered via OPEN. Prior to registration, eligibility will be reviewed via Eligibility check list verification. All reports will include a complete accounting of all patients registered to this protocol.

11.2 Principal Parameters:

11.21 Efficacy Endpoints

11.211 Primary: The proportion of patients with objective tumor response rate (complete [CR] or partial [PR]).

11.212 Secondary: Duration of progression-free survival and overall survival

11.24 Adverse effects: frequency and severity of adverse effects as assessed by CTCAE version 4.

11.26 Translational Research Endpoints: ARID1A mutation status using next-generation exon-capture sequencing performed in FFPE.

11.3 Accrual:

GOG 0254 is an ongoing study of clear cell ovarian patients (with no restriction on BAF250a expression) and has accrued approximately 1 patient per month. This planned study includes both ovarian and endometrial cancer patients, so we expect about twice as many patients available for screening, and we expect approximately 40% of patients will have loss of BAF250a expression. Therefore, we project accrual to be approximately 2 patients per month when enrolling both patients with and without loss of BAF250a expression, and approximately 0.5 patients per month when enrolling only patients with loss of BAF250a expression

Each stage of accrual is expected to take approximately 24 months.

11.4 Primary Hypothesis, Sample Size, and Design

The primary hypothesis of this study tests the proportion of patients with objective tumor response. There are no historical data available on what the response rate is in this patient population, so we will test whether the response rate is indicative of treatment activity for the agent in this patient population. We will test the null hypothesis (H_0) that the objective response rate is 10% or less against the alternative (H_1) that it is greater than 10% assuming the true response rate for the agent is 30%.

The guiding principle in selecting the design for this study is to limit the number of patients treated with clinically ineffective therapies but to estimate efficacy with reasonable precision for those agents that are clinically active.

Within each BAF250a group, the optimal, flexible design of Chen and Ng will be used. The first stage of this study will target an accrual of 15 eligible patients, but in practice will permit accrual to range from 11 to 18 patients for logistical reasons due to managing a multicenter study. If more than 1 out of 11-17 or 2 out of 18 patients experience a response (complete or partial) and clinical judgment indicates, accrual to the second stage of the trial will be initiated. Otherwise, the study will be stopped and the treatment regimen will be considered unworthy of further evaluation in this patient population. If the study advances to the second stage then an overall study accrual of 28 patients will be targeted, but the actual accrual will be permitted to range from 24 to 31 patients. If more than 3 out of 24, or 4 out of 25-28, or 5 out of 29-31 patients experience a response (complete or partial) then the regimen will be considered worthy of additional investigation in a subsequent study. If the true response rate is 10% (H_0), these decision rules limit the average probability of wrongly designating the treatment as active to 10% (type I error), and the average probability of stopping after completing the first stage of accrual is 61%. On the other hand, if the true response rate is 30% (H_1) then the average probability of correctly classifying the treatment as active is 90%. The probability of type I error and the statistical power in this design are average probabilities and were computed from the individual probabilities averaged over all permitted accrual combinations and assuming each combination is equally likely.

We target alpha and beta errors of 0.10 within each patient group without adjustment for multiplicity due to the rare nature of this disease in order to maintain reasonable sample sizes.

Due to the expected activity in the patients with loss of BAF250a expression, if the first stage results indicate a second stage in patients without loss but do not indicate a second stage in patients with loss, both groups will be enrolled in Stage 2.

The following table summarizes the accrual and decision guidelines for this study:

Stage of Accrual	Targeted Cumulative Accrual	Limits of Actual Accrual	Reject H_1 (Reject Drug) if Response Rate $\leq R_i/N_i$
1	15	11-18	1/(11-17), 2/18
2	28	24-31	3/24, 4/(25-28), 5/(29-31)
R_i: cumulative number of responses in stage i, i=1, 2. N_i: cumulative number of subjects in stage i, i=1, 2.			

11.5 *Evaluability for efficacy and toxicity*

Only those patients who are deemed "ineligible" or who receive no therapy will be eliminated from the analysis. All patients who receive any therapy will be evaluated for both treatment efficacy and toxicity. While on occasion, circumstances may prevent the determination of treatment efficacy, such patients will be included in the analysis and labeled as "unknown". This category will be listed and be reflected in the calculation of the response rate.

11.6 *Data Safety and Monitoring*

Data sheets from studies on this protocol will be reviewed before each semi-annual meeting and will also be reviewed by the Study Chairperson in conjunction with the Statistical and Data Center. In some instances, because of unexpectedly severe toxicity, the Statistical and Data Center may elect, after consultation with the Study Chairperson and the Medical Oncology Committee, to recommend early closure of a study.

The frequency and severity of all toxicities are tabulated from submitted case report forms and summarized for review by the study chairperson, Developmental Therapeutics Committee, and GOG Data Safety and Monitoring Board (DSMB) in conjunction with each semi-annual GOG meeting. For studies sponsored by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI), standardized toxicity reports are also submitted to the drug and disease monitors at the Investigational Drug Branch (IDB) and Clinical Investigation Branch (CIB). The initial overall review of toxicity is usually performed after completion of the first stage of accrual, at which point accrual is generally suspended pending formal analysis of response and toxicity.

All serious and/or unexpected events are communicated to the Study Chair, sponsor, and regulatory agencies as mandated in the protocol. These reports are reviewed by the Study Chair (or designated co-chair) within two working days for consideration of investigator notification, amendment, or immediate study suspension. All participating institutions will then receive notification of the toxicities and reason for study suspension. Under these circumstances, accrual cannot be re-activated until the study is reviewed by the GOG Data and Safety Monitoring Board. However, patients currently receiving treatment may continue

to receive treatment in accordance protocol guidelines at the discretion of their physicians, unless directed otherwise.

11.7 *Secondary Endpoints and Exploratory Analyses*
Overall survival and progression-free survival will be characterized with Kaplan-Meier plots and estimates of the median time until death or progression.

The frequency of ARID1A mutation status using next-generation exon-capture sequencing performed in FFPE will be tabulated to determine the correlation between BAF250a IHC and ARID1A mutations (NB: technology in translational research is rapidly progressing and subject to change.)

11.8 Anticipated Gender and Minority Inclusion:
This study restricts entry to women by nature of the site of disease. The table below lists the projected numbers of patients by racial/ethnic subgroup in a total of 81 patients (the maximum potential, planned sample size). There is no data that support differences in the intervention effect between racial/ethnic subgroups. Therefore, the study design does not involve race.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	5	+	0	=	5
Not Hispanic or Latino	57	+	0	=	57
Ethnic Category: Total of all subjects	62	+	0	=	62
Racial Category					
American Indian or Alaskan Native	1	+	0	=	1
Asian	1	+	0	=	1
Black or African American	2	+	0	=	2
Native Hawaiian or other Pacific Islander	1	+	0	=	1
White	57	+	0	=	57
Racial Category: Total of all subjects	62	+	0	=	62

12.0 BIBLIOGRAPHY

1. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin* 2011; **61**(4): 212-36.

2. Mackay HJ, Brady MF, Oza AM, et al. Prognostic relevance of uncommon ovarian histology in women with stage III/IV epithelial ovarian cancer. *Int J Gynecol Cancer* 2010; **20**(6): 945-52.

3. Winter WE, 3rd, Maxwell GL, Tian C, et al. Prognostic factors for stage III epithelial ovarian cancer: a Gynecologic Oncology Group Study. *J Clin Oncol* 2007; **25**(24): 3621-7.

4. Sugiyama T, Kamura T, Kigawa J, et al. Clinical characteristics of clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy. *Cancer* 2000; **88**(11): 2584-9.

5. Vaughan S, Coward JI, Bast RC, Jr., et al. Rethinking ovarian cancer: recommendations for improving outcomes. *Nat Rev Cancer* 2011; **11**(10): 719-25.

6. Ness RB. Endometriosis and ovarian cancer: thoughts on shared pathophysiology. *Am J Obstet Gynecol* 2003; **189**(1): 280-94.

7. Vigano P, Somigliana E, Chiodo I, Abbiati A, Vercellini P. Molecular mechanisms and biological plausibility underlying the malignant transformation of endometriosis: a critical analysis. *Human reproduction update* 2006; **12**(1): 77-89.

8. Wiegand KC, Shah SP, Al-Agha OM, et al. ARID1A mutations in endometriosis-associated ovarian carcinomas. *N Engl J Med* 2010; **363**(16): 1532-43.

9. Guan B, Wang TL, Shih Ie M. ARID1A, a factor that promotes formation of SWI/SNF-mediated chromatin remodeling, is a tumor suppressor in gynecologic cancers. *Cancer Res* 2011; **71**(21): 6718-27.

10. Yamamoto S, Tsuda H, Takano M, Tamai S, Matsubara O. Loss of ARID1A protein expression occurs as an early event in ovarian clear-cell carcinoma development and frequently coexists with PIK3CA mutations. *Mod Pathol* 2012; **25**(4): 615-24.

11. Katagiri A, Nakayama K, Rahman MT, et al. Loss of ARID1A expression is related to shorter progression-free survival and chemoresistance in ovarian clear cell carcinoma. *Mod Pathol* 2012; **25**(2): 282-8.

12. Miller R, Brough R, Bajrami I, Kaye SB, Lord CJ, Ashworth A. Functional profiling of clear cell ovarian cancer. *ASCO Meeting Abstracts* 2012; **30**(15_suppl): 5035.

13. Kluger HM, Dolled-Filhart M, Rodov S, Kacinski BM, Camp RL, Rimm DL. Macrophage colony-stimulating factor-1 receptor expression is associated with poor outcome in breast cancer by large cohort tissue microarray analysis. *Clin Cancer Res* 2004; **10**(1 Pt 1): 173-7.

14. Mashkani B, Griffith R, Ashman LK. Colony stimulating factor-1 receptor as a target for small molecule inhibitors. *Bioorganic & medicinal chemistry* 2010; **18**(5): 1789-97.

15. Wagle N, Berger MF, Davis MJ, et al. High-throughput detection of actionable genomic alterations in clinical tumor samples by targeted, massively parallel sequencing. *Cancer discovery* 2012; **2**(1): 82-93.

16. Chen TT and NG T. Optimal flexible designs in phase II clinical trials. *Statistics in Medicine* 1998;**17**:2301-12

17. Hunter, T. (1997). Oncoprotein networks. *Cell*. 88:333-346.

18. Investigator's Brochure. (2010). Dasatinib. BMS-354825. Bristol-Myers Squibb. Version No: 10. Version Date: November 2010.

19. Lombardo, L.J., F.Y. Lee, P. Chen, *et al*. (2004). Discovery of N-(2-chloro-6-methyl-phenyl)-2-(6-(4-(2-hydroxyethyl)-piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide (BMS-354825), a dual Src/Abl kinase inhibitor with potent antitumor activity in preclinical assays. *J Med Chem*. 47:6658-6661.

20. Demetri, G.D., P. Lo Russo, I.R.J. MacPherson, *et al.* (2009) Phase I dose-escalation and pharmacokinetic study of dasatinib in patients with advanced solid tumors. *Clin Cancer Res.* 15: 6232-6240.

21. Li S., Y. Hu, S.J. Swerdlow, *et al.* (2004). Simultaneous targeting of SRC and BCR-ABL kinases by BMS-354825 cures Ph+ acute lymphoblastic leukemia in mice. *Blood*. 104: Abstr. 1976.

22. Schittenhelm, M., S. Shiraga, F.Y. Lee, and M.C. Heinrich. (2006). Dasatinib (BMS-354825), a dual SRC/ABL kinase inhibitor, inhibits the kinase activity of wild-type, juxtamembrane, and activation loop mutant KIT isoforms associated with human malignancies. *Cancer Res.* 66: 473-481.

23. Wu, J.Y., N.J. Donato, D.S. Hong, *et al.* (2004). The SRC/ABL kinase inhibitor BMS-354825 induces apoptosis and overcomes imatinib resistance in chronic myelogenous leukemia cell lines and patient specimens. *Proc Am Assoc Can Res*. 45:A3850.

24. Hochhaus, A., and T. Hughes. (2004). Clinical resistance to imatinib: Mechanisms and implications. *Hematol Oncol Clin North Amer* 18:641-656.

25. Donato, N.J., J. Wu, L.Y. Kong, *et al*. (2004). The SRC/ABL inhibitor BMS-354825 overcomes resistance to imatinib mesylate in chronic myelogenous leukemia cells through multiple mechanisms. *Blood*. 104:A1989.

26. Lee, F.Y., L. Lombardo, R. Borzilleri, *et al*. (2004). BMS-354825 - A potent dual SRC/ABL kinase inhibitor possessing curative efficacy against imatinib sensitive and resistant human CML models *in vivo*. *Proc Am Assoc Cancer Res*. 45:A3987.

27. Shah, N.P. (2005). Loss of response to imatinib: Mechanisms and management. *Hematol*. 183-187.

28. Shah, N.P., F.Y. Lee, R. Luo, et al. (2005). Dasatinib (BMS-354825) inhibits $KITD^{816V}$, an imatinib-resistant activating mutation that triggers neoplastic growth in the majority of patients with systemic mastocytosis. *Blood.* 108:286-291.

29. Shah, N.P., C. Tran, F.Y. Lee, and C.L. Sawyers. (2004). BMS-354825 is a novel orally bioavailable small molecule ABL tyrosine kinase inhibitor that successfully and safely inhibits the kinase activity of multiple imatinib-resistant BCR-ABL isoforms *in vitro* and *in vivo*. *Proc Am Assoc Can Res*. 45:A5624.

30. Talpaz, M., N.P. Shah, H. Kantarjian, *et al.* (2006) Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. *N Engl J Med.* 354:2531-2541.

31. Tokarski, J.S., J. Newitt, F.Y. Lee, *et al.* (2004). The crystal structure of Abl kinase with BMS-354825, a dual SRC/ABL kinase inhibitor. *Blood*. 104:A553.

32. Johnson, F.M., B. Saigal, M. Talpaz, and N.J. Donato. (2005). BMS-354825 tyrosine kinase inhibitor suppresses invasion and induces cell cycle arrest and apoptosis of head and neck squamous cell carcinoma (HNSCC) and non-small cell lung cancer (NSCLC) cells. *Clin Cancer Res*. 11:6924-6932.

33. Luo F.R., Z. Yang, A. Camuso, *et al.* (2005) Pharmacodynamic biomarker. *Proc Am Assoc Cancer Res.* 46:A4183.

34. Sawyers, C.L., N.P. Shah, H.M. Kantarjian, *et al.* (2005). A phase I study of BMS-354825 in patients with imatinib-resistant and intolerant accelerated and blast phase chronic myeloid leukemia (CML): Results from CA180002. *Proc Am Soc Clin Oncol*. 24:A6520.

35. Chen, T.T. and T. H. Ng (1998). Optimal flexible designs in phase II clinical trials. *Statistics in Medicine* 17(20): 2301-2312.

Appendix I - NCI/DCTD Standard Protocol Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as

described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

APPENDIX II - NRG Oncology General Therapy Guidelines (11/2/15)

- For 21 or 28 day cycles, a patient will be permitted to have a new cycle of therapy delayed up to 7 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.
- It will be acceptable for individual doses to be delivered within a "24-hour window before and after the protocol-defined date" for "Day 1" treatment of 21 or 28 day cycles. If the treatment due date is a Friday, and the patient cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through the Monday (day 3 past due).
- For weekly regimens, it will be acceptable for individual doses to be delivered within a "24-hour window," for example; "Day 8 therapy" can be delivered on Day 7, Day 8, or Day 9 and "Day 15 therapy" can be given on Day 14, Day 15, or Day 16.
- Doses can be "rounded" according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately +/- 5% of the calculated dose).
- Doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for less than 10% weight changes.

Appendix III - Patient Medication Calendar

A PHASE II TRIAL OF DASATINIB (NSC #732517) IN RECURRENT /PERSISTENT OVARY, FALLOPIAN TUBE, PRIMARY PERITONEAL AND ENDOMETRIAL CLEAR CELL CARCINOMA WITH LOSS OF BAF250a EXPRESSION

This is a calendar on which you are to record the number of dasatinib tablets you take each day. The instructions on how to take the dasatinib are below.

Use the calendar to record date, time and number of dasatinib tablets taken each day. You will start by taking 140 mg (two 50mg tablets and two 20mg tablets) of dasatinib once each day for 28 days. This 28 day time period is called a cycle. It is possible your doctor may reduce the amount of dasatinib you take while participating in this study. Your doctor will discuss the new treatment plan with you at that time. Medication should be taken as instructed without skipping any medications. If you have missed a dose please mark down as "0" on the # slot for that day. If your doctor changes the amount of dasatinib you take, please be sure to write down the correct number of pills and correct amount taken in the columns below.

Dasatinib can be taken with or without a meal, but should be swallowed with at least 8 ounces (240 mL) of water. A light meal is not required, but may improve stomach upset from dasatinib. Tablets must be swallowed whole and may not be broken. Dasatinib can be taken in the morning or evening but should be taken at approximately the same time each day.

You should not take H2 blockers or proton pump inhibitors while on this study. You can take certain antacid medications 2 hours prior to or 2 hours after taking dasatinib. Please ask your study doctor if you think you are taking one of these medications.

Note to staff: Please give patient a drug log at initial enrollment and every week 4 visit. Instruct patient how to complete the diary log. 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, empties included.

Please note: Medication Calendar should be brought to each appointment along with medication bottles (empty included).

PATIENT MEDICATION CALENDAR

Patient Name_____ Patient Study ID_____

Total Daily Dose: ___ 50mg tablets, ___ 20mg tablets

Day	Date	Time	# of 50mg tablets	# of 20mg tablets	Comments

1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					

Patient Signature _____ Date _____

Physician's Office will complete this section:
1. Date patient started protocol treatment_____
2. Date patient started this cycle _____ This is cycle #_____
3. Patient's planned total daily dose for this cycle_____
4. Total number of tablets taken this month_____
5. Number or pills returned/unused this month _____
6. Physician/Nurse/Data Manager's Signature_____

Appendix IV - BAF250a IMMUNOHISTOCHEMISTRY TESTING

An appropriate tumor specimen from each patient must be submitted to Memorial Sloan-Kettering Cancer Center, Department of Pathology, and tested for BAF250a by immunohistochemistry (IHC). Patients must sign an approved informed consent to participate in the testing and treatment components of this study.

1. SLIDE REQUIREMENTS

Only one tumor specimen is required to test for BAF250a by IHC. If more than one tumor specimen is available, the more advanced and most recently obtained specimen should be submitted (e.g., a metastatic lesion rather than a primary; recurrent or persistent tumor rather than a primary or metastatic tumor from a previously untreated patient). **There must be clear cell carcinoma AND normal tissue present on the slides**.

Five (minimum four) unstained sections (charged, 4-6µm) must be shipped to Memorial Sloan-Kettering Cancer Center, Department of Pathology (address below) within 7 days of cutting the slides.

3. LABELING SLIDES

Label each individual slide with the Screening Patient Identifier. Slides may also be labeled with the pathology accession and block number, but these identifiers are not required. Do not label slides with any personal identifying information (e.g., patient name, patient initials, date of birth).

4. SHIPPING SLIDES

Complete the GOG-0283 BAF250a Immunohistochemistry Requisition (Appendix V). Please be sure the Screening Patient Identifier on the slides matches the Screening Patient Identifier on the requisition.

Ship the slides along with a de-identified copy of the corresponding pathology report to:

ATTN: Jessica Menzel
Memorial Sloan-Kettering Cancer Center
Department of Pathology
1275 York Ave
New York, NY 10065
Phone: 212-639-7297
Fax: 646-422-2070
Email: menzelj@mskcc.org

5. BAF250a IHC TESTING PROCEDURES

One slide will be stained for BAF250a (Sigma, St. Louis) and one with hematoxylin and eosin (H&E). The H&E will confirm that there is normal tissue present on the slide to serve as a normal control. The slides will be reviewed by a gynecologic pathologist.

The test result will be considered positive (RETAINED) if any of the tumor nuclei are immunoreactive and negative (LOSS) if all tumor nuclei show no staining. The result will be interpreted as a technical failure and subsequently repeated on an additional slide if the normal tissue shows no immunoreactivity.

6. REPORTING BAF250a IHC TESTING RESULTS

BAF250a IHC will be reported as either RETAINED or LOSS. Result reporting may be delayed if a discrepancy occurs or if required information is missing on the requisition.

Memorial Sloan-Kettering Cancer Center staff will be responsible for conveying the results to the GOG Statistical and Data Center, at which point, if the trial is open to patients with resulting BAF250a expression status, the patient can then be registered on trial. For the portion of the study where patients may be enrolled regardless of BAF250a IHC status, the result of this testing will not be communicated back to the GOG Institution where the testing was sent. This will be done to minimize the chance of bias for investigator assessed response assessments.

Appendix V - BAF250a IMMUNOHISTOCHEMISTRY REQUISITION

PROTOCOL GOG-0283: A PHASE II TRIAL OF DCTD-SPONSORED DASATINIB (NSC #732517 IND # 73969) IN RECURRENT /PERSISTENT OVARY, FALLOPIAN TUBE, PRIMARY PERITONEAL, AND ENDOMETRIALCLEAR CELL CARCINOMA CHARACTERIZED FOR THE RETENTION OR LOSS OF BAF250a EXPRESSION

TO:	**FROM**:
ATTN: Jessica Menzel	Institution: _____
Memorial Sloan-Kettering Cancer Center	GOG Site Number: _____
Department of Pathology	C/O: _____
1275 York Ave	Address:_____
New York, NY 10065	_____
Phone: 212-639-7297	Fax: _____
Fax: 646-422-2070	Phone: _____
Email: menzelj@mskcc.org	Date Sent: _____

GOG Patient ID (De-Identified): _____

Primary Tumor Site:
□ Ovary □ Fallopian Tube □ Peritoneum □ Endometrium □ Endometriosis

Unstained Slides Submitted:

Number: _____

Thickness: _____

***** Please include a de-identified copy of the corresponding pathology report. Label the pathology report with the GOG Patient ID. *****

Appendix VI - Translational Research Specimen Procedures (11/2/15)(XX/XX/XX)

I. Summary of Translational Research Specimen Requirements

If the patient gives permission for her specimens to be used for this optional translational research component, then participating institutions are required to submit the patient's specimens as outlined below (unless otherwise specified).

Required Specimen (Specimen Code)	Collection Time Point	Ship To
FFPE Primary Tumor (FP01)* 1st Choice: block 2nd Choice: 25 unstained slides (10 charged, 5µm & 15 uncharged, 10µm)	Prior to all treatment *Preferred FFPE*	GOG Tissue Bank within **1 week** of registration[1]
FFPE Metastatic Tumor (FM01)* 1st Choice: block 2nd Choice: 25 unstained slides (10 charged, 5µm & 15 uncharged, 10µm)	Prior to all treatment *Optional if FP01, FRP01, FRM01, FPP01, or FPM01 is submitted*	
FFPE **Recurrent Primary** Tumor (**FRP01**)* 1st Choice: block 2nd Choice: 25 unstained slides (10 charged, 5µm & 15 uncharged, 10µm)	Prior to study treatment *Optional if FP01, FM01, FRM01, FPP01, FPM01 is submitted*	
FFPE **Recurrent Metastatic** Tumor (**FRM01**)* 1st Choice: block 2nd Choice: 25 unstained slides (10 charged, 5µm & 15 uncharged, 10µm)		
FFPE Persistent Primary Tumor (FPP01)* 1st Choice: block 2nd Choice: 25 unstained slides (10 charged, 5µm & 15 uncharged, 10µm)	Prior to study treatment *Optional if FP01, FM01, FRP01, FRM01, or FPM01is submitted*	
FFPE Persistent Metastatic Tumor (FPM01)* 1st Choice: block 2nd Choice: 25 unstained slides (10 charged, 5µm & 15 uncharged, 10µm)	Prior to study treatment *Optional if FP01, FM01, FRP01, FRM01, or FPP01 is submitted*	
Whole Blood (WB01) 7-10mL drawn into purple top (EDTA) tube(s)	Prior to or after starting study treatment	GOG Tissue Bank the day the specimen is collected[1]

* A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the GOG Tissue Bank

1 GOG Tissue Bank / Protocol GOG-GOG-0283, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: GOGBank@nationwidechildrens.org

II. Obtaining a GOG Bank ID for Translational Research Specimens

Only one GOG Bank ID (# # # # - # # - G # # #) is assigned per patient. All translational research specimens and accompanying paperwork must be labeled with this coded patient number. A GOG Bank ID can be obtained online via the Tissue Bank Portal on the GOG website (under Tools on the Web Menu page).

Obtain the patient's study ID (GOG #) for all protocols with translational research specimen requirements before requesting a Bank ID from the Tissue Bank Portal. **Be sure to indicate if the patient has a previous GOG # when registering.** This will ensure that the patient is only assigned one Bank ID. The GOG ID – Bank ID Lookup on the Tissue Bank Portal can be used to search for an existing Bank ID.

Please contact GOG User Support if you need assistance or have assigned more than one Bank ID to a patient (Email: support@gogstats.org; Phone: 716-845-7767).

III. Requesting Translational Research Specimen Kits

Kits are not provided for this protocol.

IV. Labeling Translational Research Specimens

A waterproof permanent marker or printed label should be used to label each translational research specimen with:

GOG Bank ID (# # # # - # # - G # # #)
GOG protocol number (GOG- # # # #)
specimen code (see section I)
collection date (mm/dd/yyyy)
surgical pathology accession number (tissue specimens only)
block number (tissue specimens only)

Note: If labeling slides, only label on the top, front portion of the slide. Do not place a label on the back of the slide or over the tissue. The label must fit on the slide and should not be wrapped around the slide or hang over the edge.

V. Submitting Formalin-Fixed, Paraffin-Embedded Tissue

Formalin-fixed, paraffin embedded (FFPE) tissue should be the most representative of the specimen type (primary, metastatic, recurrent). Primary and metastatic tumor should be collected prior to all treatment. Recurrent and persistent tumor should be collected prior to the study treatment. Recurrent or persistent tumor collected from the site of primary disease should be labeled recurrent primary or persistent primary, respectively. Recurrent or persistent tumor collected from a site other than the site of primary disease (e.g., lymph node) should be labeled recurrent metastatic or persistent metastatic, respectively. Only one block may be submitted per tissue type.

Every attempt should be made to provide a FFPE block; however, if a block cannot be provided on a permanent basis, then 25 unstained slides (10 charged, 5µm and 15 uncharged, 10 µm) should be submitted. All tissue sections should be cut sequentially from the same block.

Note: Unstained slides for screening and stained slides to confirm patient eligibility by central pathology review are required for this protocol, but are NOT sent to the GOG Tissue Bank (see protocol for details). If these slides will be cut from the same block that will be submitted for translational research, your pathology department should cut these slides prior to submitting the block for translational research.

The type of specimen (block, slides) should be specified on Form TR. If submitting slides, the slide type, thickness, and count should also be specified.

All FFPE tissue should be submitted with the corresponding pathology report.

VI. Submitting Whole Blood

1. Label the lavender/purple top (EDTA) collection tube(s) as described above. Multiple tubes may be used to collect the required amount.

2. Draw 7-10mL of blood into the labeled lavender/purple top tube(s). A minimum of 3mL is needed for processing.

3. Immediately after collection, gently invert the tube 5-10 times to mix the blood and EDTA.

4. Whole blood specimens should be refrigerated (4°C) until the specimens can be shipped. Ship whole blood to the GOG Tissue Bank the day the specimen is collected. If the whole blood absolutely cannot be shipped the day it is collected, the tube(s) should be refrigerated (4°C) until the specimen can be shipped.

VII. Submitting Form TR

A completed copy of Form TR must accompany each specimen shipped to the GOG Tissue Bank (or alternate laboratory). Handwritten forms will not be accepted.

Note: A copy does not need to be sent to the GOG Tissue Bank (or alternate laboratory) if specimens are not collected.

Form TR should be printed from the Translational Research Form screen in Rave using the **"PDF File" link at the top of the form**. Clicking this link will generate a PDF of Form TR in a "SEDES style" format. Do not use the "Printable Version" or

"View PDF" links at the bottom of the form or any other method to print the form, as these formats will not be accepted.

Retain a printout of the completed form for your records.

Please contact User Support at the GOG Statistical and Data Center if you need assistance (Email: support@gogstats.org; Phone: 716-845-7767).

VIII. Shipping Translational Research Specimens

A completed copy of Form TR must be included for each translational research specimen.

A. FFPE Tissue

FFPE tissue and a copy of the corresponding pathology report should be shipped using your own container at your own expense to:

GOG Tissue Bank / Protocol GOG-GOG-0283
Nationwide Children's Hospital
700 Children's Dr, WA1340
Columbus, OH 43205
Phone: (614) 722-2865
FAX: (614) 722-2897
Email: GOGBank@nationwidechildrens.org

Do not ship FFPE tissue for Saturday delivery.

B. Whole Blood

All whole blood specimens should be shipped to the GOG Tissue Bank (address above).

Whole blood specimens can be shipped to the GOG Tissue Bank **Monday through Friday for Tuesday through Saturday delivery**. Please do not ship whole blood the day before a holiday. Use your own shipping container to ship specimens via **FedEx priority overnight**.

When shipping whole blood specimens, **please be aware that your institution must comply with IATA standards** (www.iata.org). If you have questions regarding your shipment, contact the GOG Tissue Bank at GOGBank@nationwidechildrens.org or by phoning 866-GOG-BANC (866-464-2262).

To ship whole blood specimens you will need (1) a sturdy shipping container (e.g., a cardboard or styrofoam box), (2) a leak proof biohazard envelope with

absorbent material*, (3) a puncture and pressure resistant envelope (e.g. Tyvek envelope), (4) an Exempt Human Specimen Sticker, and (5) a pre-paid FedEx air bill.

**If you will be shipping whole blood specimens from more than one patient, place each specimen in a separate plastic zip-lock bag before placing the specimens in the shipping bag. You may include up to four different blood specimens in one biohazard envelope.*

If you do not have these materials available at your institution, you may order them from any supplier (e.g., Saf-T-Pak; Phone: 800-814-7484; Website: www.saftpak.com).

Shipping Whole Blood Using Your Own Shipping Container

1. Place the whole blood specimen in a biohazard envelope containing absorbent material. Expel as much air as possible before sealing the bag.

2. Wrap the biohazard envelope in bubble wrap or another padded material.

3. Place the padded tube(s) into a Tyvek envelope. Expel as much air as possible before sealing the envelope.

4. Place the Tyvek envelope in a sturdy shipping container (e.g., cardboard FedEx box).

5. Insert a copy of Form TR for each specimen.

6. Attach an Exempt Human Specimen sticker to the outside of the shipping container.

7. Print a pre-paid FedEx air bill using the Kit Management application (found under Data Entry on the Web Menu page). Attach the air bill.

8. Make arrangements for FedEx pick-up through your usual institutional procedure or by calling 800-238-5355.

IX. Distributing Specimens for Translational Research

The GOG Statistical and Data Center and Tissue Bank (or alternate laboratory) will coordinate the distribution of specimens to approved investigators for translational research.

Investigators will not be given access to any personal identifiers.

Investigators will be responsible for the direct supervision and oversight of translational research and for keeping accurate records.

Investigators will ensure the results are linked to the appropriate specimen-specific identifiers and are responsible for transferring relevant laboratory data to the GOG Statistical and Data Center.

At the discretion of the Chair of the Committee on Experimental Medicine and the Director of the GOG Tissue Bank, investigators may be required to ship any specimens (or by-products) remaining after the completion of the translational research to the GOG Tissue Bank.

A. FFPE

FFPE will be batch shipped on a monthly basis to Dr. Robert Soslow:

ATTN: Carlene Gonzalez
Memorial Sloan-Kettering Cancer Center
Department of Pathology
1275 York Ave
New York, NY 10065
Phone: 212-639-7297
FAX: 929-321-5015
Email: gonzalc5@mskcc.org

B. Whole Blood

The GOG Tissue Bank will extract DNA from whole blood. DNA will be batch shipped on a monthly basis to Dr. David Hyman:

ATTN: Nancy Bouvier
Center for Molecular Oncology
Memorial Sloan Kettering Cancer Center
408 E 69th #Z-320
New York, NY 10021
Phone: 646-888-3761
Email: bouviern@mskcc.org, skicmopm@mskcc.org

Please email prior to shipping specimens.

X. Banking Translational Research Specimens for Future Research

Translational research specimens will remain banked in the GOG Tissue Bank and made available for approved research projects if the patient has given permission to use her specimens for future health research. The patient's choices will be recorded on the signed informed consent document and the online Specimen Consent

Application. At the time of specimen selection for project distribution, the most recent consent information will be used.

GOG institutions can amend a patient's choices regarding the future use of her specimens at any time if the patient changes her mind.

If the patient revokes permission to use her specimens, the GOG Tissue Bank will destroy (or return) any remaining specimens. The patient's specimens will not be used for any further research; however, any specimens distributed for research prior to revoking consent cannot be returned or destroyed. In addition, the patient cannot be removed from any research that has been done with her specimens prior to revoking consent.

Note: If return of specimens is requested, shipping will be at the institution's expense.