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SUMMARY OF CHANGES

For Protocol Amendment #5 to:

NCI Protocol #: GOG-0280
Local Protocol #: GOG-0280

NCI Version Date: 05/02/2016
Protocol Date:

This amendment is being submitted in response to an RA from Dr. Richard Piekarz (piekarzr@mail.nih.gov).

#	Section	Page (s)	Change
1.	Title Pages	1-2	• NCI Version Date is now 05/02//2016. • Includes Revisions #1-5.
2.	4.110	17	The PMB Phone number has been updated to 240-276-6575.
3.	4.112	17-21	CAEPR has been updated and is now Version 2.3, March 4,2016. • The SPEER grades have been updated. • [redacted]

#	Section	Page (s)	Change
			[redacted]
4.	Appendix II	51	Appendix II has been updated to the current version; the last bullet has been deleted.
	IC		Additional changes have been made to the Informed Consent.

PROTOCOL GOG-0280

A PHASE II EVALUATION OF THE POLY (ADP-RIBOSE) POLYMERASE (PARP) -1 AND -2 INHIBITOR VELIPARIB (ABT-888) (IND #77840) (NSC #737664) IN THE TREATMENT OF PERSISTENT OR RECURRENT EPITHELIAL OVARIAN, FALLOPIAN TUBE, OR PRIMARY PERITONEAL CANCER PATIENTS WHO CARRY A GERMLINE BRCA1 OR BRCA2 MUTATION **(07/09/2012)**

NCI Version Date: 05/02/2016

Includes Revisions #1 -5

POINTS:
PER CAPITA – 20 **(07/09/2012)**
MEMBERSHIP - 6

TR PER CAPITA – Award based on specimen submission with 1.0 point for pre-treatment FFPE (FR01 or FP01/FM01), frozen (RR01 or RP01/RM01), serum (SB01), whole blood (WB01), and post-treatment specimen (FR02 or PF01) (MAX TOTAL = 5.0).

PARTICIPATION OPEN GROUP-WIDE, CURRENTLY Pharmaceutical Management Branch/Industry Sponsor CAN SHIP ONLY TO US sites

Lead Organization: NRG/NRG Oncology

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SCHEMA

Veliparib 400 mg oral twice daily
Until disease progression or adverse effects prohibit further therapy One cycle = 28 days

OPEN TO PATIENT ENTRY APRIL 9, 2012; REVISED JULY 9, 2012; TEMPORARILY CLOSED TO PATIENT ENTRY JULY 23, 2012; REVISED AUGUST 21, 2012; RE-OPENED TO PATIENT ENTRY OCTOBER 15, 2012; CLOSED TO PATIENT ENTRY NOVEMBER 15, 2012; REVISED

TABLE OF CONTENTS

1.0 OBJECTIVES

1.1 Primary Objectives

1.11 To estimate the proportion of patients who have objective tumor response (complete or partial).

1.12 To determine the frequency and severity of adverse events associated with treatment with veliparib (ABT-888) as assessed by the Active Version of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

1.2 Secondary Objectives

1.21 To determine the duration of progression-free survival (PFS) and overall survival (OS).

1.22 To determine the proportion of patients who survive progression-free for at least 6 months.

1.3 Translational Research Objectives

1.31 To explore the association between single nucleotide polymorphisms (SNPs) in DNA repair genes (e.g., BRCA1, Fanconi) and clinical characteristics, response, and patient outcome (PFS and OS).

2.0 BACKGROUND & RATIONALE

2.1 Ovarian Cancer and PARP Inhibition

PARP-1 is essential to the repair of DNA single-strand breaks via the base excision repair pathway. Poly (ADP-ribose) polymerase (PARP) plays a key role in DNA repair mechanisms by detecting and initiating repair after DNA strand breaks. Inhibition of PARP in DNA repair-defective tumors (like those with BRCA1 or BRCA2 mutations) can lead to gross genomic instability and cell death. Recent in vitro and in vivo evidence suggests that PARP inhibitors could be used not only as chemo/radiotherapy sensitizers, but also as single agents to selectively kill cancers defective in DNA repair, specifically cancers with mutation in the breast cancer-associated genes, BRCA1 and BRCA2.

Much of the proof of concept and proof of principle single agent studies performed to date have centered on olaparib. A phase I study of olaparib in 60 patients with advanced solid tumors evaluated doses of olaparib beginning at 10 mg daily, two out of three weeks, up to 600 mg BID. The maximum tolerated dose was deemed to be 400 mg twice daily. Objective responses were observed only in confirmed carriers of BRCA1 or BRCA2 mutation, apart from one patient with a strong family history of BRCA mutation who declined mutational testing. Of the 60 patients entered, there were

9 partial or complete responses by RECIST criteria (8 with ovarian cancer and 1 with breast cancer). Of the 9 responders, 4 received 400 mg BID, 4 received 200 mg BID

and one 100 mg BID. A total of 21 patients with ovarian cancer and 9 patients with breast cancer were entered on the study.[1]

A phase II trial evaluating two sequential cohorts of women with recurrent ovarian cancer (with confirmed germline BRCA1 or BRCA2 mutation and measurable disease) enrolled 33 women treated at 400 mg BID and then 24 women treated at 100 mg BID. Objective response rate (RECIST) was 33% (11/33 patients) in the 400 mg BID cohort and 13% (3/24 patients) in the 100 mg BID cohort.[2] A Similar study was performed in metastatic breast cancer patients with confirmed germline BRCA1 or BRCA2 mutation and measurable disease. In this study, the objective response rate (RECIST) was 41% (11/27 patients) in the 400 mg BID cohort and 22% (6/27 patients) in the 100 mg BID cohort.[3]

In a further phase I study, 50 patients with recurrent ovarian cancer, known BRCA1 or BRCA2 mutation and measurable disease were treated with doses of olaparib ranging from 40 mg daily for 2 of 3 weeks, to 600 mg BID (11 patients). There was then a dose expansion cohort in which all patients received olaparib at 200 mg BID (39 patients). Objective response rate was 28% (14/50 patients). Objective response rates were reported according to platinum-sensitivity: Platinum-sensitive 46% (6/13 patients); Platinum-resistant 33% (8/24 patients); and Platinum-refractory 0% (0/13 patients).[4] A potential explanation for the variable response according to platinum-sensitivity is the development of secondary mutations restoring BRCA 1/2 function.[5-9]

Olaparib has also been evaluated as a single agent in a trial that included patients without germline BRCA1 or BRCA2 mutation. In this phase II trial, 86 patients were treated and evaluable for response (63 with ovarian cancer and 23 with breast cancer). Patients were entered with recurrent high grade serous and/or undifferentiated ovarian cancer or triple negative breast cancer. Patients were stratified according to whether they had a BRCA1 or BRCA2 mutation or not. In ovarian cancer, objective responses were seen in 41% (7/17 patients) with BRCA1 or BRCA2 mutation and 24% (11/46 patients) without BRCA1 or BRCA2 mutation. No objective responses were seen in breast cancer patients (8 BRCA; 15 non-BRCA).[10]

A three-arm randomized, open label, phase II trial of olaparib 200 mg BID (n=32), olaparib 400 mg BID (n=32) and pegylated liposomal doxorubicin (PLD) (n=33), in women with recurrent ovarian cancer, germline BRCA1 or BRCA2 mutation and recurrence within 12 months of prior platinum therapy has been conducted. PLD was given at 50 mg/m^2 every 4 weeks. The primary endpoint was investigator assessed progression-free survival. The progression free survival (PFS) and objective response rates (RR) were similar between the 3 arms.[11] The efficacy of olaparib was consistent with previous studies. The efficacy of PLD was greater than expected. **(07/09/2012)**

A randomized phase II maintenance trial of olaparib (400 mg BID) vs placebo was conducted in women with platinum sensitive recurrent high grade serous ovarian cancer (with and without BRCA1 or BRCA2 mutation) who had achieved a response (partial

or complete) following 2nd line (or greater) platinum-based therapy. The time to progression in the 265 patient cohort was extended from 4.8 months to 8.4 months (HR: 0.35, P<0.001). Patients were not required to undergo BRCA1 and BRCA2 testing and they were not stratified as to whether they had a BRCA1 or BRCA2 mutation or not.[12] **(07/09/2012)**

The olaparib formulation used in all the above detailed trials is a 50 mg capsule. To achieve the recommended dose of 400 mg BID, 16 large (size 0) capsules are required which may compromise patient convenience and compliance. In a phase I-pharmacokinetic study (24 patients), an equivalent tablet formulation dose of olaparib to the 400 mg BID capsule formulation (16 capsules) was established as 200 mg BID (4 tablets).[13] This tablet formulation is now entering efficacy trials.

Currently several phase I/II studies with Veliparib are ongoing in combination with chemotherapy and/or radiation therapy (50 trials listed in Clincialtrials.gov). (See Section 2.22 for details of the phase I clinical experience) Currently, in recurrent ovarian cancer, Veliparib is being combined with temozolomide in a randomized phase II study versus PLD (Doxil) in women with recurrent serous ovarian cancer (NCT01113957); and in combination with metronomically delivered cyclophosphamide versus sequential metronomic cyclophosphamide and Veliparib in patients with recurrent serous ovarian cancer (NCT01306032). The GOG is also conducting a phase I trial in combination with bevacizumab and the cytotoxic agents, paclitaxel and carboplatin in frontline ovarian cancer (GOG9923; NCT00989651). The dosing and schedule under each of these trials is profoundly influenced by the agents being co-administered. **Currently, there are no clinical efficacy data of single agent Veliparib, which is the primary objective of the current proposal.**

The single agent, dose-finding, phase I trial of ABT-888 is still ongoing (NCT00892736). This study is open to BRCA1 and BRCA2 mutation carriers, triple negative metastatic breast cancer, platinum-refractory ovarian cancer, pancreatic cancer, prostate cancer patients. The primary goal of the study is to determine the recommended phase II dose. The requirement for entered ovarian cancer patients to have platinum-refractory disease is concerning, as this is the group previously shown not to respond to olaparib, even when entry criteria were restricted to BRCA1 and BRCA2 carriers.[4] Thus a true evaluation of the activity of veliparib in recurrent, measurable disease, BRCA1 or BRCA2 mutation ovarian cancer has not been under taken.

2.2 ABT-888

ABT-888 is a potent PARP inhibitor that delays the repair of DNA damage induced by chemotherapeutics. ABT-888 increases sensitivity of tumor cells to DNA damaging agents in vitro, and demonstrates PARP inhibition in murine tumors in vivo and human peripheral blood mononuclear cells (PBMCs) ex vivo.

ABT-888 is a novel small molecule that is a potent inhibitor of both PARP-1 and PARP 2, with Ki‘s of 5 nM and 3 nM, respectively. In cells under oxidative stress, ABT-888 inhibits the PARP-induced formation of poly-(ADP-ribose) (PAR) with an EC50 of

2.4nM. Consistent with the conclusion of mechanism based efficacy, significant inhibition of PAR levels was observed with doses of ABT-888 capable of delivering significant anti-tumor efficacy in preclinical models. A facile, enzyme-linked immunosorbent assay (ELISA) for measurement of PAR formation has been developed that can be used for analysis of pharmacodynamic effects of ABT-888 in human PBMC and tumor clinical samples.[14,15]

In cellular assays, ABT-888 increases sensitivity of tumor cells to DNA-damaging agents including temozolomide (TMZ), irinotecan, cyclophosphamide, BCNU, cisplatin, and radiation. In pre-clinical tumor models, ABT-888 enhances the anti-tumor efficacy of alkylating/methylating agents (TMZ, cyclophosphamide), cross-linking agents (cisplatin, carboplatin), topoisomerase inhibitors (irinotecan), and radiation.

2.21 Pre-Clinical Experience

2.211 Pharmacokinetics

In rats and dogs, ABT-888 is primarily cleared in the urine as intact parent drug, with minor contributions from metabolism. The renal clearance and minimal metabolism observed in rats and dogs, and the minimal metabolism observed in vitro in all species evaluated are consistent with the low molecular weight (244.296 g/mol) and good solubility of ABT-888. These data support the prediction that in humans, ABT-888 will be primarily cleared as intact parent in urine.

ABT-888 is not a potent inhibitor, nor an inducer, of the major human cytochrome P450s (CYPs), suggesting a minimal potential for drug-drug interactions at the anticipated therapeutic concentrations.

[redacted]

[redacted]

2.22 Clinical Experience

A Phase 0 dose-ranging pharmacokinetic and pharmacodynamic study has been completed (NCI IND). In this trial, 13 subjects with various types of advanced cancer received a single dose of single-agent ABT-888 (10 mg, n = 3; 25 mg, n = 3; 50 mg, n = 7). The pharmacokinetic results from this study demonstrated that ABT-888 is orally bioavailable and primarily cleared through renal excretion, with a half-life of 4 to 5 hours. Additionally, this study provided proof of mechanism, as tumor PARP inhibition (> 90%) was demonstrated in 5 out of 6 human tumor biopsies that were obtained 3 to 6 hours after dosing with ABT-888. No serious adverse events, dose-limiting toxicities (DLTs), or deaths were reported for this study.[16]

Multiple Phase I studies of ABT-888 in combination with various chemotherapeutic agents are on-going. Study M06-862 is a dose-escalation study designed to assess the safety, tolerability, and pharmacokinetic profile of ABT-888 in combination with TMZ. [redacted]

The A10-153 study is a Phase I study designed to assess the safety and tolerability of ABT-888 in combination with carboplatin/paclitaxel. In this trial ABT-888 is given orally on Days 1-7, and carboplatin/paclitaxel are given on Day 3 of a 21-day cycle. The trial is accruing subjects to the dose level of 40 mg ABT-888 plus carboplatin (AUC=6) and paclitaxel (200 mg/m^2). Thus far, the treatment has been tolerated well with heavily pre-treated patients receiving a median number of 6 cycles on study. Of the six patients treated at carboplatin AUC 6, paclitaxel 175 mg/m2 and ABT-888 40 mg BID, three were able to complete all 6 cycles at the full dose. Three patients required dose reductions of paclitaxel secondary side effects. The MTD has not been reached in this study. An additional Phase I dose escalation study of ABT-888 monotherapy in BRCA carriers with solid tumors is ongoing. Treatment in this study is continuous BID dosing beginning at a dose of 50 mg BID. The recommended phase II dose from this continuous monotherapy study is 300 to 400 mg BID. Patients can experience nausea. If nausea is seen with the 400 mg BID dose, the recommendation is to lower the dose to 300 mg BID (Personal Communication: Alice Chen, MD and Shannon Puhalla, MD).

2.3 Translational Research Background

Polymorphisms in Fanconi pathway genes may alter DNA repair efficiency. This alteration may predispose individuals to sensitivity to PARP inhibition. Thus, the optional translational research component of this study will examine single nucleotide polymorphisms (SNPs) in DNA repair genes. To examine SNPs that may alter DNA repair efficiency, formalin-fixed, paraffin-embedded tumor and whole blood will be collected from patients who agree to participate. SNPs in DNA repair genes (e.g., BRCA1, Fanconi) will be examined using the best platform identified at the time of testing. The association between SNPs and response, survival, and clinical characteristics will be examined.

2.4 Inclusion of Women and Minorities

The Gynecologic Oncology Group (GOG) 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 ovarian, fallopian tube, and primary peritoneal cancer population treated by participating institutions.

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Eligibility Criteria

3.11 Patients must have recurrent or persistent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma AND carry a germline mutation in BRCA1 or BRCA2 (confirmation required via genetic test report). Histologic documentation of the original primary tumor is required via the pathology report. **(07/09/2012)**

3.12 All patients must have measurable disease as defined by RECIST 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.

3.13 Patient must have at least one "target lesion" to be used to assess response on this protocol as defined by RECIST 1.1 (Section 8.1). Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

3.14 Patients who have received one prior cytotoxic regimen must have a GOG Performance Status of 0, 1, or 2.

Patients who have received two or three prior cytotoxic regimens must have a GOG Performance Status of 0 or 1.

3.15 Recovery from effects of recent surgery, radiotherapy, or chemotherapy

3.151 Patients should be free of active infection requiring antibiotics (with the exception of uncomplicated UTI).

3.152 Any hormonal therapy directed at the malignant tumor must be discontinued at least one week prior to registration. Continuation of hormone replacement therapy is permitted.

3.153 Any other prior therapy directed at the malignant tumor, including chemotherapy, biologic/targeted (non-cytotoxic) agents and immunologic agents, must be discontinued at least three weeks prior to registration. Patients receiving nitrosoureas or mitomycin C must discontinue 6 weeks prior to registration.

3.154 Any prior radiation therapy must be discontinued at least four weeks prior to registration.

3.16 Prior therapy

3.161 Patients must have had one prior platinum-based chemotherapeutic regimen for management of primary disease containing carboplatin, cisplatin, or another organoplatinum compound. This initial treatment may have included intraperitoneal therapy, consolidation, biologic/targeted (non-cytotoxic) agents or extended therapy administered after surgical or non-surgical assessment.

3.162 Patients are allowed to receive, but are not required to receive, two additional **cytotoxic regimens** for management of recurrent or persistent disease.

3.163 Patients are allowed to receive, but are not required to receive, biologic/targeted (non-cytotoxic) therapy for management of recurrent or persistent disease. Patients are allowed to receive, but are not required to receive, biologic/targeted (non-cytotoxic) therapy as part of their primary treatment regimen.

3.164 Patients with both platinum-sensitive and platinum-resistant disease are eligible. Patients with platinum-refractory disease are NOT eligible.

Definitions:

- Platinum sensitive ovarian cancer is defined as patients who respond to platinum-based therapy (complete or partial) and then progress/recur more than 6 months after their last platinum dose (i.e., platinum-free interval is > 6 months).
- Platinum resistant ovarian cancer is defined as patients who respond to platinum-based therapy (complete or partial) and then progress/recur within 6 months of their last platinum dose (i.e., platinum-free interval is <= 6 months).
- Platinum refractory ovarian cancer is defined as patients who have progression of disease while receiving platinum-based chemotherapy or who fail to achieve at least a partial response to platinum-based chemotherapy (i.e., best response to platinum-based chemotherapy is stable disease).

3.17 Patients must have adequate:

3.171 Bone marrow function: Absolute neutrophil count (ANC) greater than or equal to 1,500/mcl. Platelets greater than or equal to 100,000/mcl.

3.172 Renal function: Creatinine less than or equal to 1.5 x institutional upper limit normal (ULN).

3.173 Hepatic function: Bilirubin less than or equal to 1.5 x ULN. AST and ALT less than or equal to 3 x ULN. Alkaline phosphatase less than or equal to 2.5 x ULN.

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

3.19 Patients must meet pre-entry requirements as specified in section 7.0.

3.110 Patients of childbearing potential must have a negative pregnancy test prior to the study entry and be practicing an effective form of contraception.

3.111 Patients must be 18 years or older.

3.2 Ineligibility Criteria

3.21 Patients who have had previous treatment with veliparib (ABT-888) or any other PARP inhibitor (including olaparib). Note: Iniparib (BSI-201) cannot inhibit PARP1 at pharmacologically achievable concentrations, therefore prior iniparib therapy is allowed.

3.22 Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer and other specific malignancies as noted in Sections 3.23 and 3.24, are excluded if there is any evidence of other malignancy being present within the last three years. Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy.

3.23 Patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis OTHER THAN for the treatment of ovarian, fallopian tube, or primary peritoneal cancer within the last three years are excluded. Prior radiation for localized cancer of the breast, head and neck, or skin is permitted, provided that it was completed more than three years prior to registration, and the patient remains free of recurrent or metastatic disease.

3.24 Patients who have received prior chemotherapy for any abdominal or pelvic tumor OTHER THAN for the treatment of ovarian, fallopian tube, or primary peritoneal cancer within the last three years are excluded. Patients may have received prior adjuvant chemotherapy for localized breast cancer, provided that it was completed more than three years prior to registration, and that the patient remains free of recurrent or metastatic disease.

3.25 Patients with seizures or history or seizures are ineligible.

Patients with history or evidence upon physical examination of CNS disease, including primary brain tumor, , any CNS metastases, or history of cerebrovascular accident (CVA, stroke), transient ischemic attack (TIA) or subarachnoid hemorrhage within six months of the first date of treatment on this

study are ineligible. Patients with CNS metastases must be stable for >3 months after treatment and off steroid treatment prior to study enrollment. **(08/21/2012)**

3.26 Inability or unwillingness to swallow pills.

3.27 Patients with clinical symptoms or signs of gastrointestinal obstruction and/or who require parenteral hydration or nutrition.

3.28 Patients who are pregnant or nursing.

4.0 STUDY MODALITIES

4.1 ABT-888 Capsule, Veliparib, A-861695.0 (IND #77840) (NSC #737664)

4.11 Chemical Name/Molecular Formula: 1H-Benzimidazole-7-carboxamide, 2-[(2R)-2-methyl-2-pyrrolidinyl]-

C13H16N4O M.W.: 244.29

[redacted]

4.13 Mode of Action: ABT-888 inhibits the formation of poly (ADP-ribose) (PAR) polymers in vitro and in vivo. It inhibits the repair of DNA when the DNA is damaged by cytotoxic agents. ABT-888 increases antitumor efficacy when added to DNA-damaging therapies such as temozolomide, cisplatin, carboplatin, cyclophosphamide, irinotecan, or radiation therapy.

[redacted]

4.16 Route of Administration: Oral

[redacted]

4.19 Potential Drug Interactions**:** Clinical studies evaluating the metabolism of ABT-888 have not been conducted. However, results from the in vitro analysis reveal that this agent is metabolized by multiple isoenzymes – CYP1A1, 2D6, 2C19 and 3A4. ABT-888 is neither a potent inhibitor nor a potent inducer of the

CYP-450 isoenzymes. Use caution when concomitantly administered with drugs that are substrate, inhibitor, inducer of CYP1A1, 2D6, 2C19 and 3A4.

ABT-888 clears primarily in the urine as intact parent drug along with metabolites suggesting that renal function plays an important role in the drug clearance and its metabolites. Use caution when concomitantly administered with oxaliplatin, carboplatin, cisplatin, and topotecan in patients with pre-existing renal impairment.

4.110 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 agent be shipped directly to the institution where the patient is to be 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 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). 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. **( )**

4.111 Agent Inventory Records: 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 DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

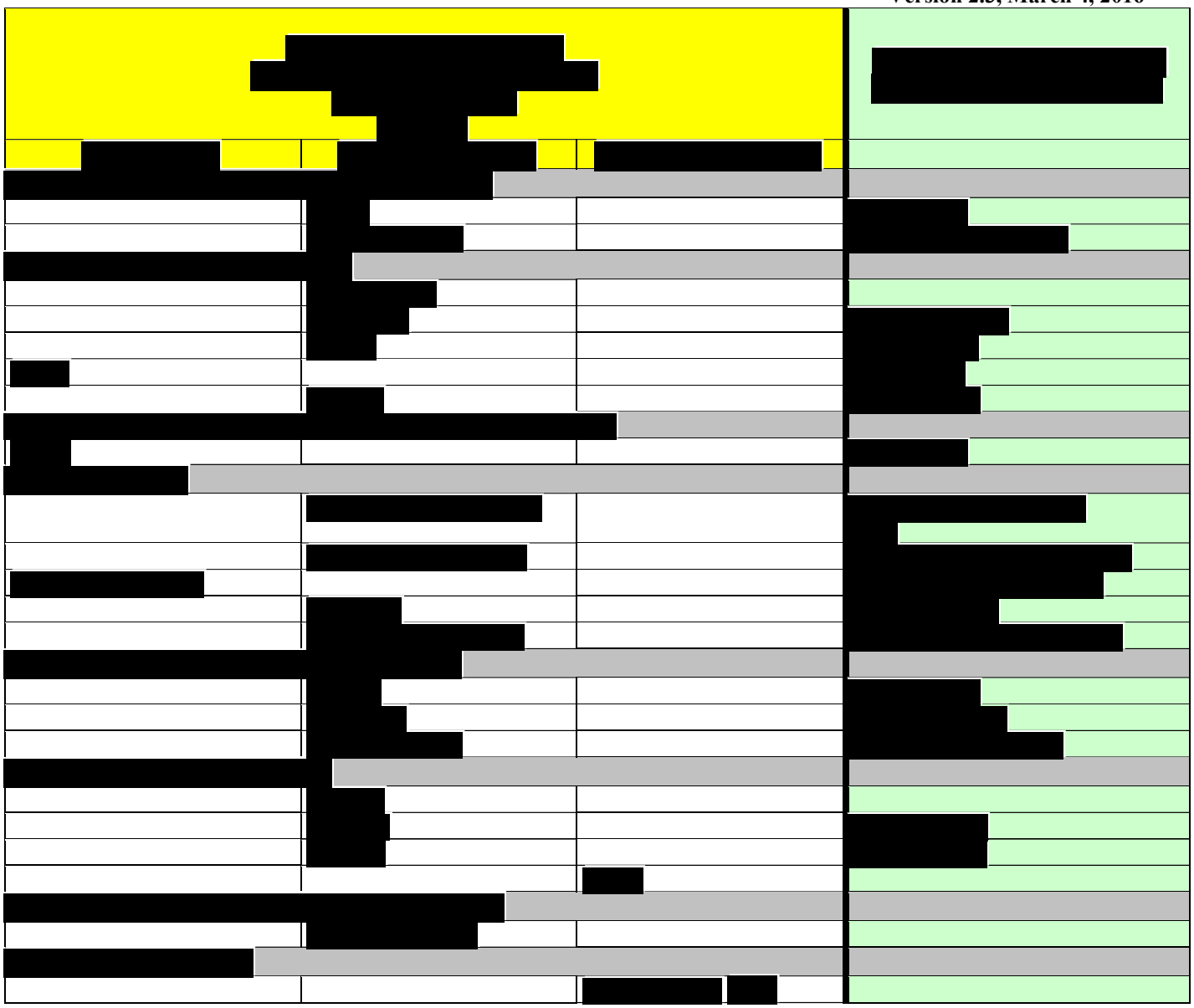
4.112 Comprehensive Adverse Events and Potential Risks list (CAEPR) For Veliparib (ABT-888, NSC 737664) **(08/21/2012) ( )**

The Comprehensive Adverse Event 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

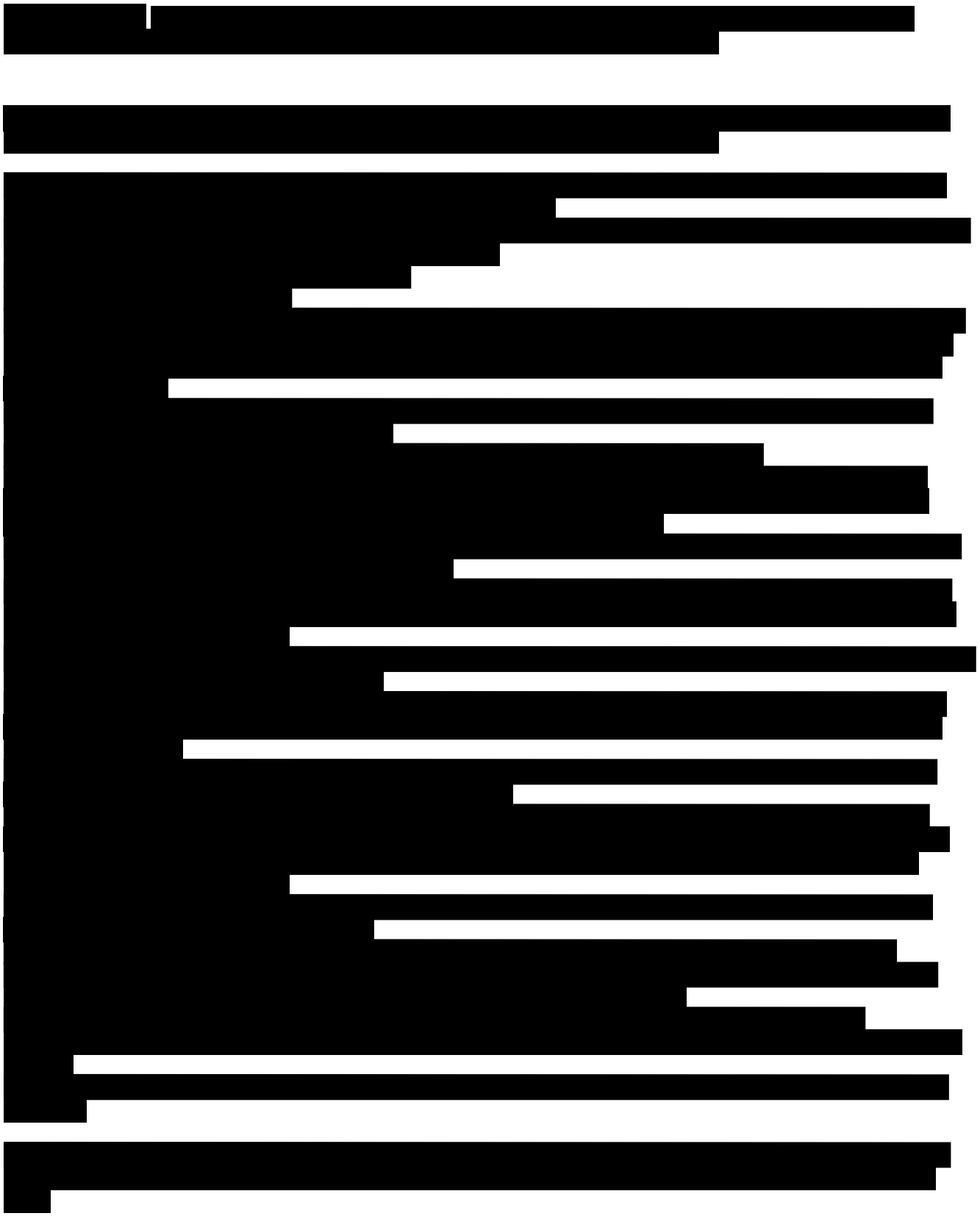
and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via AdEERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2310 patients.* Below is the CAEPR for Veliparib (ABT-888).

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 2.3, March 4, 2016[1]



[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.



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 Entry and Registration

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

OPEN Registration: All site staff will use OPEN to enroll patients to this study. OPEN can be accessed on the GOG web menu page by 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.
- Sites will provide documentation of germline BRCA 1 or 2 mutation status
- 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.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

5.2 Treatment Plan

5.21 Treatment:

Veliparib 400 mg will be taken orally twice daily (about the same time every day). The doses should be taken about 12 hours apart.

If a patient is more than 4 hours late in taking a dose, the dose should be skipped.

Pills may be taken with or without food. Pills should be swallowed with approximately 8 ounces of water.

One cycle = 28 days. Patients will receive therapy until disease progression or adverse effects prohibit further therapy.

Patients will self administer Veliparib and record doses on a pill calendar. See Patient Pill Calendar (Appendix III). Patients should be instructed to bring any unused pills, pill bottles and completed pill calendar to each appointment.

5.22 See the GOG General Chemotherapy Guidelines (Appendix II)

5.3 Criteria for removal from treatment

5.31 Inability to tolerate veliparib (ABT-888) at the lowest doses because of toxicity.

5.32 Patients who experience a seizure while on study should be removed from study therapy.

5.33 Patients who become pregnant while on study should be removed from study therapy.

5.34 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.

6.0 TREATMENT MODIFICATIONS

Study Drug	2 Level reduction	1 Level reduction	Initial dose level
ABT-888	200 mg oral twice daily	300 mg oral twice daily	400 mg oral twice daily

Please note: Patients may manifest nausea. Dose reduction for non-tolerable grade 1-2 nausea is allowed. Dose reductions can be made during a treatment cycle or at the start of the next cycle. Dose reduction is preferable to prolonged treatment interruption or study discontinuation. Grade 3 (or greater) nausea requires reduction of one dose level and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1. See section 6.21.

Please note all CTCAE grading below refers to version 4.0.

A maximum of two dose reductions is allowed for each patient. Patients experiencing toxicity (hematologic or non-hematologic) that meets criteria for further dose reduction, after this maximum, will be removed from study therapy.

6.1 Hematologic toxicity

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

6.111 Patients will NOT receive prophylactic G-CSF.

6.112 Patients will NOT receive prophylactic thrombopoietic agents.

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

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

6.13 Subsequent cycles of therapy will not begin until the ANC is ≥ 1500 cells/mcl and the platelet count is ≥ 100,000/mcl. Therapy will be delayed for a maximum of three weeks until these values are achieved. Patients who achieve adequate counts after a delay will receive ABT-888 with a 1 dose level reduction. Patients who fail to recover adequate counts within three weeks will be removed from study therapy.

6.14 For febrile neutropenia, and/or documented grade 4 neutropenia persisting ≥ 7 days, reduce ABT-888 by one dose level on subsequent cycles.

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

6.16 Patients with grade 3 or 4 thrombocytopenia or active bleeding will have a 1 level dose reduction.

6.2 Non-hematologic toxicity

6.21 Patients may manifest nausea. Dose reduction for non-tolerable grade 1-2 nausea is allowed. Dose reductions can be made during a treatment cycle or at the start of the next cycle. Dose reduction is preferable to prolonged treatment interruption or study discontinuation. Grade 3 (or greater) nausea requires reduction of one dose level and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1.

6.22 Grade 2 (or greater) peripheral neuropathy requires reduction of one dose level and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1.

6.23 Grade 2 (or greater) renal toxicity (and elevations in creatinine), requires reduction of one dose level and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1.

6.24 Grade 3 (or greater) elevations in AST, ALT, alkaline phosphatase or bilirubin requires reduction of one dose level and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1.

6.25 There will be no dose modifications for alopecia or fatigue.

6.26 It is expected that patients with diarrhea or constipation will receive appropriate medical management without dose modification. However, patients with persistent (greater than 24 hours) grade 3 (or greater) toxicity in spite of optimal medical management require reduction of one dose level and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1.

6.27 Other non-hematologic toxicities with an impact on organ function of grade 2 (or greater) require reduction of one dose level and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1, or pre-therapy baseline.

6.3 Dose escalations

There will be no dose escalations or re-escalations on this study.

7.0 STUDY PARAMETERS & SERIAL OBSERVATIONS

7.1 Observations and Tests
The following observations and tests are to be performed and recorded on the appropriate form(s). **Specimen requirements for translational research are provided in Section 7.3.**

Parameter	Pre-Therapy	Prior to Each cycle	Every Other Cycle	Off of all study therapy
History & Physical	1	X		
Vital Status				7
Performance status	1			
Toxicity Assessment	2	X		7, 8
CBC/Differential/Platelets	2	4		
Electrolytes, BUN, creatinine, Ca, Mg	2	X		
Urinalysis	2			
Bilirubin, AST, ALT, Alkaline Phosphatase	2	X		
Pregnancy test (for patients of child bearing potential)	3			
Chest imaging (X-ray or CT of the chest)	1		5	5†
Radiographic tumor measurement	1, 6		6	6†
CA-125	2	X		
Genetic Testing Report(s) (BRCA) **(07/09/2012)**	9			
Electrocardiogram (ECG)	1			

Patient Pill Calendar		10		

† **Until disease progression or until patient initiates a subsequent cancer therapy**

Notes:

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. Must be obtained within 7 days prior to initiating protocol therapy.
4. CBC/Differential/Platelets must be obtained within 4 days before re-treatment with protocol therapy.
5. Repeat chest imaging if initially abnormal or if required to monitor tumor response. CT scan to follow lesion for measurable disease every other cycle (or equivalent time frame for patients off treatment prior to disease progression) for the first 6 months; then every 3 months thereafter until disease progression is confirmed; also repeat at any other time if clinically indicated based on symptoms or physical signs suggestive of progressive disease. Responses (CR and PR) require confirmation at greater than or equal to 4 weeks from initial documentation (see section 8).
6. CT scan or MRI every other cycle (or equivalent time frame for patients off treatment prior to disease progression) for the first 6 months; then every 3 months thereafter until disease progression is confirmed; also repeat at any other time if clinically indicated based on symptoms or physical signs suggestive of progressive disease. Responses (CR and PR) require confirmation at greater than or equal to 4 weeks from initial documentation (see section 8).
7. Follow-up every 3 months for 2 years and then every 6 months for 3 years. Follow-up forms (Form Q) are collected for the 5 year follow-up period or until study termination.
8. Report all adverse events that occur within 30 days of last protocol treatment on the T form for the last cycle of therapy administered. For reporting of delayed toxicity, see section 10.14.
9. Patients enrolled on this trial are required to have a known germline mutation in BRCA1 or BRCA2. Submission of the reports detailing this testing is required. The following is the usual method for BRCA testing: If the patient is of Ashkenazi Jewish/Eastern European Jewish descent, testing begins with Multisite3 BRCAnalysis, continuing on to ("Reflex to") Comprehensive BRCAnalysis if negative. Testing of non-Ashkenazi patients starts with Comprehensive BRCAnalysis. Patients who are negative for the above testing can have BRCAnalysis Rearrangement Testing (BART). Genetic counseling is strongly recommended before and after BRCA1/2 testing.
10. See Appendix III.

7.2 Pathology Requirements

7.21 Pathology report for histologic confirmation of primary tumor

7.22 Pathology report for recurrent or persistent disease if histologically documented.

7.23 Stained slides to confirm eligibility by Central Pathology Committee Review are not required for this protocol.

7.3 Translational Research

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).

Required Specimen (Specimen Code)	**Collection Time Point**	**Ship To**
Pre-Treatment FFPE Recurrent Tumor (FR01) 1st Choice: Block 2nd Choice: Unstained Slides (10 5µm charged + 10 10µm uncharged)	Prior to Veliparib treatment	GOG Tissue Bank within 8 weeks of registration[1]
Pre-Treatment FFPE Metastatic Tumor (FM01) 1st Choice: Block 2nd Choice: Unstained Slides (10 5µm charged + 10 10µm uncharged)	Prior to Veliparib treatment (may be archival pre-treatment) *If FR01or FP01 cannot be submitted*	GOG Tissue Bank within 8 weeks of registration[1]
Pre-Treatment FFPE Primary Tumor (FP01) 1st Choice: Block 2nd Choice: Unstained Slides (10 5µm charged + 10 10µm uncharged)	Archival pre-treatment *If FR01 or FM01 cannot be submitted*	GOG Tissue Bank within 8 weeks of registration[1]
Pre-Treatment Frozen Recurrent Tumor (RR01) 1st Choice: Snap Frozen 2nd Choice: OCT Embedded	Prior to Veliparib treatment	GOG Tissue Bank within 2 weeks of registration[1]
Pre-Treatment Frozen Metastatic Tumor (RM01) 1st Choice: Snap Frozen 2nd Choice: OCT Embedded	Prior to Veliparib treatment (may be archival pre-treatment) *If RR01or RP01 cannot be submitted*	GOG Tissue Bank within 2 weeks of registration[1]
Pre-Treatment Frozen Primary Tumor (RP01) 1st Choice: Snap Frozen 2nd Choice: OCT Embedded	Archival pre-treatment *If RR01 or RM01 cannot be submitted*	GOG Tissue Bank within 2 weeks of registration[1]
Pre-Treatment Serum (SB01) prepared from 7-10mL blood drawn into a plain red top tube	Prior to Veliparib treatment	GOG Tissue Bank within 2 weeks of registration[1]
Whole Blood (WB01) 7-10mL drawn into purple top (EDTA) tube(s)	Prior to or after initiating Veliparib treatment	GOG Tissue Bank the day the blood is collected[1]
Post-Treatment FFPE Biopsy, FNA or surgical resection (FR02) 1st Choice: Block	**Optional** - Post-treatment, if patient has biopsy, FNA or surgery at time of progression as part of standard care	GOG Tissue Bank within 32 weeks of registration[1]

2nd Choice: Unstained Slides (10 5µm charged ; 10 10µm uncharged, if possible)	**(07/09/2012)**	
Post-Treatment FFPE Cell Pellet from Peritoneal Fluid (PF01) 1st Choice: Block 2nd Choice: Unstained Slides (10 5µm charged ; 10 10µm uncharged, if possible)	**Optional** - Post-treatment, if patient has peritoneal fluid removed at time of progression as part of standard care **(07/09/2012)** *If FR02 cannot be submitted*	GOG Tissue Bank within 32 weeks of registration[1]

1 GOG Tissue Bank / Protocol GOG-0280, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: GOGBanc@nationwidechildrens.org

7.31 Laboratory Testing

Formalin-fixed, paraffin-embedded specimens and DNA isolated from whole blood will be shipped to Drs. Michael Birrer and Elizabeth Swisher for analysis of single nucleotide polymorphisms (SNPs) in DNA repair genes (e.g., BRCA1, Fanconi). SNP analysis will be run using the best platform identified at the time of testing.

Serum will be banked for future research.

7.32 Future Research

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

7.4 Quality of Life

Not applicable.

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 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 ≥10 mm with CT scan, as ≥20 mm by chest x-ray, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in 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.

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. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal/pelvic masses (identified by physical exam and not CT or MRI), are considered as non-measurable.

Notes:
Bone lesions: Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

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, and 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.

8.12 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, subsequent image acquisitions should use the same type of scanner and follow the baseline imaging protocol as closely as possible. If possible, body scans should be performed with breath-hold scanning techniques.

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.**

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

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

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.

CA-125 (Ovarian, fallopian tube and primary peritoneal cancer trials): **CA125 cannot be used to assess response or progression in this study.** 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 that are to be integrated with objective tumor assessment for use only 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.

It is mandatory to obtain cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when measurable disease has met criteria for response or stable disease. This confirmation is necessary to differentiate response or stable disease versus progressive disease, as an effusion may be a side effect of the treatment.

8.13 Response Criteria

Determination of response should take into consideration all target (See 8.131) and non-target lesions (See 8.132) and, if appropriate, biomarkers (See 8.133).

8.131 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.

8.132 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If CA-25 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)
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.

Not evaluable (NE): When at least one non-target lesion is not evaluated at a particular time point.

Although a clear progression of only "non-target" lesions 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).

8.133 Evaluation of Biomarkers

If serum CA-125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response.

Progression **cannot** be based upon biomarkers, such as serum CA-125, for this study.

8.134 Evaluation of Best Overall (unconfirmed) Response

The best overall response is the best time point response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest sum

recorded since baseline). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria in some circumstances.

Time Point Response for Patients with Measurable Disease at baseline (i.e., Target Disease)

Target Lesions	Non-Target Lesions	Biomarker CA-125	New Lesions*	Time Point Response
CR	CR	Within normal limits	No	CR
CR	Non-CR/Non-PD	Any value	No	PR
CR	NE	Any value	No	PR
PR	Non-PD or NE	Any value	No	PR
SD	Non-PD or NE	Any value	No	SD
NE	Non-PD	Any value	No	NE
PD	Any	Any value	Yes or No	PD
Any	PD**	Any value	Yes or No	PD
Any	Any	Any value	Yes	PD

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Time Point Response for Patients with only Non-Measurable Disease at baseline (i.e., Non-Target Disease)

Non-Target Lesions	Biomarker CA-125	New Lesions*	Time Point Response
CR	Within normal limits	No	CR
CR	Above normal limits	No	Non-CR/non-PD*
Non-CR/non-PD	Any value	No	Non-CR/non-PD*
NE	Any value	No	NE
Unequivocal PD	Any value	Yes or No	PD
Any	Any value	Yes	PD

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion

** '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

8.135 Best Overall Confirmed Response

Confirmation of CR and PR for determination of best overall response is required for studies with a primary endpoint that includes response.

Confirmed CR and PR for best overall confirmed response

Time Point Response First time point	Time Point Response Subsequent time point	BEST overall confirmed response
CR	CR	CR
CR	PR	SD, PD or PR*
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

*If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR or SD, not CR at the first time point. Under these circumstances, the original CR should be changed to PR or SD and the best response is PR or SD.

In non-randomized trials where response is part of the primary endpoint, confirmation of CR or PR is needed to deem either one the "best overall response." **Responses (CR and PR) require confirmation at greater than or equal to 4 weeks from initial documentation.**

For this study, the minimum criteria for SD duration is 8 weeks.

Patients with a global deterioration of health status requiring discontinuation of treatment or die without objective evidence of disease progression at that time should be reported to be off study treatment due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

8.14 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 date of study entry, including the baseline measurements.

8.15 Progression-Free Survival

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

8.16 Survival

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

9.0 DURATION OF STUDY

9.1 Patients will receive therapy until disease progression or intolerable toxicity intervenes. 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, initiation of a subsequent cancer treatment or study withdrawal. Patients will then be followed 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 Q forms submitted to the GOG Statistical and Data Center, unless consent is withdrawn. Q forms will no longer be required if the study is terminated prior to the completion of the 5-year follow-up period.

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 Form D2R and adverse events on Form T until the patient qualifies as being off study therapy.

10.0 STUDY MONITORING & REPORTING PROCEDURE

10.1 ADVERSE EVENT REPORTING FOR AN INVESTIGATIONAL AGENT (CTEP IND)

10.11 Definition of Adverse Events (AE)

Adverse event (21 CFR 312.32(a)): Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov). The CTCAE v4.0 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 AdEERS reports 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 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP 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.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour 3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>7 Calendar Days</td></tr>
</table>

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; 3 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 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 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 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[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.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements:

- Reference the SPEER (Specific Protocol Exceptions to Expedited Report) for the subset of AEs that are protocol specific exceptions to expedited reporting via AdEERS. Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If the CAEPR for a protocol agent 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. For questions or comments regarding the SPEER or CAEPR, please contact the AdEERS MD Help Desk at adeersmd@tech-res.com.

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 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. **(07/09/2012)**

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.

10.2 GOG DATA MANAGEMENT FORMS

The following forms must be completed and submitted to the GOG Statistical and Data Center (SDC) in accordance with the schedule below. All forms except the BDR form, Pathology Report and BRCA Report(s) **must** be submitted via the SDC Electronic Data Entry System (SEDES) which is available through the GOG website (www.gogstats.org). The BDR Form should be submitted via mail. The GOG Uploader Application in SEDES is an alternate method for submitting pathology reports, BDR form and BRCA Report(s) to the GOG SDC.

Form	Due within		Copies *	Comments
	Weeks	Event		
Specimen Consent Application	1	Registration	N/A	Complete online
Form R (Registration Form)	2	Registration	1	Mandatory Submission via SEDES
Form OHR (Recurrent Gynecologic Cancer-On Study History Form)	2	Registration	1	Mandatory Submission via SEDES
Form DR (Pre-Treatment Summary Form)	4	Registration	1	Mandatory Submission via SEDES
Form BDR (Pre-Treatment Body Diagram Form)	4	Registration	2	Submit to SDC via postal mail or via report uploader in SEDES
Form D2M (Solid Tumor Evaluation Form)	4	Registration	1	Mandatory Submission via SEDES
Primary disease:** Pathology Report Recurrent or Persistent Disease:** Pathology Report (only if histologically documented)	 6 6	 Registration Registration	 1 1	Submit to SDC via postal mail or via report uploader in SEDES
Genetic Test Report (e.g., **BRC*Analysis*** Report [actual report is required])*** **(07/09/2012)**	6	Registration	2	Submit to SDC via postal mail or via report uploader in SEDES
BRC*Analysis* Rearrangement (BART) Report (actual report, if performed)*** **(07/09/2012)**	6	Registration	2	Submit to SDC via postal mail or via report uploader in SEDES
Form BMR (CA-125 reporting) (Biomarker Reporting Form)	2	Registration and completion of each cycle of therapy and disease assessment	1	Submit via SEDES
Form D2R (Cycle Dose Drug Form)	2	Completion of each cycle of therapy	1	Mandatory Submission via SEDES
Form D2M (Solid Tumor Evaluation Form)	2	Clinical response assessment	1	Mandatory Submission via SEDES
Form T (Common Toxicity	2	Beginning of each	1	Mandatory Submission

Reporting Form)		subsequent cycle		via SEDES
Form SP-FR01-0280 Pre-Rx FFPE Recurrent EOC, FT, PPC	8	Registration	N/A	Mandatory Submission via SEDES†
Form SP-FM01-0280 (optional) Pre-Rx FFPE Metastatic Tumor	8	Registration	N/A	Mandatory Submission via SEDES†
Form SP-FP01-0280 (optional) Pre-Rx FFPE Primary EOC, FT, PPC	8	Registration	N/A	Mandatory Submission via SEDES†
Form SP-RR01-0280 Pre-Rx Frozen Recurrent EOC, FT, PPC	2	Registration	N/A	Mandatory Submission via SEDES†
Form SP-RM01-0280 (optional) Pre-Rx Frozen Metastatic Tumor	2	Registration	N/A	Mandatory Submission via SEDES†
Form SP-RP01-0280 (optional) Pre-Rx Frozen Primary EOC, FT, PPC	2	Registration	N/A	Mandatory Submission via SEDES†
Form SP-SB01-0280 Pre-Rx Serum	2	Registration	N/A	Mandatory Submission via SEDES†
Form SP-WB01-0280 Whole Blood for DNA Extraction	32	Registration	N/A	Mandatory Submission via SEDES†
Form SP-FR02-0280 (optional) Post-Rx FFPE EOC, FT, PPC Biopsy or FNA	32	Registration	N/A	Mandatory Submission via SEDES†
Form SP-PF01-0280 (optional) Post-Rx FFPE Cell Pellet from Peritoneal Fluid	32	Registration	N/A	Mandatory Submission via SEDES†
Form Q0 (Treatment Completion Form)	2	Completion of study Rx and change in Rx	1	Mandatory Submission via SEDES
Form Q (Follow-up Form)	2	Disease progression; death; normal follow-up	1	Mandatory Submission via SEDES quarterly for 2 years, semi-annually for 3 more years

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

** **Pathology slides for Central Pathology Committee Review are not required on this study.**

*** Patients enrolled on this trial are required to have a known germline mutation in BRCA1 or BRCA2. Submission of the reports detailing this testing is required. The following is the usual method for BRCA testing: If the patient is of Ashkenazi Jewish/Eastern European Jewish descent, testing begins with Multisite3 BRCAnalysis, continuing on to ("Reflex to") Comprehensive BRCAnalysis if negative. Testing of non-Ashkenazi patients starts with Comprehensive BRCAnalysis. Patients who are negative for the above testing can have BRCAnalysis Rearrangement Testing (BART). Genetic counseling is strongly recommended before and after BRCA1/2 testing.

† Form SP must be submitted regardless of whether the specimen is submitted for research.

This study will be monitored by the Complete Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

11.0 STATISTICAL CONSIDERATIONS

The primary objective of this study is to assess the efficacy of the study agent in patients with recurrent or persistent ovarian, fallopian tube, or primary peritoneal cancer who carry a germline BRCA1 or BRCA2 mutation. The primary measures of efficacy will be objective response.

11.1 This is a Phase II study and no randomization is involved, however, patient registration will be accomplished in the usual fashion.

11.11 Primary Endpoints:

11.111 The frequency of patients who have objective tumor response.

11.112 Frequency and severity of adverse effects as assessed by CTCAE v4.0.

11.12 Secondary Endpoints:

11.121 Duration of progression-free survival and overall survival.

11.122 The proportion of patients who survive progression-free for at least 6 months.

11.13 Translational Research and Exploratory Endpoints:

11.131 SNPs with DNA repair genes, tumor response, PFS, OS, and patient demographics (e.g. age, race, tumor grade).

11.132 BRCA mutation in primary tumor tissue.

11.2 The anticipated annual accrual is 50 patients.

11.21 The anticipated period of active accrual for the first stage is 5.5 months.

11.22 The anticipated period of active accrual for the second stage is 6.0 months.

11.3 The study plan is a single arm, 2-stage phase II clinical trial.

End point and design selection
The agent studied in this particular protocol is expected to reduce tumor burden, producing objective responses.

The guiding principle in selecting the design for this study is to limit the number of patients treated with clinically ineffective therapies; yet tend to estimate efficacy with reasonable precision for those agents that are clinically active. Strict adherence to a two-stage sampling design with 'optimal' early stopping rules is not practical because the accrual is complicated by the logistics of managing a multi-center phase II study. Instead, flexible stopping rules are used that tend to maximize the probability of

rejecting the treatment when the agent is indeed not active. When the targeted sample size is attained, those patients who have already been approached will be permitted to register.

Historical Data and Design Parameters
There is not a substantial historical control available that examines the proportion of patients responding or PFS who have germline BRCA1 or BRCA2 mutations. Audeh et al.[2] studied a PARP inhibitor, olaparib, in a phase II study with recurrent ovarian cancer patients at two dose levels: 100 mg BID and 400 mg BID. The first cohort of 33 patients enrolled on the study evaluated the dose at 400 mg. Another cohort of 24 patients was enrolled at the 100 mg dose. 11 of 33 (33%; 95% CI 20-51%) evaluable patients responded to the drug at the 400 mg dose whereas 3 of 24 (13%; 95% CI 4-31%) responded to the 100 mg dose. Approximately 15 of 33 (45%) patients remained progression-free at 6 months with the 400 mg dose, and 5 of 24 (21%) remained progression-free at 6 months with the 100 mg dose. Another internal ancillary study of patients with high grade serous cancer, which are believed to have a higher proportion of patients with BRCA mutations, concluded that the proportion of patients responding or PFS at 6 months was approximately the same as the general ovarian cancer population (at least for inactive agents). Based on this data, we propose the following null hypothesis for uninteresting activity:

H_0: $\pi_r \leq 0.10$

To evaluate this hypothesis in a two-stage design, a method provided by Chen and Ng will be used to decide whether there are sufficient numbers of patients with objective responses to continue study in a second stage (at the interim analysis) or deem the drug worthy of further investigation in a randomized study (at the end of stage 2).[17] In particular, the following decision rule will be applied where $X_{r(1)}$ is the number of patients with objective tumor responses (partial or complete) after the first stage, X_r is the cumulative number of patients with responses after stage 2, $C_{r(1)}$ is the critical value for $X_{r(1)}$, and C_r is the critical value for X_r:

Decision Rule: If $X_{r(1)} > C_{r(1)}$ after the first stage, then the study will open to a second stage of accrual to further evaluate the activity of the drug. If $X_r > C_r$ after the second stage and clinical judgment indicates, then the agent will be deemed clinically interesting and worthy of further investigation.

The targeted accrual for the first stage will be 23 eligible and evaluable patients but permitted to range from 19 to 26 for administrative reasons. The cumulative targeted accrual for the second stage will be 48 eligible and evaluable patients but permitted to range from 44 to 51 for administrative reasons. Critical values for each stage are provided below:

Table 11.1: Critical values for the number of patients with objective responses.

Stage 1								
$n(1)^*$	19	20	21	22	23	24	25	26
$C_{r(1)}$	2	2	2	2	2	2	2	3

* n(1) is the sample size for the first stage of accrual.

Table 11.2: Critical values for the number of patients with objective responses.

Stage 2								
n*	44	45	46	47	48	49	50	51
C_r	6	6	7	7	7	7	7	7

* n is the cumulative sample size after the second stage of accrual.

This study has 10% alpha and 90% power when the probability of response is 25%.

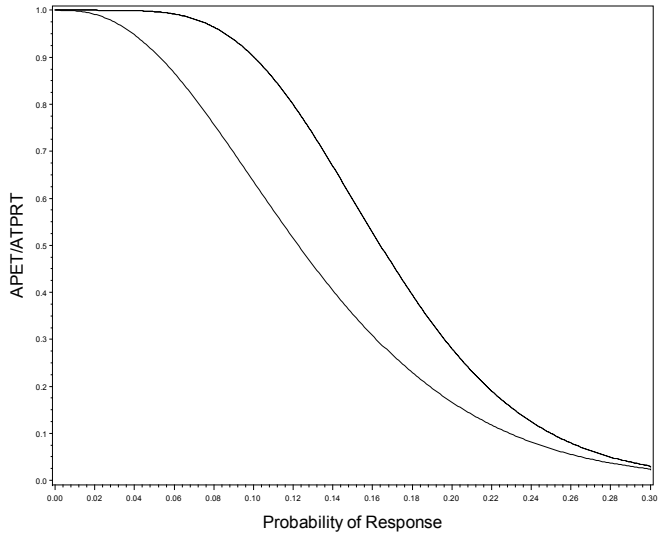


Figure 11.1: Average Probability of Early Termination (APET; solid line) and Average Total Probability of Rejecting the Treatment (ATPRT; dashed line) as a function of the true probability of response.

11.4 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 "indeterminate". This category will be listed and be reflected in the calculation of the response rate or proportion surviving progression-free for at least 6 months.

11.5 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 Safety Review Committee (SRC) 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) 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 SRC. However, patients currently receiving treatment may continue to receive treatment in accordance protocol guidelines at the discretion of their physicians, unless directed otherwise.

11.6 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.

If the clinical trial goes to the second stage and there is sufficient variability in the SNPs, then patients can be categorized by the nature of their SNPs and assessed for prognostic value through survival analysis (e.g. log-rank tests and Cox proportional hazards modeling). These analyses will be conducted as hypothesis generating rather than hypothesis testing. If the variability in SNPs is relatively low, assessment of prognostic value can be conducted with odds ratios of patients responding or surviving progression-free for at least 6 months. These techniques will use exact methods such as Fisher's Exact Test. In addition, associations with demographic characteristics, for example race, cell type, and tumor grade, will be examined with methods that use categorical data (e.g. exact Chi-square tests), and tables may be provided for those associations deemed interesting.

BRCA mutational status will be tabulated against the germline mutation to see what proportion of patients have a mutation reversal within the tumor and whether such reversals can explain resistance to the regimen under study.

11.7 Accrual Targets

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	0	+		=	0
Not Hispanic or Latino	51	+		=	51
Ethnic Category: Total of all subjects	51	+		=	51
Racial Category					
American Indian or Alaskan Native	0	+		=	0
Asian	1	+		=	1
Black or African American	2	+		=	2
Native Hawaiian or other Pacific Islander	0	+		=	0
White	48	+		=	48
Racial Category: Total of all subjects	51	+		=	51

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APPENDIX I

NCI/ DCTD Standard Language to Be Incorporated into All Protocols Involving Agent(s) Covered by a Clinical Trials Agreement (CTA) a Cooperative Research and Development Agreement (CRADA)or a Clinical Supply Agreement, hereinafter referred to as Collaborative Agreement:

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) ontained 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 - GOG General Chemotherapy Guidelines

- For 21 or 28 day cycles, a patient will be permitted to have a new cycle of chemotherapy 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 chemotherapy 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 chemotherapy doses to be delivered within a "24-hour window," for example; "Day 8 chemotherapy" can be delivered on Day 7, Day 8, or Day 9 and "Day 15 chemotherapy" can be given on Day 14, Day 15, or Day 16.
- Chemotherapy 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).
- Chemotherapy 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 <10% weight changes.

APPENDIX III - PATIENT PILL CALENDAR

Patient Name: _________________________ Month/Date of first dose on calendar: ____________________
Patient Study ID______________________________ Visit Log is returned at: each visit

This is a calendar on which you are to record the number of pills you take each day for 4 weeks. You will get a new calendar for each 4-week cycle.

- You should take your dose of Veliparib two times a day, about the same time every day.
- The doses should be taken about 12 hours apart.
- If you are more than 4 hours late in taking a dose, the dose should be skipped.
- Pills may be taken with or without food, please swallow pills with about 8 ounces of water.
- If you develop any side effects, please record side effects, the day they occurred and anything else you would like to tell the doctor in the space provided below the calendar.
- If you are more than 4 hours late in taking a dose, the dose should be skipped. Call your doctor's office if you do not know what to do.
- Bring any unused pills, pill bottles and your completed calendar to your next appointment.
- Please record the date drug was taken in each box.

Date: AM Time ___ # of pills ___ PM Time ___ # of pills ___	Date: AM Time ___ # of pills ___ PM Time ___ # of pills ___	Date: AM Time ___ # of pills ___ PM Time ___ # of pills ___	Date: AM Time ___ # of pills ___ PM Time ___ # of pills ___	Date: AM Time ___ # of pills ___ PM Time ___ # of pills ___	Date: AM Time ___ # of pills ___ PM Time ___ # of pills ___	Date: AM Time ___ # of pills ___ PM Time ___ # of pills ___
Date: AM Time ___ # of pills ___ PM Time ___ # of pills ___	Date: AM Time ___ # of pills ___ PM Time ___ # of pills ___	Date: AM Time ___ # of pills ___ PM Time ___ # of pills ___	Date: AM Time ___ # of pills ___ PM Time ___ # of pills ___	Date: AM Time ___ # of pills ___ PM Time ___ # of pills ___	Date: AM Time ___ # of pills ___ PM Time ___ # of pills ___	Date: AM Time ___ # of pills ___ PM Time ___ # of pills ___
Date: AM Time	Date: AM Time	Date: AM Time	Date: AM Time	Date: AM Time	Date: AM Time	Date: AM Time

___ # of pills ___ PM Time ___ # of pills ___	___ # of pills ___ PM Time ___ # of pills ___	___ # of pills ___ PM Time ___ # of pills ___	___ # of pills ___ PM Time ___ # of pills ___	___ # of pills ___ PM Time ___ # of pills ___	___ # of pills ___ PM Time ___ # of pills ___	___ # of pills ___ PM Time ___ # of pills ___
Date: AM Time ___ # of pills ___ PM Time ___ # of pills ___	Date: AM Time ___ # of pills ___ PM Time ___ # of pills ___	Date: AM Time ___ # of pills ___ PM Time ___ # of pills ___	Date: AM Time ___ # of pills ___ PM Time ___ # of pills ___	Date: AM Time ___ # of pills ___ PM Time ___ # of pills ___	Date: AM Time ___ # of pills ___ PM Time ___ # of pills ___	Date: AM Time ___ # of pills ___ PM Time ___ # of pills ___

Side effects:

_____

_____

_____

_____

_____

SIGNATURE OF PATIENT DATE

Note to staff: Please give patient a drug log at initial enrollment and prior to each cycle.

Appendix IV - Specimen Procedures

Specimen Procedures

I. Summary of Specimen Requirements

Required Specimen (Specimen Code)	Collection Time Point	Ship To
Pre-Treatment FFPE Recurrent Tumor (FR01) 1st Choice: Block 2nd Choice: Unstained Slides (10 5µm charged + 10 10µm uncharged)	Prior to Veliparib treatment	GOG Tissue Bank within 8 weeks of registration[1]
Pre-Treatment FFPE Metastatic Tumor (FM01) 1st Choice: Block 2nd Choice: Unstained Slides (10 5µm charged + 10 10µm uncharged)	Prior to Veliparib treatment (may be archival pre-treatment) *If FR01or FP01 cannot be submitted*	GOG Tissue Bank within 8 weeks of registration[1]
Pre-Treatment FFPE Primary Tumor (FP01) 1st Choice: Block 2nd Choice: Unstained Slides (10 5µm charged + 10 10µm uncharged)	Archival pre-treatment *If FR01 or FM01 cannot be submitted*	GOG Tissue Bank within 8 weeks of registration[1]
Pre-Treatment Frozen Recurrent Tumor (RR01) 1st Choice: Snap Frozen 2nd Choice: OCT Embedded	Prior to Veliparib treatment	GOG Tissue Bank within 2 weeks of registration[1]
Pre-Treatment Frozen Metastatic Tumor (RM01) 1st Choice: Snap Frozen 2nd Choice: OCT Embedded	Prior to Veliparib treatment (may be archival pre-treatment) *If RR01or RP01 cannot be submitted*	GOG Tissue Bank within 2 weeks of registration[1]
Pre-Treatment Frozen Primary Tumor (RP01) 1st Choice: Snap Frozen 2nd Choice: OCT Embedded	Archival pre-treatment *If RR01 or RM01 cannot be submitted*	GOG Tissue Bank within 2 weeks of registration[1]
Pre-Treatment Serum (SB01) prepared from 7-10mL blood drawn into a plain red top tube	Prior to Veliparib treatment	GOG Tissue Bank within 2 weeks of registration[1]
Whole Blood (WB01) 7-10mL drawn into purple top (EDTA) tube(s)	Prior to or after initiating Veliparib treatment	GOG Tissue Bank the day the blood is collected[1]
Post-Treatment FFPE Biopsy	Optional - Post-treatment, if	GOG Tissue Bank within 32

or FNA (FR02) 1st Choice: Block 2nd Choice: Unstained Slides (10 5µm charged ; 10 10µm uncharged, if possible)	patient has biopsy or FNA at time of progression	weeks of registration[1]
Post-Treatment FFPE Cell Pellet from Peritoneal Fluid (PF01) 1st Choice: Block 2nd Choice: Unstained Slides (10 5µm charged ; 10 10µm uncharged, if possible)	Optional - Post-treatment at time of progression *If FR02 cannot be submitted*	GOG Tissue Bank within 32 weeks of registration[1]

1 GOG Tissue Bank / Protocol GOG-0280, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: GOGBanc@nationwidechildrens.org

II. Obtaining a GOG Bank ID

Only one GOG Bank ID (# # # # - # # - G # # #) is assigned per patient. All specimens and accompanying paperwork must be labeled with this coded and confidential tracking 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 study ID for all protocols with specimen requirements before requesting a GOG Bank ID from the Tissue Bank Portal.

Please contact the User Support Department at the GOG Statistical and Data Center at support@gogstats.org or by phoning 716-845-7767 if you need assistance.

III. Requesting Specimen Kits

A. Ordering Specimen Kits

Specimen kits may be ordered online via the Kit Management link on the GOG website (under Data Entry on the Web Menu page).

Please contact the GOG Tissue Bank at GOGBank@nationwidechildrens.org or by phoning 866-GOG-BANC (866-464-2262) if you need assistance.

Please plan ahead to allow time for kits to be shipped by ground transportation.

B. Materials Provided in the Specimen Kits

One specimen kit will be provided per patient for the collection and shipment of frozen specimens. Each kit will consist of:

- single-chamber shipping container
- five cryovials
- one transfer pipettes

- one 15mL conical tubes
- one piece of foil
- one secondary shipping envelope(s) with absorbent material
- one Tyvek envelope(s)
- Dry ice label (UN1845)
- Exempt Human Specimen sticker

If there are supplies needed to satisfy the specimen requirements that are not provided in the kit (and are not available at your site), please contact the GOG Tissue Bank.

C. Unused Materials and Specimen Kits

Unused materials and specimen kits should be returned to the GOG Tissue Bank. Contact the bank if you have any questions about the return of unused materials.

IV. Submitting Formalin-Fixed, Paraffin-Embedded Tumor

A. Requirement

If the patient gives permission for her tumor specimens to be used for this optional translational research component, then the participating institution is required to submit specimens as outlined in Section I.

Every attempt should be made to provide FFPE blocks.

If tumor blocks cannot be provided, please provide unstained slides – 10 5µm charged and 10 10µm uncharged.

If FFPE biopsy or FNA blocks cannot be provided, please provide unstained slides - at least 10 5µm charged; if possible, also provide 10 10µm uncharged.

The type of specimen (block or slides) should be specified on Form SP.

B. Purpose

DNA extracted from FFPE tumor will be used for genomic analysis.

C. Time Points

Pre-treatment FFPE tumor should be collected prior to Veliparib treatment.

Recurrent tumor is the preferred specimen. If recurrent tumor cannot be submitted, submit metastatic tumor collected prior to Veliparib treatment (or archival metastatic tumor). If recurrent or metastatic tumor cannot be submitted, submit archival, pre-treatment primary tumor.

Post-treatment FFPE biopsy or FNA should be collected post-Veliparib treatment, if the patient has a biopsy or FNA at the time of progression.

D. Format for Labeling the Specimen

Label the specimen with the GOG protocol number (GOG-0280), GOG Bank ID (# # # # - # # - G # # #), specimen code (FP01 for primary, FM01 for metastatic, FR01 for recurrent, FR02 for post-treatment biopsy or FNA), and collection date (mm/dd/yyyy).

V. Submitting Frozen Tumor

A. Requirement

If the patient gives permission for her tumor specimens to be used for this optional translational research component, then the participating institution is required to submit specimens as outlined in Section I.

Please submit at least 0.2 grams of frozen tissue.

Every attempt should be made to provide snap frozen tissue; however, if snap frozen tissue cannot be provided, frozen tissue may be OCT-embedded.

The type of specimen (snap frozen or OCT-embedded) should be specified on Form SP.

B. Purpose

DNA extracted from frozen tumor will be used for genomic analysis.

C. Time Points

Pre-treatment frozen tumor should be collected prior to Veliparib treatment.

Recurrent tumor is the preferred specimen. If recurrent tumor cannot be submitted, submit metastatic tumor collected prior to Veliparib treatment (or archival metastatic tumor). If recurrent or metastatic tumor cannot be submitted, submit archival, pre-treatment primary tumor.

D. Format for Labeling the Specimen

Label the specimen with the GOG protocol number (GOG-0280), GOG Bank ID (# # # # - # # - G # # #), specimen code (RP01 for primary, RM01 for metastatic, RR01 for recurrent), and collection date (mm/dd/yyyy).

VI. Submitting Serum

A. Requirement

If the patient gives permission for her blood specimens to be used for this optional translational research component, then the participating institution is required to submit specimens as outlined in Section I.

B. Purpose

Pre-treatment serum will be banked for future research.

C. Time Points

Serum should be collected at prior to Veliparib treatment.

D. Format for Labeling the Specimen

Label the specimen with the GOG protocol number (GOG-0280), GOG Bank ID (# # # # - # # - G # # #), specimen code (SB01), and collection date (mm/dd/yyyy).

E. Instructions for Preparing the Specimen

1. Label five screw-cap cryotubes as described above.

2. Draw 7-10mL of blood into plain red top tube(s).

3. Allow the blood to clot at room temperature for at least 30 minutes*.

   **If the clotted blood cannot be centrifuged immediately, it can be stored at 4°C (or in a bucket with ice) for up to 3 hours.*

4. Centrifuge the clotted blood to separate the serum (transparent, straw colored liquid) from the fibrin clot and blood cells.

   When the appropriate equipment is available, centrifuge blood at 3500g at 4°C for 10 minutes. Blood must be centrifuged at a minimum of 1000g at room temperature for 15 minutes* (the longer centrifugation time will help compensate for the slower speed).

   **Avoid centrifugation without refrigeration longer than 15 minutes as excess heat may damage the serum.*

5. Transfer the serum into a 15mL conical tube and gently mix. Quickly, evenly dispense (aliquot) the serum into the pre-labeled cryotubes and cap the tubes securely.

6. Immediately freeze the serum in an upright position using an appropriate freezing/storage space (i.e., ultra cold ≤-70^{o}C freezer, liquid nitrogen, or direct exposure with dry ice). Frozen serum specimens should be stored in an ultra cold freezing/storage space until the specimens can be shipped.

VII. Submitting Whole Blood

A. Requirement

If the patient gives permission for her blood specimens to be used for this optional translational research component, then the participating institution is required to submit specimens as outlined in Section I.

B. Purpose

DNA extracted from whole blood will be used for genomic analysis.

C. Time Points

Whole blood can be collected at any time prior to or after initiating Veliparib treatment.

D. Format for Labeling the Specimen

Label the specimen with the GOG protocol number (GOG-0280), GOG Bank ID (# # # # - # # - G # # #), specimen code (WB01), and collection date (mm/dd/yyyy).

E. Instructions for Preparing the Specimen

1. Label the purple top whole blood collection tube(s) (containing EDTA) as described above.

2. Draw 7-10mL of blood into the labeled purple top tube(s).

3. Mix the blood with the EDTA by gently inverting the tube 5-10 times.

4. Ship the whole blood specimen to GOG Tissue Bank the day the specimen is collected*. Whole blood specimens should be stored at room temperature until the specimens can be shipped.

   ** If the whole blood absolutely cannot be shipped the day it is collected, the tube may be placed in the refrigerator overnight. Please note that the blood was refrigerated overnight in the comment box on Form SP (item 15).*

VIII. Submitting Formalin-Fixed, Paraffin-Embedded Cell Pellet from Peritoneal Fluid

A. Requirement

If the patient gives permission for her peritoneal specimens to be used for this optional translational research component, then the participating institution is required to submit specimens as outlined in Section I.

Every attempt should be made to provide FFPE cell pellet blocks.

If blocks cannot be provided, please provide unstained slides - at least 10 5µm charged; if possible, also provide 10 10µm uncharged.

The type of specimen (block or slides) should be specified on Form SP.

B. Purpose

DNA extracted from FFPE cell pellets will be used for genomic analysis.

C. Time Points

Post-treatment FFPE cell pellets from peritoneal fluid should be collected post-Veliparib treatment at the time of progression, if a biopsy or FNA is not collected.

D. Format for Labeling the Specimen
Label the specimen with the GOG protocol number (GOG-0280), GOG Bank ID (# # # # - # # - G # # #), specimen code (PF01), and collection date (mm/dd/yyyy).

IX. Submitting Form SP

A. Form SP Requirements

Form SP must be completed and submitted online to the GOG Statistical and Data Center (SDC) using the SDC Electronic Data Entry System (SEDES). Form SP must be submitted for each specimen required for the protocol regardless of the specimen submission status. Specific instructions for completing Form SP are available via SEDES by scrolling down to the SP Forms for the specific protocol.

B. Instructions for Submitting Form SP Online

Form SP must be submitted online using SEDES which is available on the GOG Web Menu under *Registration/Data Entry*. A copy of the completed form must also accompany each specimen shipped to the GOG Tissue Bank. Retain a printout of the completed form for your records. Form SP does not need to be sent to the GOG Tissue Bank when specimens are not collected.

To access Form SP for online submission, log onto the GOG Web Menu and use SEDES to electronically enter Form SP data. Any questions about access or problems should be directed to the User Support Department at the GOG Statistical and Data Center at support@gogstats.org or by phoning 716-845-7767.

X. Shipping Specimens

A. FFPE

FFPE specimens should be shipped using your own container at your own expense to:

GOG Tissue Bank / Protocol GOG-0280

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

B. Whole Blood

All whole blood specimens should be shipped to the GOG Tissue Bank using your own container and a pre-paid FedEx shipping label:

GOG Tissue Bank / Protocol GOG-0280
Nationwide Children's Hospital
700 Children's Dr, WA1340
Columbus, OH 43205
Phone: (614) 722-2865
FAX: (614) 722-2897
Email: GOGBank@nationwidechildrens.org

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, please put 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).

Instructions for 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 contained (e.g., cardboard FedEx box).

5. Insert a copy of the SP Form(s) into the box.

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.

C. Frozen Serum and Tumor

Frozen specimens can be shipped to the GOG Tissue Bank using the kit provided. Ship frozen specimens Monday through Thursday for Tuesday through Friday delivery. Please do not ship frozen specimens on Fridays or the day before a holiday.

Instructions for Shipping Frozen Specimens Using a Specimen Kit

1. Pre-fill the specimen kit about 1/3 full with dry ice.

2. Place each frozen specimen in a separate zip-lock bag.

3. Put the zip-lock bags in the biohazard envelope containing absorbent material. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible before sealing all envelopes.

4. Place the Tyvek envelope containing the frozen specimens into the kit and fill the chamber to the top with dry ice.

5. Insert the SP Forms.

6. Place the styrofoam cover on top of the kit. Tape the outer box of the kit closed with filament or other durable sealing tape. Please do not tape the inner (styrofoam) chamber.

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. Attach the dry ice label (UN1845) and the Exempt Human Specimen sticker.

9. Arrange for FedEx pick-up through your usual Institutional procedure or by calling 800-238-5355.

XI. Distributing Specimens for Laboratory Testing

The GOG SDC and Tissue Bank (or alternate laboratory) will coordinate the distribution of specimens to approved investigators for laboratory testing. Specimen selection will be based on information regarding specimen procurement and condition as well as patient eligibility, evaluation criteria, statistical considerations, and relevant clinical information.

For each shipment, bank staff will provide the investigator and the SDC an electronic file that includes an inventory of all specimens included in the shipment.

The SDC will provide the investigator an electronic file containing the specimen identifiers with relevant information regarding specimen condition, suitability for testing, eligibility/evaluability for a given component of the research study, and fields for the laboratory data. Investigators will not be given access to any personal identifiers.

Investigators will be responsible for the direct supervision and oversight of the laboratory testing performed and for keeping accurate records of all specimen testing.

Investigators will ensure that the laboratory testing results are linked to the appropriate specimen-specific identifiers and are responsible for transferring relevant laboratory data to the SDC.

A. FFPE

Unstained sections of FFPE will be batch shipped to:

Dr. Michael Birrer
Massachusetts General Hospital
Yawkey 9072
55 Fruit St.
Boston, MA 02114
Phone: 617-726-8624
Fax: 617-724-6898
Email: mbirrer@partners.org

B. Whole Blood

DNA extracted from whole blood will be batch shipped to:

Dr. Michael Birrer
Massachusetts General Hospital
Yawkey 9072
55 Fruit St.
Boston, MA 02114

Phone: 617-726-8624
Fax: 617-724-6898
Email: mbirrer@partners.org

C. Frozen Tumor

Frozen tumor will be batch shipped to:

Dr. Michael Birrer
Massachusetts General Hospital
Yawkey 9072
55 Fruit St.
Boston, MA 02114
Phone: 617-726-8624
Fax: 617-724-6898
Email: mbirrer@partners.org

XII. Banking Specimens for Future Research

Specimens will remain banked in the GOG Tissue Bank and made available for approved cancer and/or non-cancer research projects if the patient in question has provided permission for the use of her specimens for future cancer and/or non-cancer research. The patient's choices will be recorded on the informed consent document the patient signs and electronically via the online Specimen Consent Application.

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 does not give permission for the use of her specimens, the GOG Tissue Bank will be instructed to destroy (incinerate) any remaining specimens to insure that the patient's wishes are honored.