SWOG CANCER RESEARCH NETWORK

Version Date: August 07, 2024

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office (E-mail: protocols@swog.org)

RE: S1416: "Phase II Randomized Placebo-Controlled Trial of Cisplatin with or Without ABT-888 (Veliparib) in Metastatic Triple-Negative Breast Cancer and/or BRCA Mutation-Associated Breast Cancer, with or Without Brain Metastases" Study Chairs: Drs. E. Rodler, P. Sharma, J.R. Gralow, J.B. Hicks and P. Kuhn.

REVISION #8

Study Chair: Eve Rodler, M.D.
Phone number: 916/734-3772
E-mail: S1416question@swog.org

Action Codes
(✓) Expedited review allowed
(✓) Patients Must be Informed*
(✓) Verbal notification allowed
* See "Patient Notification" and "Regulatory Considerations" instructions below.

Key Updates
(✓) Treatment / Study Calendar changes

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice.

REVISION #8

The above-referenced protocol has been revised to accommodate the discontinuation of the ABT-888 (veliparib) development program and the associated study drug supply. This amendment is in response to Dr. Ivy's April 26, 2023, request for amendment.

All participating sites, where patients are currently receiving ABT-888 (veliparib) treatment, will receive this information through both the "Investigator Letter" and the "Participant Information Letter."

Protocol Changes

The above-referenced protocol has been updated as follows:

1. Formatting, typographical errors, and section links were updated throughout the protocol.

2. The version date and table of contents has been updated.

3. **Section 3.0:** A note has been included specifying the expiration dates for the existing unblinded ABT-888 (veliparib) supplies and the end of treatment date.

4. **Section 3.1d and 7.2:** A note has been included to provide the rationale for unblinding the last

patient on treatment and to provide additional guidance.

5. **Section 7.4c:** A subsection has been inserted to provide additional guidance for the remaining patient on treatment.

6. **Section 9.0:** Footnote "**" has been updated to reflect patient visits and scans after the five (5) year follow-up time frame is at the discretion of the physician.

Model Consent Form Changes

The Model Consent Form has been updated as follows:

1. The version date has been updated.

2. "How long will I be in this study?": A note has been inserted regarding the discontinuation of the ABT-888 (veliparib) development program.

Investigator and Patient Letter

The Investigator and Patient Letter has been included due to the following:

1. The letters have been provided to explain the rationale for unblinding the last patient on treatment and to provide additional guidance.

Patient Notification:

Please note that the information provided below regarding patient notification and amendments to local consent forms reflects SWOG's minimum requirements. Sites should refer to the policies/procedures of the IRB of record to determine whether they have any more stringent requirements.

SWOG has determined that the changes above may affect a patient's willingness to participate in the study; therefore, SWOG requires that patients be notified of these changes.

Who must be informed?
- All patients currently on study treatment with ABT-888 (veliparib).

How must patients be notified?
- For patients currently receiving ABT-888 (veliparib): Notification must take place via distribution of the patient letter or verbally by the next study visit.

What is the notification deadline and process?
- For patients currently receiving treatment with ABT-888 (veliparib): It is recommended that the patient be notified as soon as possible to make the determination of whether to continue treatment.

Regulatory Considerations:

Do local consent forms need to be updated?
- It depends. If your site will utilize the updated consent form for notification and formal reconsent then local consent forms must be updated. If your site will not utilize updated consent form for notification and formal reconsent then local consent forms need not be updated.

The updated protocol, model informed consent form, and patient letter can be accessed from the CTSU website (www.ctsu.org). Please discard any previous versions of the documents and replace with the updated versions.

This study has been reviewed and approved by the NCI's Central Institutional Review Board (CIRB). This memorandum serves to notify the NCI, and SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Elizabeth Swisher, M.D. – King/Swisher Laboratory
Ruu Hsu – Kuhn-Hicks Laboratory
Katie Von Derau – WPC

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

Activation Date July 7, 2016

SWOG CANCER RESEARCH NETWORK

PHASE II RANDOMIZED PLACEBO-CONTROLLED TRIAL OF CISPLATIN WITH OR WITHOUT ABT-888 (VELIPARIB) IN METASTATIC TRIPLE-NEGATIVE BREAST CANCER AND/OR BRCA MUTATION-ASSOCIATED BREAST CANCER, WITH OR WITHOUT BRAIN METASTASES

NCT #02595905

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AGENTS:

NCI Supplied Investigational Agent:
ABT-888 (veliparib)/placebo (NSC 737664;
)
IND-Exempt Agent:
Cisplatin (CDDP) (Platinol®, Platinol-AQ)
(NSC-119875)

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NRG/NRG Oncology
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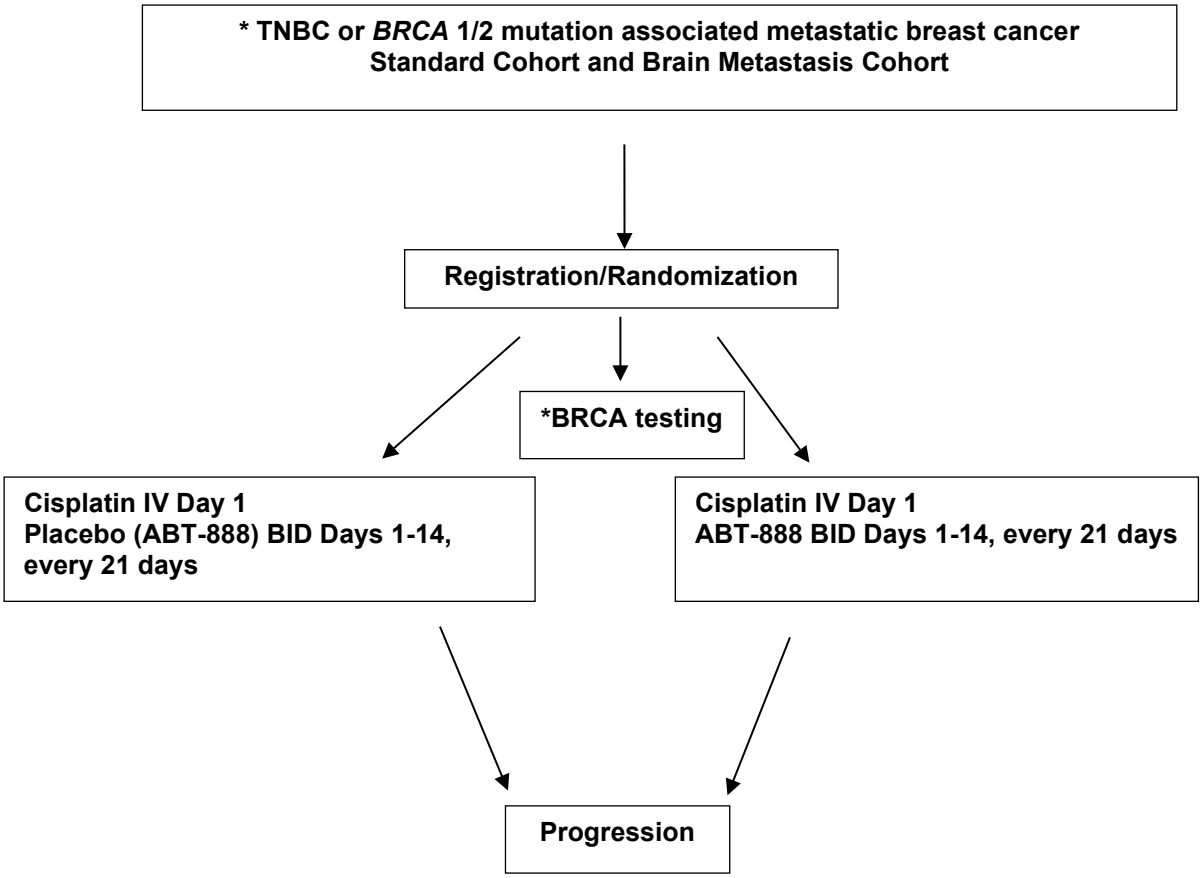
S1416 PROTOCOL CONTACT INFORMATION

Patient Advocate	Ginny Mason, R.N., B.S.N. via Email: masonvirginia@msn.com Elda Railey via Email: erailey@researchadvocacy.org
Eligibility, RAVE, Data Submission:	SWOG Statistics and Data Management Center E-mail: breastquestion@crab.org or Phone: 206/652-2267
Medical Queries (treatment or toxicity related questions):	Email: S1416question@swog.org
Translational Medicine questions:	Email: S1416question@swog.org
Investigational Drug questions:	See Protocol Section 3.0 or PMBAfterHours@mail.nih.gov
Requests for Investigator's Brochures:	See Protocol Section 3.0 or http://ctep.cancer.gov/branches/pmb/agent_order_processing.htm
Access issues for the PMB Online Agent Ordering Processing (OAOP) application:	IBCoordinator@mail.nih.gov
Specimen Tracking System (STS) Amendments, Errors, Connectivity Issues and Technical issues with the SWOG CRA Workbench:	technicalquestion@crab.org
Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM):	To review CTEP-IAM account (new requests, reset passwords): https://ctepcore.nci.nih.gov/iam/index.jsp
Access to iMedidata Rave:	See Protocol Section 14.3 or contact CTSU Help Desk: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
Questions related to: Oncology Patient Enrollment Network (OPEN)	See Protocol Section 13.3 or contact CTSU Help Desk: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
Participant Transfers:	patienttransfer@crab.org
Serious Adverse Event Reporting questions:	See Protocol Section 16.1 Email: adr@swog.org
Regulatory, Protocol, Informed Consent:	SWOG Operations Office E-mail: protocols@swog.org or Phone: 210/614-8808

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	For patient enrollments:	For data submission:
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 866-651-2878 to receive further information and support. Contact the CTSU Regulatory Help Desk at 866-651-2878 for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN related questions by phone or email : 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password.		
For clinical questions (i.e. patient eligibility or treatment-related) contact the SWOG Statistics and Data Management Center by phone or email: 206-652-2267 breastquestion@crab.org **For treatment or toxicity related questions** contact the Study PI of the Coordinating Group at S1416question@swog.org.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or email: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

SCHEMA



* **All patients will have specimens submitted for germline *BRCA* testing (BROCA-HR) after randomization and before beginning protocol treatment. Patients will be assigned to the appropriate groups for analysis based on germline *BRCA* status.**
- **BRCA testing results provided to the enrolling site via Rave® in 4-8 weeks.**
- **Genetic counseling services available for sites if needed (provided by Dr. Swisher, Appendix 18.5)**

Treatment assignment at randomization is not affected by this classification. Treatment may begin before results are received.

1.0 OBJECTIVES

1.1 Primary Objectives

a. To compare the efficacy of cisplatin with or without ABT-888 (veliparib) on progression-free survival (PFS) in each of the following groups:

1. Patients with germline *BRCA* (*gBRCA*) mutation-associated breast cancer

2. Patients with germline *BRCA* wild-type breast cancer who have evidence of BRCAness phenotype

3. Patients with germline *BRCA* wild-type breast cancer who do not have evidence of BRCAness phenotype.

b. Brain Metastases Cohort: To compare the efficacy of cisplatin with or without ABT-888 on PFS in patients with triple negative and/or gBRCA mutation-associated breast cancer and brain metastases.

1.2 Secondary Objectives

a. For patients with *gBRCA* mutation associated breast cancer (group “i” above) or TNBC with (group “ii”) or without (group “iii”) BRCAness phenotype, to compare the efficacy of cisplatin with or without ABT-888 on overall survival (OS), response rate, and clinical benefit rate.

b. To compare the differential benefit of ABT-888 across the three groups using both PFS and OS as outcomes.

c. For patients in the brain metastases cohort, to compare the efficacy of cisplatin with or without ABT-888 on OS.

d. For patients in the brain metastases cohort, to compare the efficacy of cisplatin with or without ABT-888 on intracranial and extracranial response rates (intracranial by RANO and extracranial by RECIST 1.1).

e. To compare toxicities of ABT-888 to placebo in each of the four groups separately.

1.3 Translational Objectives (see Appendix 18.5)

a. To evaluate the impact of Homologous Recombination Deficiency score (independent of other BRCAness markers) on response rate (RR) and PFS in patients treated with chemotherapy versus chemotherapy plus ABT-888.

b. To evaluate the overlap among various markers utilized to define the BRCAness phenotype.

c. To evaluate the combined impact of PAM50 basal subtype and BRCAness phenotype on RR and PFS in patients treated with chemotherapy versus chemotherapy plus ABT-888.

d. To evaluate the impact of BRCA1 mRNA expression (independent of other BRCAness markers) on response rate (RR) and PFS in patients treated with chemotherapy versus chemotherapy plus ABT-888.

e. Application of somatic BRCAness phenotype markers on metastatic tumor tissue to identify patients likely to benefit from platinum-based therapy and ABT-888.

f. To determine the overlap of BRCA phenotype (germline BRCA, BRCA-like, Non-BRCA-like) with tissue PD-L1 status and to determine if ABT-888 (veliparib) benefit in BRCA-like patients is maintained when adjusting for PD-L1 status.

g. To evaluate CTC-HRD status as a predictive biomarker of response to treatment with cisplatin plus ABT-888 (veliparib) versus cisplatin plus placebo.

h. To evaluate ctDNA HRR (Homologous recombination repair) mutation status as a predictive marker of response to treatment with cisplatin plus ABT-888 (veliparib) versus cisplatin plus placebo.

2.0 BACKGROUND

2.1 General

Triple-negative breast cancer (TNBC) refers to a subgroup of breast carcinomas that do not express the estrogen receptor (ER), progesterone receptor (PR), and exhibit normal expression of the human epidermal growth factor receptor type (HER) 2. Due to a lack of well-defined molecular targets, chemotherapy is the standard of care treatment for TNBC. The triple-negative phenotype is found in approximately 10-17% of all breast cancers, and is associated with a poor prognosis, characterized by early relapse and a significantly shorter survival following recurrence compared with non-triple-negative cancers. *(1,2,3,4,5,6)* Data suggest that the triple-negative phenotype is an independent predictor of distant metastasis and cause-specific survival. *(7)* In the metastatic setting, patients with TNBC have a median survival of approximately 13 months, and short duration of response to treatment (median duration of response equals 12 weeks for first-line treatment; 9 weeks for second-line; and 4 weeks for third-line). *(8)* Thus, there is an unmet clinical need for more effective treatments in this group of patients.

2.2 *BRCA* deficiency as a therapeutic target in triple-negative breast cancer

Triple-negative breast cancers and *BRCA1* germline mutation-associated breast cancers share many histopathologic and molecular features. The phenotypic and molecular similarities between *BRCA1* mutation-associated and sporadic TNBC have led many to surmise that a significant proportion of *gBRCA* wild-type TNBCs may involve *BRCA1* pathway dysfunction through non-germline mutational means and *BRCA1*-directed therapeutic approaches (such as platinum agents and poly(ADP-ribose) polymerase (PARP) inhibitors) are being explored for TNBC. Approximately 10-20% of TNBCs harbor detectable germline *BRCA1* mutations and have an underlying defect in homologous recombination (HR) DNA repair. *(9,10,11,12,13)* However, DNA repair may be altered through other mechanisms, such as somatic or germline mutation in other genes, DNA methylation or attenuated mRNA expression. It is estimated that if these factors beyond germline *BRCA* mutations are comprehensively evaluated, 50-60% of TNBC will demonstrate HR deficiency or BRCAness making it an attractive therapeutic target for this subtype. *(14,15,16)* The combination of platinum therapy and PARP inhibition may be most active in tumors with *gBRCA* mutations and in *gBRCA* wild-type tumors that harbor the BRCAness phenotype.

2.3 Poly (ADP-ribose) polymerase (PARP) inhibitors in TNBC and *BRCA*-deficient breast cancer

PARP enzymes recognize DNA damage and facilitate DNA repair to maintain genomic stability. Preclinical studies demonstrate that PARP inhibition in the presence of BRCA deficiency leads to synthetic lethality. PARP inhibitors have shown preclinical and clinical activity in targeting tumors with pre-existing DNA repair defects, in particular *BRCA1* and *BRCA2*-deficient tumors. *(17,18,19,20,21,22,23,24,25)* A PARP inhibitor olaparib has recently been approved as monotherapy by the FDA as a first-in-class drug to treat germline *BRCA* mutation-associated advanced refractory ovarian cancers (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427554.htm). As a significant proportion of TNBC are thought to harbor DNA repair defects, it might be possible to extend the observation of PARP inhibitor sensitivity of *gBRCA* mutation-associated tumors to *gBRCA* wild-type TNBC that harbor BRCAness. Preclinical studies also demonstrate that basal-like cell lines exhibit increased sensitivity to PARP inhibition. *(26)* Accordingly, PARP inhibitors are being explored in the general population of patients with TNBC (www.clinicaltrials.gov.Identifier NCT02032277). *(27)*

As monotherapy PARP inhibitors have demonstrated limited activity in non-*BRCA* mutation-associated breast cancer. However, this information is only inferred from small Phase I studies and there could be several reasons for the lack of activity observed. These studies included a small number of unselected TNBC patients, whereas PARP inhibitors are expected to work only in the 40-50% of *gBRCA* wild-type TNBC with a BRCAness phenotype and not in all gBRCA wild-type TNBC. A recent Phase I study of ABT-888 monotherapy reported modest clinical benefit rate of 19% (4/24) in *BRCA* mutation-negative TNBC. *(28)* Furthermore, *gBRCA* wild-type TNBC with a BRCAness phenotype likely harbor only partial homologous recombination defects and PARP inhibitor monotherapy may lead to “synthetic sickness” rather than synthetic lethality, necessitating the presence of robust DNA damaging chemotherapy to achieve cell death. To date, most studies reporting lack of significant activity in sporadic TNBC utilized PARP inhibitor monotherapy. *(29,30)*

2.4 Efficacy of ABT-888

ABT-888 is an oral small molecule inhibitor of PARP-1 and PARP-2 and inhibits PARP activity in xenograft models and human tumor tissue. *(31,32,33)* ABT-888 monotherapy has shown clinical activity in *BRCA* mutation positive breast, ovarian and prostate cancer patients in a Phase I dose escalation study, and in *BRCA* mutation-positive breast and ovarian cancer patients in Phase II studies. *(34,35)* Ongoing studies are evaluating ABT-888 as a single agent or in combination with chemotherapeutic agents such as temozolomide, platinum compounds and platinum-taxane doublets, in germline *BRCA* mutation-associated breast cancers (ClinicalTrials.gov Identifier NCT01506609, NCT 02158507). Although preclinical studies demonstrate that talazoparib (BMN673) has the strongest PARP trapping activity, clinically there is no evidence of superiority of one PARP inhibitor over others. Furthermore, preclinical studies demonstrate that trapping potency is directly correlated with hematopoietic progenitor cell toxicity and PARP trapping is not detectable nor required for activity when PARP inhibitors are combined with cisplatin. *(36)* ABT-888 traps PARP1 onto damaged DNA at clinically relevant concentrations as monotherapy and is capable of catalytic inhibition at concentrations where trapping is undetectable with regimens in which trapping is not required for activity.

Information on activity of ABT-888 in combination with chemotherapy in germline *BRCA* wild-type TNBC is available from three Phase I studies. *(37,38,39)* No responses were noted in sporadic TNBC with the combination of ABT-888 (low dose) and temozolomide. (40) In the second Phase I study, the combination of carboplatin, paclitaxel and ABT-888 did show promising activity with objective responses noted in 10 out of 17 (59%) BRCA wild-type TNBC patients. (41) The third Phase I trial which used cisplatin, vinorelbine and ABT-888 showed objective responses in 10 out of 26 (38%) confirmed BRCA wild-type TNBC patients. (42)

In the BRCAness population, data from other trials suggests it will be necessary to combine PARP inhibition with chemotherapy to be effective. To date, ABT-888 is the only PARP inhibitor able to combine with standard doses of platinum-based therapy. Olaparib has been difficult to combine with cisplatin/gemcitabine and with carboplatin at full doses and we have no data on how well the other PARP inhibitors will combine with chemotherapy. Based on a recently completed Phase I study discussed below, we have a safety profile for cisplatin and ABT-888, and evidence that adequate doses of cisplatin can be delivered in combination with a near maximal single agent dose of ABT-888.

ABT-888 has also shown activity in lung cancer patients, none of whom are expected to harbor a *BRCA* mutation. A recent study in squamous cell lung cancer reported a two month improvement in PFS with the addition of ABT-888 to carboplatin/paclitaxel chemotherapy. (43)

When comparing across different studies various PARP inhibitors (ABT-888, olaparib, rucaparib, BMN 673) have typically shown a 26-40% response rate in germline BRCA mutation-positive patients. (44,45,46,47,48) The variability in responses seen in the ovarian cancer studies is highly influenced by the number of platinum sensitive vs. resistant patients in each study. A recent ABT-888 monotherapy study demonstrates a RR of 35% in platinum sensitive and 20% in platinum resistant ovarian cancer (which is in line with observations with other PARP inhibitors). *(49)* In germline *BRCA* mutation-positive breast cancer a recently completed Phase I study evaluated 9 dose levels of ABT-888 and demonstrated an overall RR (at all dose levels combined) of 29% and a much higher RR of 60% at the RP2D. *(50) This* suggests a dose response relationship of ABT-888 and emphasizes the importance of being able to combine chemotherapy with the highest dose possible of ABT-888 to test for BRCAness in sporadic TNBC. All ongoing major trials of PARP inhibitors in metastatic breast cancer are focusing on the germline *BRCA* mutation-positive breast cancer population. **S1416** is the only trial that proposes to use a combination of robust doses of both the PARP inhibitor and cisplatin to test for activity in the BRCAness phenotype in TNBC.

2.5 Platinum agents in TNBC and *BRCA*-deficient breast cancer

Platinum agents are not new to the treatment of breast cancer. In the 1980's, cisplatin was evaluated in advanced breast cancer in two Phase II studies and demonstrated significant single-agent frontline activity with response rates in the range of 50-54%. *(51,52)* Cisplatin was subsequently replaced by other agents in breast cancer with more favorable toxicity profiles until more recently, when there has been renewed interest in platinum agents in *BRCA* mutation-associated breast cancer and TNBC. Repair of platinum-induced interstrand crosslinks invokes *BRCA1*-mediated homologous recombination, and there is abundant clinical and *in vitro* evidence that *BRCA1*-deficient cells are hypersensitive to platinum agents. *(53,54,55,56,57)* Observational studies, small neoadjuvant and metastatic studies have demonstrated that *BRCA 1/2* mutation-associated breast cancers are very sensitive to platinum agents. *(58,59,60,61,62,63)* In a Phase II study, single agent cisplatin yielded an impressive 80% response rate in *BRCA1* mutation-associated MBC. *(64)* A recent randomized Phase III trial (TNT study, Tutt A, et al. S3-01 2014 San Antonio Breast Cancer Symposium) demonstrated that in unselected

metastatic TNBC, carboplatin was equal in efficacy to docetaxel in the first-line metastatic setting. However, in *gBRCA* mutation-associated TNBC, carboplatin yielded a superior response rate and progression-free survival compared to docetaxel. This data from the TNT study strongly supports investigating the use of platinum (and not taxane)-based chemotherapy backbone combined with a PARPi in *gBRCA* mutation-associated metastatic TNBC and also provides reassurance regarding the activity of platinum-based chemotherapy in unselected metastatic TNBC. For treatment of solid tumors, cisplatin and carboplatin are the two commonly used platinum agents. Superiority of cisplatin over carboplatin has been shown in multiple solid tumors in the early stage curative setting, including germ cell, bladder, esophageal, and head and neck tumors, though this concept has never been tested in breast cancer. *(65)* A non-randomized Phase II study reported efficacy of single-agent cisplatin (75 mg/m2 every 3 weeks) or carboplatin (AUC 6 every 3 weeks) as fırst or second-line therapy in metastatic TNBC. In this study an encouraging ORR of 55% was noted in patients with *BRCA1* or *BRCA2* germline mutations (compared to 26% in *BRCA* wild-type patients) and interestingly cisplatin demonstrated a numerically higher ORR (37%) compared to carboplatin (23%). *(66,67)* This was a non-randomized study so these results must be interpreted with caution. In a recent single institution retrospective study of 144 TNBC patients treated with platinum based neoadjuvant chemotherapy, superior progression-free and overall survival was noted for those receiving cisplatin-based regimens compared to those receiving carboplatin-based regimens. *(68)*

Recent data from the ovarian cancer literature demonstrates that patients with a deleterious *BRCA1/2* mutation have increased susceptibility and shortened time to carboplatin hypersensitivity reactions, independent of other risk factors for hypersensitivity reactions. *(69) BRCA1* mutation carriers have an increased therapeutic susceptibility to platinum agents and are more likely to receive multiple cycles of platinum-based therapy. Thus, cisplatin (compared to carboplatin) may improve the tolerability and durability of the platinum-based combination regimens in *BRCA* mutation carriers and may be a better platinum partner to PARP inhibitors. Furthermore, given the recent data from randomized trials on the efficacy of neoadjuvant carboplatin in TNBC, several patients might already have been exposed to carboplatin in the neoadjuvant setting which also makes cisplatin a more attractive choice for a metastatic regimen. Based on the above rationale and the below described Phase I data the current proposal includes a cisplatin-based chemotherapy backbone.

2.6 **Rationale for combination of Cisplatin and a PARP inhibitor:**

Although platinum agents and taxanes are generally considered synergistic for breast cancer, this may not hold true for *BRCA* mutation-associated breast cancer. Several in vitro studies have demonstrated that *BRCA1*- deficient cells are resistant to taxanes. *(70,71,72)* Cisplatin has demonstrated synergy with the PARP inhibitor, ABT-888, in breast cancer xenograft models. *(73)* Based on these rationales a Phase I study utilizing ABT-888 in combination with cisplatin and vinorelbine for patients with advanced TNBC and/or *BRCA* mutation-associated breast cancer was initiated. This study demonstrated safety, tolerability and a suggestion of significant efficacy in a heavily pretreated population (results described in detail in the section below). A Phase II trial is needed to further elucidate the relative contribution of PARPi in this setting. Thus, the clinical results from this Phase I study, in addition to the preclinical rationale, provide the basis for the **S1416** Phase II randomized trial.

2.7 **Phase I study using Cisplatin and Vinorelbine with Veliparib: in Metastatic Triple-Negative Breast Cancer and *BRCA* Mutation-Associated Breast Cancer.**

Preclinically, cisplatin is synergistic with vinorelbine and the poly (ADP-ribose) inhibitor, ABT-888 and has anti-neoplastic activity in TNBC and BRCA1-deficient breast cancer. A Phase I study was conducted to define the tolerability of ABT-888 with cisplatin/vinorelbine. In the dose escalation study ABT-888 was administered BID for 14 days with cisplatin (75 mg/m2 Day 1) and vinorelbine (25 mg/m2 Days 1, 8) for a minimum of 6 cycles as tolerated, and up to 10 cycles followed by ABT-888 monotherapy. (74)

A total of 50 eligible patients with advanced triple-negative and/or BRCA mutation-associated breast cancer were enrolled in the trial between July 2010 and February 2014. Forty-five patients were enrolled in 9 dose levels and 5 patients in a safety expansion cohort. Fourteen patients (28%) were confirmed BRCA1 or BRCA2 mutation carriers. Most patients entered the trial with a heavy disease burden; 3 or more sites of disease. The most common sites were the lymph nodes, lungs, and liver. Seven patients started the trial with treated brain metastases. The majority of patients had received prior chemotherapy for metastatic disease, with a median of 1 prior regimen (range 0 to 13). Seventeen patients (34%) received prior platinum chemotherapy. Ten patients (20%) received vinorelbine before the study regimen, with 8 having prior exposure to both platinum and vinorelbine.

The study regimen was reasonably well tolerated. For the 50 patients receiving study therapy, a median of 6 cycles of combined chemotherapy plus ABT-888 was delivered (range 0-9 cycles). Compared to the intended combination therapy (full dose for 6 cycles) the median delivery for cisplatin was 90%, vinorelbine was 73%, and ABT-888 was 93%. Thirty-one patients (62%) completed at least 6 cycles of combined chemotherapy and ABT-888, and 23 patients proceeded to monotherapy with ABT-888. The most common treatment-related adverse events (AEs) of all grades were nausea, fatigue, thrombocytopenia, anemia, and neutropenia. A majority of patients experienced these AEs, mainly Grade 1/2. Grade 3/4 AEs included neutropenia (36%, 3/18 febrile), anemia (30%), and thrombocytopenia (12%). No Grade 3/4 AEs of neuropathy, creatinine elevation or hearing loss were observed in the trial.

Six of 23 patients reported AEs while on monotherapy, including one with Grade 3 anemia. The most common AEs of any grade on monotherapy were dyspepsia, nausea and vomiting (each 17%).

There was no increase in short-term or long-term nephrotoxicity in the Phase I trial despite the common renal elimination of ABT-888 and cisplatin. There were no Grade 3 or 4 platinum-related toxicities including elevated creatinine, peripheral sensory or motor neuropathy, or ototoxicity, which is in line with prior cisplatin/vinorelbine use in metastatic breast cancer. (75) In-vivo data from animal models suggest that PARP inhibitors can protect against the nephrotoxicity and peripheral neuropathy of cisplatin, though only a larger randomized trial could support this hypothesis. (76,77,78,79)

The maximum tolerated dose (MTD) of ABT-888 was not reached in this Phase I trial. Single dose limiting toxicity (DLT) events were rare and occurred in 3 dose cohorts. A patient at dose level 3 (40 mg) with Grade 4 thrombocytopenia was subsequently found to have bone marrow involvement of breast cancer. A patient in dose level 4 (60 mg), with 10 prior lines of therapy in the metastatic setting, had a DLT of Grade 4 neutropenic fever. The patient had a pericardial effusion at the time and died of disease progression before completing one cycle of treatment. A patient at dose level 8 (200 mg) experienced Grade 3 neutropenic fevers in the setting of a breast abscess. This patient recovered from the acute infection and was able to remain on study for 10 months.

As monotherapy, the current recommended Phase II dose for ABT-888 is 400 mg BID throughout a 28-day cycle. At this dose, the most notable toxicities have been

gastrointestinal. (80) Since nausea and vomiting could compromise the dose-intensity of the chemotherapy backbone, doses of ABT-888 exceeding 300 mg BID were not pursued in combination chemotherapy. Unlike other PARP inhibitor combination chemotherapy regimens in which myelotoxicity has significantly limited dose delivery of the agents, this platinum doublet/PARP inhibitor regimen offered high dose-intensity of cisplatin and ABT-888, though more frequent dose reductions and delays occurred with vinorelbine. (81,82)

Seven serious adverse events during combination therapy were likely related to treatment: five episodes of Grade 3/4 neutropenia; one of Grade 4 thrombocytopenia, and one of Grade 3 dehydration. Five patients (2 at 20 mg, 1 at 40 mg, 1 at 60 mg, and 1 at 120 mg of ABT-888) died within 30 days of stopping study therapy. These deaths were attributed to rapid disease progression soon after enrollment (within the first cycle in 3 patients).

Of 50 patients evaluable for safety, two were not evaluated for response due to withdrawal before the first radiographic response for reasons other than disease or toxicity; one of these died within 6 months and is assessable for progression-free survival. Best overall response was a complete response for 4/48 patients (8%) and partial response for 17 patients (35%), for an overall response rate of 44% (95% CI 31%-58%). Seventeen patients (35%) had stable disease, and 10 (21%) had progressive disease as best response or were not assessed due to disease or toxicity. BRCA mutation presence versus absence appears to be associated with both response (CR+PR, 64% vs 39%, mid-p=0.15) and progression-free survival at 6 months (PFS6) (71% vs 30%, mid-p=0.01).

Median PFS was 5.5 months (95% CI 4.1 -6.7), and the median OS was 9.6 months (95% CI 8.1 – 20.7). PFS and OS were greater for patients with a germline BRCA mutation (median 9.2 months PFS, 22.6 months OS) than for germline BRCA wild-type (4.2 months, 8.7 months) or unknown mutational status (4.0 months, 6.2 months) (log-rank test, $p<0.001$ for PFS, $p=0.003$ for OS).

Two patients who achieved a CR are long-term responders. A patient in the 60 mg dose cohort with a BRCA1 mutation (exon 13 insert 6kb rearrangement) received 6 cycles of combination therapy. Complete radiographic response of liver and distant lymph node lesions occurred at 36 weeks, and she has been maintained through 57 cycles of monotherapy (40 months since starting study therapy) and remains on trial. The second long-term responder with radiographic CR (120 mg dose cohort) tested negative for a BRCA1/2 mutation. She received 6 cycles of combination therapy. Radiographic complete response was achieved at 54 weeks. She remains on ABT-888 monotherapy 37 cycles after starting study therapy.

This Phase I trial demonstrated that the combination of cisplatin, vinorelbine and ABT-888 is generally well tolerated in patients with advanced TNBC and/or BRCA mutation-associated breast cancer. The 300 mg BID dose of ABT-888 that can be combined with this cytotoxic regimen is close to the maximal PARP inhibitor dose and is a clinically active single agent dose. Anti-neoplastic activity was observed in both BRCA mutation carriers and in germline BRCA 1/2 wild-type patients.

The Phase I study results show better response rate and median PFS than other trials of platinum monotherapy. In our study, the ORR and median PFS (44% and 5.5 months respectively) is higher compared to that observed in the TBCRC0009 Phase II non-randomized trial in metastatic TNBC patients (25% and 2.9 months respectively) and in the Phase III TNT trial (31% and 3.1 months respectively), despite a more heavily pretreated population. *(83,84)* The suggestion of greater clinical activity warrants further investigation of this combination in metastatic TNBC patients and provided a rationale for the SWOG Phase II study.

The recommended randomized Phase II dose (RPTD) of ABT-888 in combination with cisplatin and vinorelbine is 300 mg BID, the highest dose of ABT-888 reached to date in combination chemotherapy trials for breast cancer. This is significant because there is

evidence for a dose response relationship with ABT-888, and single-agent activity is observed beginning at 300 mg BID. (85) In BRCA mutation-positive cancer, a recently completed Phase I study evaluated 9 dose levels of ABT-888 and demonstrated an ORR (at all dose levels combined) of 29% and a much higher response rate of 60% at the recommended Phase II dose. (86) Tutt and colleagues also observed a dose response relationship with the oral PARP inhibitor olaparib in BRCA mutation-associated breast cancer. (87) The finding of higher clinical response rates with higher doses of ABT-888, despite achieving 90% PARP inhibition at lower doses by PAR assay, suggests that combinations which allow for higher PARP inhibitor dosing are preferred in order to achieve the best therapeutic response. (88,89)

In this Phase I study, it was not possible to determine the relative contribution of the chemotherapy backbone and the PARP inhibitor. The patient who has remained on trial for the longest duration (over 40 months), BRCA1 mutation-positive, converted from a partial to a complete response while on ABT-888 monotherapy (300 mg BID), providing evidence of the antineoplastic activity of single-agent ABT-888 at a high dose. Prolonged response to PARP inhibitor monotherapy was also observed in a patient with confirmed BRCA mutation-negative TNBC, supporting the hypothesis that a BRCAness phenotype exists which will respond to PARP inhibition. The SWOG Phase II study has selected biomarkers to identify TNBC tumors with BRCAness. Since several mechanisms can result in a HR deficiency, a single biomarker is unlikely to detect all patients with the BRCAness phenotype. Thus a multipronged approach is being utilized.

Although less commonly used in breast cancer, cisplatin may be a better platinum partner than carboplatin for ABT-888 in TNBC and BRCA mutation-positive breast cancer. In contrast to the high dose of ABT-888 attained with cisplatin-based therapy in this Phase I study, myelosupression has limited the dose of ABT-888 that can be combined with carboplatin as a single agent or with a carboplatin and paclitaxel doublet. *(90,91)*

The Phase I study noted a higher response rate in *BRCA* mutation carriers compared to *BRCA* wild-type TNBC patients (64% versus 39%) and a higher 6-month PFS (71% versus 30%). This is congruent with results from other studies. In the TBCRC trial, the ORR was higher in patients with BRCA1 or BRCA2 germline mutations (55%) compared to BRCA wild-type TNBC patients (26%), again demonstrating the heterogeneity of response in this population. Similarly, in the Phase III TNT trial, single-agent carboplatin offered superior response for BRCA mutation-positive TNBC patients compared to docetaxel but this was not the case in BRCA wild-type TNBC patients. (92) A significant number of BRCA wild-type patients in the Phase I study did respond to treatment, indicating a need for further development and validation of correlative studies to identify which patients have tumors with a HR defect, BRCAness phenotype that will render them sensitive to platinum plus PARP inhibition.

The clinical results from this Phase I study, in addition to the preclinical rationale, provide the basis for the proposed SWOG Phase II randomized trial. The Phase II trial will determine the relative contribution of the PARP inhibitor to cisplatin chemotherapy.

The Phase II trial will utilize a multipronged biomarker approach to define a BRCAness phenotype and will test the hypothesis that the combination of platinum therapy and ABT-888 will be most active in breast cancers associated with germline *BRCA* mutations and in *BRCA* wild-type breast cancers harboring the BRCAness phenotype, but less active in the non-BRCA-like phenotype.

2.8 Incorporation of BRCAness phenotype as an integral biomarker:

In patients with wild-type *gBRCA*, and perhaps even in patients with *gBRCA* mutations, several mechanisms can result in a HR deficiency that leads to the BRCAness phenotype. A single test is unlikely to detect all patients with the BRCAness phenotype. It is speculated

that if other factors beyond germline *BRCA* mutations are comprehensively evaluated, 50-60% of TNBC will demonstrate HR deficiency or BRCAness. *(93,94,95)* Thus a multipronged approach which utilizes various assays for identification of a BRCAness phenotype is incorporated in this proposal. These BRCAness phenotype markers have been incorporated as integral biomarkers in this Phase II study. The combination of platinum therapy and ABT-888 may be most active in tumors with a germline *BRCA1* deficiency and in tumors that harbor the BRCAness phenotype. The primary analysis assumes that all patients with a BRCAness phenotype can be identified so the analysis cannot be performed in the absence of these integral biomarkers.

There is a clear need to improve outcomes in patients with metastatic TNBC. Homologous deficiency (which leads to BRCAness phenotype) may serve as a potential therapeutic target for a large fraction of TNBC patients. Both platinum agents and PARP inhibitors can potentially target the BRCAness phenotype. Single arm studies have demonstrated the preliminary activity of single-agent platinum compounds, PARP inhibitors and platinum/PARPi combinations in *BRCA* mutation-associated breast cancer and in unselected TNBC. *(96,97,98,99,100,101,102)* A recent Phase I study (discussed above) demonstrated very promising response rates in advanced *BRCA* mutation-associated breast cancer and TNBC utilizing a combination of platinum-based cytotoxic chemotherapy and the PARP inhibitor ABT-888. Several ongoing randomized studies are evaluating the efficacy of PARP inhibitors in the presence of platinum-based chemotherapy in germline *BRCA* mutation carriers but randomized studies evaluating PARP inhibitors in the general population of advanced TNBC patients are lacking. An ongoing Phase II/III AbbVie-sponsored trial is evaluating temozolomide plus ABT-888 or carboplatin and paclitaxel with or without ABT-888 in patients with *BRCA* mutation-associated advanced breast cancer. (ClinicalTrials.gov Identifier NCT01506609) This trial will be informative about the contribution of a PARP inhibitor to a carboplatin-based regimen in *BRCA*-associated breast cancer, but it does not include sporadic TNBC patients, is using carboplatin (instead of cisplatin) and is using a lower, intermittent dose of ABT-888 that is not anticipated to have single-agent activity. **S1416** uses a cisplatin-based cytotoxic chemotherapy regimen and is designed to determine if the addition of a PARP inhibitor (ABT-888) improves patient outcomes in advanced *BRCA* mutation-associated breast cancer and TNBC with an underlying BRCAness phenotype. It is now becoming increasingly clear that upfront incorporation of biomarkers indicative of BRCAness is needed in trial designs for successful evaluation of BRCA-directed therapies (platinum agents and PARPi) in the clinical setting.

S1416 trial design is unique as it plans to use an a priori determined multi-pronged integral biomarker *approach* to assess the effectiveness of a PARP inhibitor in TNBC subpopulations with and without BRCAness phenotype. It is anticipated that **S1416** will provide data on the efficacy of a new class of targeted therapy (PARP inhibitors) in the BRCAness phenotype TNBC patients and serve to validate the activity of PARP inhibitors in *BRCA* mutation-associated breast cancer. Clinical and biomarker Information learned from this trial will be utilized to design a larger Phase III study with chemotherapy with or without ABT-888 in TNBC patients with a BRCAness phenotype. This trial design includes a platinum-based regimen which is devoid of anthracycline/cyclophosphamide. Cisplatin has potential advantages over the conventional regimens. Anthracycline/cyclophosphamide, although effective in early stage breast cancer, does have rare long-term serious cardiac and hematological side effects. Recent in vitro and animal data demonstrate that *BRCA1* is an essential response molecule that shields cardiomyocytes from DNA damage, apoptosis and heart dysfunction and the presence of a germline *BRCA2* mutation is associated with increased anthracycline-associated cardiac toxicity. *(103,104,105)* Several in vitro studies have demonstrated that *BRCA1*-deficient cells are resistant to taxanes and a recent retrospective analysis demonstrated that *BRCA1* mutation-associated advanced TNBCs are less sensitive to single-agent taxanes than sporadic TNBCs. *(106,107,108,109)* Thus a platinum plus PARPi regimen which is devoid of anthracyclines and taxanes may be attractive for early stage TNBC especially if it is *BRCA* mutation-associated and has the potential of being valuable in the neoadjuvant

setting in selected patients. The knowledge gained from the biomarkers will be valuable for future clinical research involving DNA damaging agents in TNBC. Specifically, one of the exploratory objectives is to evaluate the germline *BRCA* mutation status and BRCAness phenotype markers as platinum response biomarkers. This information will be helpful for the future interpretation of the ongoing and planned studies involving platinum agents. See Appendix 18.5 for information regarding the Translational Medicine studies.

A brief summary of the integral markers is described below.

- **Germline *BRCA1/2* testing:** Germline BROCA-HR utilizes a targeted capture and massively parallel sequencing approach and detects germline mutations in *BRCA1/2* (and additional genes known to be involved in the homologous recombination pathway). *(110)* BROCA-HR will be performed by Dr. Elizabeth Swisher's CLIA certified lab at the University of Washington on all patients, prioritizing patients who enter the trial with unknown *BRCA* mutation status. A CLIA certified report for all confirmed deleterious mutations will be provided to the sites within 6 weeks. Germline testing will not delay treatment randomization. Upon enrollment, patients will be randomly assigned to ABT-888 or not. Assignment to the *gBRCA* confirmed positive or negative groups will occur after the BROCA-HR testing results are available.

- **BRCAness phenotype assessment**: The following set of markers will be utilized to designate BRCAness phenotype in *gBRCA* wild type subjects (Table 1), which also describes the prioritization order of the tests in case of insufficient material). A positive result on ≥1 of the below described markers will place the subject in the BRCAness group. Extrapolating from prior studies, the estimation is that approximately 50% of *gBRCA* negative TNBC patients will have a BRCAness phenotype, i.e. will be positive on at least one of the measures below. (111,112,113) A brief description of the markers is provided below. A detailed description of all the BRCAness phenotype markers (a-d) is provided in Section 18.5 Translational Medicine.

Table 1: BRCAness phenotype assignment markers (description and priority list)

Marker	Material needed	BRCAness phenotype *	Priority order
HRD score	Tumor gDNA (500 ng)	High HRD score	1
Somatic BRCA 1/2 mutations	Tumor gDNA (1 ugm)	Mutation/s present	2
BRCA1 Promoter methylation (PM)	Tumor gDNA (100 ng)	PM present	3
Non-BRCA germline HR mutations	Germline DNA	Mutation/s present	4

* A positive result on ≥ 1 of the markers will place the subject in the BRCAness

a) Homologous Recombination Deficiency (HRD) assay: HRD assay (Myriad Inc) combines genomic patterns of loss of heterozygosity (LOH) "footprint", telomeric allelic imbalance (TAI) and large-scale state transitions (LST) scores to generate an HRD score (using a custom Agilent SureSelect XT capture followed by sequencing on Illumina HiSeq250). (114) The HRD score has shown a robust correlation with HR insufficiency and allows for the detection of HR deficiency regardless of its etiology or mechanism. Preliminary studies demonstrate that a high HRD score is noted in 40-60% of TNBC and significantly correlates with response to platinum therapy in early stage TNBC

and response to a PAPRi in ovarian cancer. The assay is compatible with FFPE tumor tissue, requires 500 ng of tumor DNA and has high sensitivity for identification of BRCA-deficient tumors. (115,116) Tumor HRD assay will be performed for the entire study population; Results for *gBRCA1/2* mutation negative patients will be utilized for determination of BRCAness and results for *gBRCA* mutation positive patients will be utilized to evaluate the impact of HRD score on outcomes for this group as an exploratory objective. HRD score will be evaluated using pre-specified cut point of 42.

b) Somatic mutations in BRCA 1/2 genes: In addition to providing a score, the HRD assay also detects somatic mutations (point mutations, insertions/deletions, gene rearrangements) in BRCA1 and BRCA2. Patients with somatic BRCA 1/2 mutations will be assigned to the BRCAness group.

c) BRCA1 promoter methylation (PM): Hypermethylation of the BRCA1 promoter has been proposed as one of the mechanisms for functionally inactivating the *BRCA1* gene in sporadic breast cancers and is associated with a gene expression profile similar to that of inherited *BRCA1* mutation-associated breast cancer. BRCA1 promoter methylation (PM) is observed in 20-40% of sporadic TNBC and in vitro data suggests that epigenetic silencing of *BRCA1* via promoter methylation confers the same degree of sensitivity to PARP inhibitors as does a deleterious *BRCA1* mutation. (117.118,119,120,121) One hundred micrograms of tumor DNA Methylation-specific PCR will be utilized to detect hypermethylation of the areas of interest in the CpG islands of the BRCA1 promoter for patients who are confirmed *gBRCA 1/2* mutation negative.

d) Germline mutations in non-BRCA Fanconi Anemia/HR pathway genes: All study participants will undergo germline BROCA-HR testing *for gBRCA* status determination. This test also detects germline mutations in 37 additional genes (involved in the FA/HR pathway, e.g. PALB2, RAD51C, RAD51D). Patients identified to have deleterious germline mutations in these additional genes will be assigned to the BRCAness group. (122

2.9 **Rationale for Brain Metastases Cohort**:

Recent studies illustrate high rates of brain metastases (BM) in TNBC (as high as 50%), with survival following CNS recurrence often less than 6 months, and a median PFS of ~ 2–3 months. *(123, 124, 125, 126, 127)* The mainstay of treatment of CNS disease in breast cancer remains local therapies, including radiation (whole brain radiation treatment (WBRT)), stereotactic radiosurgery (SRS), gamma knife (GK)), and/or surgical resection. While no systemic therapies are approved for treatment of BM, chemotherapy is frequently used in an attempt to control systemic disease, as despite its poor prognosis, TNBC is quite sensitive to cytotoxics. In particular, TNBC can respond well to anthracyclines as monotherapy or in combination with taxanes, or to taxanes or platinums as monotherapy. *(128, 129, 130)* Despite this sensitivity, the risk of relapse/recurrence remains quite high, and treatment of intracranial disease with systemic agents is limited by the ability of drugs to achieve sufficient concentration in the CNS. Novel approaches are clearly needed.

In the past two decades, both clinicians and laboratory scientists have increasingly recognized that breast cancer is a clinically and biologically heterogeneous disease, well beyond the traditional clinical classifications based on hormone and HER2 status. Five major and one rare molecular subtype of breast tumors have been identified and validated, including basal-like, HER2 enriched, normal breast tissue-like, luminal-like (including luminal A and B), and more recently claudin-low. *(131, 132)* The subtype basal-like breast cancer (BBC; ~10-25% of all breast cancer) comprises 50-75% of TNBC, with the remaining TNBC falling within the other subtypes. *(133)* Common features of BBC include unique expression of cytokeratins 5, 6 or 17, an aggressive rate of proliferation (likely due to deficient RB and p53, very common in this subtype), and association with *BRCA1* mutations. In fact, the majority of *BRCA1* mutant patients who develop breast cancer develop the basal-like subtype. *(89)* Paradoxically, this defect can render these cancers

more sensitive to DNA damaging agents such as doxorubicin and the platinum agents, and also increases their dependence on alternative (i.e., non-defective) DNA repair mechanisms, such as those mediated via the nuclear enzyme poly(ADP-ribose)-polymerase (PARP). *(134)* PARP recognizes DNA damage, and expedites its repair. In-vitro studies have demonstrated the striking sensitivity of tumor cells deficient in *BRCA* to PARP inhibition. *(135)* Further, preclinical tumor models exposed to PARP inhibitors become sensitized to a variety of DNA-damaging agents, including cisplatin, leading to higher rates of cell death. *(136)*

S1416 is evaluating the efficacy of enhancing the cytotoxic effect of cisplatin with PARP inhibition in germline BRCA mutation positive and germline BRCA wild type patients with BRCAness phenotype. This strategy may also be effective in TNBC patients with similar molecular phenotypes who have developed BM since several PARP inhibitors in clinical development are able to cross the blood brain barrier and; platinum agents, such as cisplatin and carboplatin have been shown to cross the blood brain barrier, albeit with comparable but limited penetration of the CNS in preclinical models. *(137,138,139)* Interestingly, a recent report showed that histone deacetylase inhibitor treatment induced BRCAness and synergistic lethality with ABT-888 and cisplatin against human TNBC cells. (140) Further, an investigation of carboplatin and ABT-888 in mouse models of TNBC BM, both *BRCA* mutant and WT, demonstrated that both agents reached CNS tumors, as evidenced by evaluation of dynamic changes in gene expression and intracranial tumor PARP levels. *(141)* The combination yielded improved OS in *BRCA*-mutant but not WT models of TNBC as compared to controls. Based on these data, DNA damage response via GH2AX and apoptosis via CC3 was measured in one *BRCA* mutant and one *BRCA* wild type model; increased DNA damage and apoptosis in response to carboplatin and carboplatin/ABT-888 was observed in the *BRCA* mutant model only.

Further support for enrolling a cohort of patients with BM in **S1416** is based on the successful treatment of breast cancer patients with BM with platinum agents in the clinic. A recent study of carboplatin in combination with bevacizumab in breast cancer patients with BM reported reductions in the volume of CNS disease, including the subgroup with TNBC. (142) Importantly, the safety of the combination of ABT-888 with carboplatin has been established in breast cancer (I-SPY2). *(143)* Collectively, preclinical and clinical data strongly support the conduct of a clinical trial evaluating platinum-based DNA damaging chemotherapy with ABT-888 in patients with TNBC who have BM. Given that approximately half of the patients with TNBC will develop CNS metastases, it is important to identify novel combinations that successfully treat intracranial as well as extracranial disease with the goal of improving survival for patients facing this challenging disease.

2.10 Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. Males can be enrolled, though only 1-2 are expected to be enrolled. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below. The numbers below are for the total number of patients.

Enter actual estimates, whole numbers only (percentages, fractions, or decimals are not acceptable).

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	1	0	0	0	1
Asian	2	0	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	30	0	0	0	30
White	281	1	17	0	299
More Than One Race	1	0	0	0	1
Total	315	1	17	0	333

3.0 DRUG INFORMATION

For information regarding Investigator Brochures, please refer to SWOG Policy 15.

For this study, cisplatin is commercially available; therefore, Investigator Brochures are not applicable to this drug. Information about commercial drugs is publicly available in the prescribing information and other resources.

For this study, ABT-888 and matching placebo are investigational and are being provided under an IND held by the National Cancer Institute. The current version of the Investigator Brochure for the agent will be accessible to site and investigators and research staff through the PMB Online Agent Ordering Process (OAOP) application (http://ctep.cancer.gov/branches/pmb/agent_order_processing.htm). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" status and a "current" password. Questions about IB access may be directed to the PMB IB Coordinator via e-mail (ibcoordinator@mail.nih.gov).

NOTE: AbbVie has notified NCI CTEP of their intent to discontinue development of ABT-888 (veliparib). As a result, ABT-888 (veliparib) will not be available for treatment of patients after December 31, 2024. Please discuss this with any patients currently receiving ABT-888 (veliparib) to make alternate treatment arrangements, if appropriate.

3.1 ABT-888 (Veliparib) (NSC 737664) (CTEP IND #77840)

a. DESCRIPTION

Chemical Name: 2-[(R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide

Other Names: A-861695.0, Veliparib

Classification: Poly (ADP-ribosome) polymerase (PARP) Inhibitor

Molecular Formula: $C_{13}H_{16}N_4O$

Molecular Weight: 244.29

Description: White opaque capsule

b. TOXICOLOGY

Comprehensive Adverse Events and Potential Risks List (CAEPR) for ABT-888 (NSC 737664)

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 CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm for further clarification. *Frequency is provided based on 2310 patients.* Below is the CAEPR for ABT-888 (veliparib).

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 2.4, May 13, 2018[1]

Adverse Events with Possible Relationship to ABT-888 (Veliparib) (CTCAE 5.0 Term) [n= 2310]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***

Adverse Events with Possible Relationship to ABT-888 (Veliparib) (CTCAE 5.0 Term) [n= 2310]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
INVESTIGATIONS			
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 3)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
		Treatment related secondary malignancy	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 3)***
		Seizure	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		
VASCULAR DISORDERS			
		Thromboembolic event[2]	

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

[2] Thromboembolic events, including deep vein thrombosis and pulmonary embolism, have been observed at a higher frequency compared to control arm when administered in combination with temozolomide.

Adverse events reported on ABT-888 (Veliparib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that ABT-888 (Veliparib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Blood and lymphatic system disorders - Other (pancytopenia)
CARDIAC DISORDERS - Cardiac disorders - Other (Takotsubo cardiomyopathy); Heart failure; Left ventricular systolic dysfunction; Palpitations; Sinus bradycardia; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Vertigo
EYE DISORDERS - Blurred vision
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Colitis; Colonic obstruction; Dental caries; Dry mouth; Duodenal ulcer; Dyspepsia; Dysphagia; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Lower gastrointestinal hemorrhage; Mucositis oral; Obstruction gastric; Rectal hemorrhage; Rectal pain; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Fever; Flu like symptoms; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (cirrhosis)
INFECTIONS AND INFESTATIONS - Appendicitis; Catheter related infection; Infections and infestations - Other (peritonsillar abscess); Lung infection; Lymph gland infection; Mucosal infection; Sepsis; Shingles; Skin infection; Upper respiratory infection; Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Dermatitis radiation; Radiation recall reaction (dermatologic)
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Cardiac troponin I increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; Lipase increased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hypernatremia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Arthritis; Back pain; Bone pain; Generalized muscle weakness; Muscle cramp; Myalgia; Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) -Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysarthria; Extrapyramidal disorder; Intracranial hemorrhage; Lethargy; Memory impairment; Movements involuntary; Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Presyncope; Reversible posterior leukoencephalopathy syndrome; Stroke; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Psychiatric disorders - Other (emotional instability); Psychosis; Restlessness
RENAL AND URINARY DISORDERS - Dysuria; Hematuria; Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Epistaxis; Hypoxia; Nasal congestion; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Respiratory failure

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Nail changes; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Purpura; Rash acneiform
VASCULAR DISORDERS - Flushing; Hot flashes; Hypertension; Hypotension; Vascular disorders - Other (brainstem infarction)

Note: ABT-888 (Veliparib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

c. PHARMACOLOGY

Storage: Store intact bottles between 15° and 25°C (59°–77°F).

Stability: Shelf-life stability studies for ABT-888 capsules are ongoing.

Route(s) of Administration: Oral. ABT-888 and matching placebo capsules may be administered without regard to meals.

d. SUPPLIER

Clinical Supplies: ABT-888 (NSC 737664/IND 77840) and matching Placebo will be provided free of charge by AbbVie Inc. and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Veliparib 100 mg and 0 mg matching placebo will be supplied as immediate release capsules. The veliparib capsule contains veliparib, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, gelatin, sodium lauryl sulfate, and titanium dioxide. May contain FD&C blue #1, FD&C yellow #6, or FD&C yellow #5. The matching placebo capsule contains microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, gelatin, sodium lauryl sulfate, and titanium dioxide. May contain FD&C blue #1, FD&C yellow #6, or FD&C yellow #5. Lime green with two black bars.

ABT-888 and matching Placebo will be supplied in bottles containing 64 capsules with a child-resistant cap and a tamper-evident seal.

Each blinded, patient-specific bottle will be labeled with …

- the protocol number (i.e., "**S1416**")
- the bottle number (i.e., "Bottle 1 of 2" and "Bottle 2 of 2")
- the number of capsules (i.e., "64 capsules")
- the patient ID number (e.g.,"**S1416**-XXX", which represents the unique patient identifier assigned at registration)
- the patient initials (i.e., Last initial, First initial, Middle initial [e.g., "LFM"])
- the agent identification (i.e., "ABT-888 100 mg or Placebo")
- a blank line for the pharmacist to enter the patient's name
- administration instructions (i.e., "Take __ capsules two times daily for 14 out of 21 days as directed.")
- storage instructions (i.e., "Store at room temperature (15ºC to 25ºC; 59ºF to 77ºF)."
- emergency contact instructions
- a Julian date

The Julian date indicates the day the bottle was labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2014 = 14, 2015 = 15)

and a day count (e.g., January 1 = 001, December 31 = 365). For example, a bottle labeled and shipped on January 1, 2014 would have a Julian date of '14001' and a bottle labeled and shipped on December 31, 2014 would have a Julian date of '14365'. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all bottles (i.e., both ABT-888 and Placebo) shipped on or before that date thus eliminating any chance of 14 breaking the blind. The Julian Date – Order number (e.g., 2014352-0003) from the patient-specific label must be used as the Lot number on the NCI DARF.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30am and 4:30pm Eastern Time. You may also contact the PMB via e-mail at PMBAfterHours@mail.nih.gov.

Agent Orders: No starter supplies will be available for this study. Patient-specific supplies will be sent to the registering investigator at the time of registration/randomization and should arrive within 5 business days. Patients will be registered/randomized by the SWOG Statistics and Data Management Center in Seattle, WA. The assigned patient ID number must be recorded by the registering institution at the time of randomization for proper clinical supply dispersion. Once a patient has been randomized, the SWOG Statistics and Data Management Center will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the SWOG Statistics and Data Management Center the day the patient is randomized and will be processed by PMB the next business day and shipped the following business day. Shipments within the United States will be sent by Standard FedEx (generally two day delivery). Thus, if a patient is registered on Monday, the SWOG Statistics and Data Management Center would enter a clinical drug request for that patient on Monday and PMB would process that request on Tuesday and ship the drug on Wednesday. Sites could expect to receive their orders on Friday.

The initial request will be for 6 x 64 count bottles of ABT-888/placebo, a sufficient amount to complete the initial **3 cycles (9 weeks)** of treatment. After 7 weeks (two weeks before needed), sites may reorder an additional 6 x 64 count bottles (3 cycle supply) by submitting an agent request through the PMB Online Agent Order Processing (OAOP) application (https://eappsctep.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. The assigned patient ID number (e.g., "**S1416**-XXX") and the patient initials (e.g., "LFM") should be entered in the "Patient or Special Code" field. All drug orders should be shipped directly to the physician responsible for treating the patient.

Note: Initial supplies will be provided based on sites dispensing 2 full bottles per cycle. If a site is required by local practice to dispense an exact quantity for each cycle, ABT-888/placebo capsules may be repackaged from the supplied HDPE bottles into amber (or other low-actinic) child resistant pharmacy dispensing bottles. The bottles should be labeled according to State regulations and must include all of the information from the original patient specific bottle sent from the PMB (including the Julian Date.) Expiration will be 30 days from the repackaging date when stored at 15°C to 25°C (59°F to 77°F).

Special Ordering Procedures for Patients Transitioning to ABT-888/placebo Monotherapy: If the patient is switched from combination therapy to monotherapy (ABT-888/placebo 400 mg BID daily for 21 days), a request for additional supplies

to accommodate the new dose and schedule must be ordered through the PMB Online Agent Order Processing (OAOP) application. The person ordering the supplies through OAOP should answer “Yes” to the question “Is a dose adjustment required?” The Dose Adjustment to “ABT-888/placebo 400 mg BIB QD for 21 days” can then be selected. This will populate the appropriate quantity to send (3 bottles) for the new dose and schedule.

Agent Transfers: Capsules MAY NOT be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating clinical site to another participating clinical site, the principal investigator at a given clinical site changes) must be approved in advance by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 240-276-7893) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. The patient ID number (e.g., "**S1416**-XXX"') and the patient initials (e.g., "LFM") should be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e., "***NCI S1416***").

Agent Returns: Only undispensed clinical supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed or undispensed partial bottles remaining when a patient permanently discontinues protocol treatment, expired bottles recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Drug List available on 15 the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. The patient ID number (e.g., "**S1416**-XXX") and the patient initials (e.g., "LFM") should be entered in the "Lot Number" field. Opened bottles (returned by the patient) with remaining capsules should be documented on the patient-specific Oral NCI Investigational Agent Accountability Record (i.e., logged in as “returned by patient” and logged out as “destroyed on site”) and destroyed on-site in accordance with institutional policy.

Agent Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the Oral NCI Investigational Agent Accountability Record available on the CTEP home page (http://ctep.cancer.gov). A separate Oral NCI Investigational Agent Accountability Record must be maintained for each patient ID number (e.g., "**S1416**-XXX") on this protocol. NOTE: The Julian Date – Order number combination found in the upper right-hand portion of the patient-specific label must be used as the Lot Number. This number will be used in the event of a stock recovery or recall of the investigational agent.

Emergency Unblinding:
In the event of an emergency or severe adverse reaction necessitating identification of the medication for the welfare of the patient, please contact the **Washington Poison Center (WPC) at 206-526-2121** (see Appendix 18.2). This service is available 24 hours a day, 365 days a year. The WPC will require the protocol number (i.e., “**S1416**”), the patient ID number (e.g., “**S1416**-XXX”), and the patient initials (e.g., “LFM”) to unblind the patient. Please note that, if a patient is emergently unblinded, he/she is considered to be off-therapy and must discontinue protocol treatment.
NOTE: The remaining patient on treatment has been unblinded to reveal their usage and dosage of ABT-888 (veliparib). The unblinding was prompted by the pharmaceutical collaborator’s (AbbVie) notification of the discontinuation of the ABT-888 (veliparib) development program. See Section 7.4c for additional guidance.

3.2 Cisplatin (CDDP) (Platinol®, Platinol-AQ) (NSC-119875)

a. PHARMACOLOGY

Mechanism of Action:

Cisplatin (cis-diamminedichloroplatinum) is a heavy metal complex containing a central platinum atom surrounded by two chloride atoms and two ammonia molecules in the cis position. It is water soluble and acts as a bifunctional alkylating agent with cell cycle nonspecific characteristics. The intra-strand cross-links, in particular with guanine and cytosine, change DNA conformation and inhibit DNA synthesis leading to the cytotoxic and anti-tumor effects of cisplatin. Although cisplatin seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents and that cisplatin does not exhibit cross-resistance with other alkylating agents or nitrosoureas.

b. PHARMACOKINETICS

1. Absorption: Following rapid IV injection of cisplatin over up to one hour, peak plasma drug and platinum concentrations occur immediately. When cisplatin is administered by IV infusion over 6 or 24 hours, plasma concentrations of total platinum increase gradually during the infusion and peak immediately following the end of the infusion.

2. Distribution: Following intravenous dosing, cisplatin distributes rapidly into tissues, with highest concentrations in the liver, prostate and kidney. Plasma levels of cisplatin decay in a biphasic mode with an initial half-life of 25 to 49 minutes, and a secondary phase ranging from 58 to 73 hours. This prolonged phase is due to protein binding, which exceeds 90%. Cisplatin penetrates poorly into the CNS.

3. Metabolism: Cisplatin is non-enzymatically transformed to one or more metabolites that are extensively protein bound and have minimal cytotoxic activity. The non-protein bound (unchanged) fraction is cytotoxic.

4. Elimination: Urinary excretion is incomplete. Following bolus injection or infusion over a dose range of 40-140 mg/m2 varying in length from 1-24 hours, from 10 to about 40% of the administered platinum is excreted in the urine in 24 hours. Renal clearance of free platinum exceeds the glomerular filtration rate, indicating that cisplatin or other platinum-containing molecules are actively secreted by the kidneys. Renal clearance of free platinum is nonlinear and variable, and is dependent on dose, urine flow rate, and individual variability in the extent of active secretion and possible tubular reabsorption.

c. ADVERSE EFFECTS

1. Possible Side Effects of cisplatin:

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Adverse effects reported in > 20% of subjects treated with cisplatin include: nausea, vomiting, myelosuppression, anemia, leukopenia, thrombocytopenia, nephrotoxicity (acute renal failure and chronic renal insufficiency), and ototoxicity.

Adverse effects reported in 4% to 20% of subjects include: alopecia, dysgeusia, diarrhea, hypersensitivity reaction, confusion, vestibular dysfunction, peripheral neuropathy, and blurred vision or altered color perception.

Serious adverse effects reported in ≤ 3% of subjects include: secondary malignancy, and seizure.

2. Pregnancy and Lactation: Category D. Cisplatin can cause fetal harm when administered to a pregnant woman. In mice, cisplatin is teratogenic and embryotoxic. This drug has been found to be excreted in human milk and because of the potential for serious adverse reactions in nursing infants, patients receiving cisplatin should not breast feed.

3. Drug Interactions: During cisplatin therapy, plasma levels of anticonvulsant agents (valproic acid, phenytoin, and carbamazepine) may become sub-therapeutic and should be monitored. Concomitant use with aminoglycosides and amphotericin B increase risk of nephrotoxicity. Concomitant use with loop diuretics and aminoglycosides increase risk of ototoxicity. Concurrent use with lithium may result in reduced lithium plasma concentration. Concurrent use with warfarin may result in increased INR. Concurrent use with thioctic acid may result in decreased cisplatin effectiveness and should be avoided.

Due to potential drug interactions, a complete patient medication list, including cisplatin, should be screened prior to initiation of and during treatment with cisplatin. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

Cisplatin is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

4.0 STAGING CRITERIA

Note: All staging will be based on the American Joint Committee on Cancer 2010 Staging System, 7th Edition.

M1 Distant detectable metastases as determined by classical clinical and radiographic means and/or histologically proven larger than 0.2 mm.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the SWOG Statistics and Data Management Center in Seattle at 206/652-2267 or breastquestion@crab.org prior to registration. NCI policy does not allow for waiver of any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 3 weeks later would be considered Day 21. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 21, 42 or 56 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease Related Criteria

a. Patients must have metastatic and/or recurrent (distant or locoregionally recurrent*) breast cancer and be HER2 non-over expressing per 2013 ASCO-CAP HER testing guidelines (0 or 1+ by IHC; and/or HER2 ratio < 2.0 and HER2 copy number < 4 signals/cell by ISH).

* Local Regional Recurrence
- In the breast (after preserving therapy)
- In the chest wall (after mastectomy)
- In the ipsilateral/parasternal/infra-or supraclavicular lymph nodes
- In the skin of the chest wall (not breast)
- In the reconstructed breast

b. Patients must also meet at least one of the following criteria:

1) Triple Negative: Histologically confirmed primary and/or metastatic site that is ER-negative (≤ 1%), PR-negative (≤ 1%), and HER2–negative.

2) *BRCA* mutation: Previously confirmed deleterious *BRCA*1 or *BRCA*2 germline mutation or suspected deleterious BRCA1 or BRCA2 germline mutation if the classification being used is the 5-tier classification. Documentation of germline test results are required. (Note that submission of specimens as outlined in Section 5.1e is still required.)

c. Patients must have measurable or non-measurable disease (see Section 10.1). Patients must have a chest/abdominal/pelvis CT scan (or PET/CT of diagnostic quality, conventional or spiral) prior to registration. If the patient is unable to undergo CT with IV contrast due to allergy or renal insufficiency, a non-contrast CT may be performed. All scans needed for assessment of measurable disease

must be performed within 28 days prior to registration. Non-measurable disease must be assessed within 42 days prior to registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form.

d. Patients must be women or men ≥ 18 years of age.

e. Patients must have adequate tissue available and must agree to have specimens submitted for germline BRCA DNA sequencing and other correlative studies per Sections 15.1, 15.2, 15.3 and 15.4.

NOTE: Blood for BRCA mutation testing is to be collected and submitted after registration but before treatment.

5.2 Prior/Concurrent Therapy Criteria

a. Patients must have had ≤ 1 prior cytotoxic regimen for metastatic disease (unless enrolling in the Progressive Brain Metastases Cohort; see Section 5.5). Note that endocrine and immunotherapies do not count as cytotoxic regimens.

b. Patients must have completed any prior radiation therapy and hormonal therapy at least 14 days prior to registration.

c. Patients must not have received prior cisplatin or PARP inhibitors. Prior carboplatin in the adjuvant/neoadjuvant setting is allowed, if completed more than 12 months prior to study entry.

d. Patients must not have received any chemotherapy within 14 days prior to registration.

e. Patients must not have received any immunotherapy, biologic or any investigational drug within 28 days prior to registration. Patients must not have received bevacizumab within 42 days prior to registration.

f. Patients may receive bisphosphonates or denosumab concurrently with study treatment. If started prior to registration, it must be started at least 7 days prior to registration. See Section 7.2 for information regarding starting bisphosphonates or denosumab after registration.

g. Patients must have recovered to ≤ Grade 2 following a significant adverse event or toxicity attributed to previous anti-cancer treatment except neurotoxicity which must be ≤ Grade 1.

5.3 Clinical/Laboratory Criteria

a. Patients must have a performance status of 0-2 by Zubrod criteria (see Section 10.4).

b. Patients must have adequate bone marrow function, as defined by Absolute Neutrophil Count (ANC) of >/= 1,500/mcL, hemoglobin >/= 10 g/dL and a platelet count >/= 100,000/ mcL within 21 days prior to registration. Patients must not have had a blood transfusion within 28 days prior to registration.

c. Patients must have adequate hepatic function obtained within 21 days prior to registration and documented by all of the following:

- Bilirubin ≤ 1.5 mg/dL (or ≤ 3.0 mg/dL if due to Gilbert's Syndrome or if liver metastases are present)

- ALT and AST ≤ 2.5 x Institutional Upper Limit of Normal (IULN) (or ≤ 5 x IULN if liver metastases are present)

d. Patients must have adequate renal function with serum creatinine level ≤ IULN within 21 days prior to registration.

e. Patients must have serum chemistries (including potassium and magnesium) done within 21 days prior to registration to obtain baseline values.

f. Patients must not have a clinically relevant hearing impairment ≥ Grade 2.

g. Patients must be able to swallow whole capsules.

h. Patients with a history of uncontrolled seizure disorder; including focal or generalized seizure may not have had a seizure within one year prior to registration.

i. Patients with known brain metastases must either meet the additional criteria in Section 5.5 and enroll as part of the Progressive Brain Metastases Cohort, or have clinically controlled neurologic symptoms, defined as surgical excision and/or radiation therapy followed by 14 days of stable neurologic function prior to registration. Patients with incidentally discovered or asymptomatic brain metastasis(es) must receive surgical excision and/or radiation therapy prior to registration. Patients with progressive brain metastases following prior treatment are not eligible for the Standard Cohort, but may be considered for the Progressive Brain Metastases Cohort (see Section 5.5).

j. Patients must not have treatment-related AML (t-AML)/MDS or features suggestive of AML/MDS.

k. Patients must not have had prior allogeneic bone marrow transplant or double umbilical cord blood transplantation.

l. Patients must not have any incidence of or uncontrolled medical illness (e.g. active cardiac symptoms, active systemic infection, etc.) that would limit the patient's ability to participate in the protocol.

m. Patients must not have baseline peripheral neuropathy that exceeds Grade 1.

n. Patients must have a complete history and physical examination within 28 days prior to registration.

o. Patients of childbearing potential must not be pregnant (negative pregnancy test) or nursing due to the possibility of harm to a fetus or nursing infant from this treatment regimen. Men and women of reproductive potential must have agreed to use an effective contraceptive method for 6 months after completion of study treatment. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

p. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for five years.

5.4 Regulatory Criteria

a. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

b. As a part of the OPEN registration process (see Section 13.3 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

5.5 Progressive Brain Metastases Cohort

S1416 is one study with two cohorts. Patients who have progressive brain metastases after surgical excision and/or intracranial radiation will be in the Progressive Brain Metastases Cohort and will require a baseline MRI. Patients with previously treated brain metastases, stable disease and stable neurologic function for 14 days prior to trial registration will be in the Standard Cohort and may obtain MRI of the brain at the physician's discretion. Randomization and treatment is the same for both cohorts.

In addition to all of the previous eligibility criteria, patients with progressive brain metastases who do not satisfy the conditions in Section 5.3i to enroll in the Standard Cohort (neurologic stability for 14 days following surgery and/or radiation therapy) must also meet the following criteria to enroll as part of the Progressive Brain Metastases Cohort:

a. Patients with progressive brain metastases must have a baseline brain MRI within 28 days prior to registration. Brain metastases must be progressive and ≥ 10 mm in longest dimension on radiographic imaging AFTER prior intracranial radiation (IR) therapy (i.e., WBRT, SRS, GK or local equivalent). Patients must not have evidence of diffuse leptomeningeal disease on brain MRI or by previously documented CSF cytology. Discrete dural metastases are permitted. There must be no evidence of hemorrhage or impending herniation on baseline brain imaging. Patients with contraindication to gadolinium-enhanced MRI imaging are not eligible.

b. Patients must be on a stable or decreasing dose of steroids for ≥ 7 days prior to registration.

c. If patient has had an open brain biopsy, at least 28 days must have elapsed between biopsy and registration.

d. Patients enrolling in the Progressive Brain Metastases Cohort can have received up to 3 prior lines of cytotoxic chemotherapy for metastatic disease. Note that for enrollment in the standard cohort, patients must have had ≤ 1 prior cytotoxic regimen for metastatic disease.

6.0 STRATIFICATION FACTORS

Patients will be stratified at registration by cohort: Progressive Brain Metastases Cohort vs Standard (no progressive brain metastases) Cohort.

Patient randomization will be stratified by number of prior cytotoxic regimens for metastatic disease: 0 prior regimens vs. ≥1 prior regimens.

Additionally, patients within the brain metastases cohort will be stratified by Modified Breast Graded Prognostic Assessment Index (modified breast-GPA) *(144)*: ≤ 1 vs >1. (See Appendix 18.6)

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact **Dr. Eve Rodler *at 916/734-3772* (S1416question@swog.org) or Dr. Priyanka Sharma at 913/588-6029 (S1416question@swog.org).** For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at https://www.swog.org/sites/default/files/docs/2017-11/Policy38.pdf.

7.1 BRCA1/2 testing

All patients will have BRCA1/2 testing completed as outlined in Section 15.3 and Appendix 18.5.

Results of BRCA1, BRCA2 and other ten actionable genes in the BROCA-HR panel (ATM, BARD1, BRIP1, CHEK2, NBN, PALB2, PTEN, RAD51C, RAD51D, TP53) will be provided to the treating physician within 4-8 weeks. Only deleterious mutations will be reported, and variants of uncertain significance will not be reported. Mutations in other FA-HR pathway genes included in this BROCA-HR panel which are not known to have clear evidence of increased cancer risk will not be provided to the treating physicians since this part of the test is “research use” only and not considered to be of clinical significance.

The genetic testing results for all trial patients will be provided back to the enrolling site via Rave® as a report uploaded in the Genetic Testing Results folder and will include both “positive” and “negative” results for 12 genes (BRCA1, BRCA2, ATM, BARD1, BRIP1, CHEK2, NBN, PALB2, PTEN, RAD51C, RAD51D, TP53). As stated above a positive result will only include “deleterious mutation”. Mutations of uncertain significance will not be reported.

Providers will also have access to phone genetic counseling and advice regarding management guidelines for patients with deleterious mutations. This may specifically be needed for mutations in non *BRCA* genes. If a site/provider wishes to make use of this resource please contact Dr. Swisher at swishere@uw.edu. Do not contact Dr. Swisher’s lab for genetic counseling if the patient has not consented. For further questions you can also contact Dr. Sharma at S1416question@swog.org. Please note that genetic counseling services are available to sites, not individual patients.

7.2 Treatment

Patients will be randomized to one of the following arms:

- Arm 1: cisplatin + placebo (ABT-888)
- Arm 2: cisplatin + ABT-888

Agent	Dose	Route	Day	Schedule*
Cisplatin	75 mg/m^2	IV (over 1 hour) [a]	Day 1	
ABT-888/ Placebo	300 mg per dose (600 mg per day)	PO	Days 1-14	Twice daily

* Note: One cycle = ***21*** days

[a] Sites may use institutional guidelines for duration of cisplatin administration. Appropriate pre- and post-hydration for the cisplatin chemotherapy and electrolyte replacement including at least 1 liter of pre-hydration solution are recommended according to institutional guidelines. Furosemide, mannitol, and electrolyte supplementation may be included according to local practices as well. With the inclusion of high-dose cisplatin, anti-emetic prophylaxis should also be administered according to institutional guidelines and must follow NCCN guidelines including a corticosteroid, 5-HT3, and NK1 receptor antagonist.

NOTE: Patients may begin bisphosphonates, denosumab, or myeloid growth factor support after completion of Cycle 1 of protocol therapy.

Patients with stable disease/PR/CR may continue both drugs until disease progression. However, if after 4 cycles of combination therapy a patient experiences an unacceptable toxicity, cisplatin can be discontinued at the discretion of the treating physician and patients may continue ABT-888/placebo until progression. If patients have intolerable toxicity to cisplatin after three cycles, despite dose reductions, then they should discontinue therapy and be removed from protocol treatment. If monotherapy is selected after at least 4 cycles of cisplatin, the dose will be 400 mg BID of ABT-888/placebo to be taken continuously for 21 days of each 21-day cycle. An optional “run-in” period of at least two weeks will be allowed during which the patient can start with an ABT-888/placebo monotherapy dose of 300 mg po BID and if tolerated, the patient may transition to the higher 400 mg BID dose to be taken continuously for 21 days of each 21-day cycle.

For patients who continue on ABT-888/placebo, the investigator should notify PMB so that the ABT-888/placebo supplies can be adjusted to accommodate the extended dosing.

In order for patients to receive the potential benefits of cisplatin plus ABT-888/placebo followed by the option of ABT-888/placebo monotherapy and not exclude those patients who may have difficulty tolerating 6 cycles of cisplatin, 4 cycles are required before a switch to monotherapy. Rationale for at least 4 cycles of cisplatin: Patients may enter this trial with baseline peripheral neuropathy Grade 1 due to prior taxane treatment in the (neo) adjuvant or metastatic setting which could progress to Grade 2 or greater with multiple cycles of cisplatin. We would like patients to receive the potential benefits of cisplatin plus ABT-888/placebo followed by the option of ABT-888/placebo monotherapy and not exclude those patients who may have difficulty tolerating 6 cycles of cisplatin. Therefore, we require 4 cycles before a switch to monotherapy (6 should be encouraged), and if patients cannot tolerate at least 3 cycles despite dose reductions, then the patient should be removed from protocol treatment due to toxicity.

NOTE: The remaining patient on treatment has been unblinded to reveal their usage and dosage of ABT-888 (veliparib). The unblinding was prompted by the pharmaceutical

collaborator's (AbbVie) notification of the discontinuation of the ABT-888 (veliparib) development program. See Section 7.4c for additional guidance.

7.3 Drug Compliance Documentation

Drug compliance will be recorded by patients on the ABT-888/Placebo Intake Calendar (see Appendix 18.1). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart.

7.4 Unblinding Procedures

Patients who have progression of disease as defined in Section 10.2 have the option to be unblinded in planned fashion, as described in this section. Any request for unblinding other than for progression of disease will follow the procedures for emergency unblinding as outlined in Appendix 18.2. There will be no crossover to ABT-888 for patients who were on the placebo arm.

a. Criteria for Planned Unblinding:

Planned unblinding procedure applies to patients who experience progression as defined in Section 10.2. It is vital to properly apply the protocol specified definition of progression. If any questions arise with regard to progression for a patient, please contact the Breast Data Coordinator in Seattle by telephone at 206/652-2267, 6:30 a.m. to 4:00 p.m. Pacific Time, Monday through Friday, excluding holidays, or the **S1416** Study Chair, Dr. Rodler or in her absence, Dr. Sharma.

Prior to planned unblinding, the tumor assessment forms must be submitted and processed by the **S1416** Study Chair Dr. Rodler (or Dr. Sharma in her absence). To request a planned unblinding, submit the Baseline Tumor Assessment Form and all appropriate Follow Up Tumor Assessment forms for the patient in Rave, then email breastquestion@crab.org with the subject line "**S1416** Patient #XXXXXX, Requesting Planned Unblinding" to notify the **S1416** Data Coordinator who will review the documentation for completeness in Rave before contacting the Study Chairs. Please allow a minimum of 2 working days for review of forms. Dr. Rodler (or Sharma) will provide a written confirmation to the site that the patient has an adequately documented progression. This documentation must be uploaded to the Planned Unblinding Form in Rave®.

b. Planned Unblinding Procedures

Patients may be unblinded at time of disease progression using the Planned Unblinding Form in Rave®. The Planned Unblinding Form is available in the "Add Event" dropdown box on the "Subject" tab in Rave®. Complete both questions and click the "Save" button to see the unblinded treatment assignment displayed on the form.

c. Discontinuation of Blinded Supplies for ABT-888 (Veliparib) (NSC # 737664)

Due to the discontinuation of the ABT-888 (veliparib) development program, the blinded supplies of ABT-888 (veliparib) expired in October 2023 and additional blinded treatment is not available. Upon notification of the plan to discontinue the ABT-888 (veliparib) development program, any investigators with patients currently on treatment with ABT-888 or placebo must unblind their patients to determine if their patients are receiving ABT-888 (veliparib) or placebo. If a patient

is found to be receiving ABT-888 (veliparib), the treating investigator should discuss alternative treatment options, as well as a suitable transition date prior to the expiration of the blinded supplies. Treating investigators may request that the patient be allowed to continue open-label ABT- 888 (veliparib), noting the agent will no longer be available after December 31, 2024.

Sites are expected to continue the protocol-specified data submission requirements in Section 14.0 for all patients.

7.5 Full CDUS Reporting Requirement

Because this study contains an investigational drug for which CTEP holds the IND, it falls under CTEP requirements for full reporting. This involves required submission of cycle-specific toxicity and dose information (see Section 14.4c, the **S1416** Treatment Form, and the **S1416** Adverse Event Form). A cycle is defined as 21 days.

7.6 Criteria for Removal from Protocol Treatment

a. Progression of disease or symptomatic deterioration (as defined in Section 10.2).

b. Unacceptable toxicity and discontinuation of ABT-888/placebo. (NOTE: Patients who continue on ABT-888/placebo monotherapy after discontinuation of cisplatin due to toxicity are still on protocol treatment.)

c. Treatment delay > **4** weeks for events that are clearly not related to the study drug treatment (i.e. planned surgical procedures or acute viral illnesses). Treatment delay > **3** weeks for any other reason.

d. Start of alternative anti-cancer agent during the study period. Use of palliative radiotherapy and surgery related to the goal of rendering or maintaining a complete remission is acceptable.

e. Patient becomes pregnant or begins breastfeeding during the treatment portion of the study.

f. The patient may withdraw from the study at any time for any reason.

7.7 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.8 Follow-Up Period

All patients will be followed until death or 5 years after registration, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

Two different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used on this study.

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 will be utilized **for SAE reporting only**. The CTCAE Version 5.0 can be

downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 4.0 for routine toxicity reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Considerations

c. Missed doses are to be omitted rather than made up. If the patient misses a scheduled dose of ABT-888/placebo and less than 6 hours have passed since the scheduled dosing time, the dose should be taken immediately. Otherwise, the dose should be considered missed. If the patient vomits, the dose should be omitted.

d. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.

e. Reductions are based on the dose given in the preceding reporting period and are based on toxicities observed since the prior toxicity evaluation.

f. Once dose is reduced on combined therapy, patients will continue at new dose. No dose re-escalations are allowed while on combined therapy.

g. If a patient is on monotherapy he/she may have at least a trial 2 week period ("run-in") of taking ABT-888/placebo 300 mg BID, prior to taking the 400 mg BID monotherapy dose. If the monotherapy dose is reduced, patients will continue at new dose. No dose re-escalations are allowed.

h. The dose modifications are for events that are possibly, probably or definitely related to the study drug.

i. Gastrointestinal toxicities, predominantly nausea and vomiting, have been observed with ABT-888 as single-agent therapy and most frequently at higher doses (300-400 mg BID). These toxicities most commonly occurred within the first few days or weeks of ABT-888 treatment and were most often Grade 2 or lesser severity. However 5% of subjects experienced Grade 3 nausea during the first 4 weeks of ABT-888 treatment at 400 mg BID. To optimize dose intensity and maintain patient quality of life, early initiation of scheduled anti-emetic therapy (5HT-3 antagonists, metoclopramide, prochlorperazine) and/or lorazepam should be considered. In addition, management should include counseling regarding these toxicities and may include interruption of dosing, dose modification or ABT-888 discontinuation. In addition to the use of anti-emetic medications, investigators should rely on standard clinical practice for nausea management.

8.3 Dose Levels for ABT-888/placebo (as combined therapy)

Dose Levels	Dose
Full	3 capsules BID (100 mg x 3 for a total dose of 300 mg/dose – 600 mg/day)
-1 Level	2 capsules BID (100 mg x 2 for a total dose of 200 mg/dose – 400 mg/day)
-2 Level	1 capsule BID (100 mg/dose – 200 mg/day)
-3 Level	Discontinue ABT-888

8.4 Dose Levels for ABT-888/placebo (as monotherapy)

Dose Levels	Dose
Full	4 capsules BID (100 mg x 4 for a total dose of 400 mg/dose – 800 mg/day)
-1 Level	3 capsules BID (100 mg x 3 for a total dose of 300 mg/dose – 600 mg/day)
-2 Level	2 capsules BID (100 mg x 2 for a total dose of 200 mg/dose – 400 mg/day)
-3 Level	Discontinue ABT-888

8.5 Dose Levels for Cisplatin

Dose Levels	Dose
Full	75 mg/m^2
-1 Level	60 mg/m^2
-2 Level	50 mg/m^2
-3 Level	Discontinue cisplatin

8.6 Dose Modifications for ABT-888/Placebo

The dose levels and the general approach to dose modification of ABT-888 therapy is shown in Sections 8.3 and 8.4. Specific dose modification information for some AEs are provided in other sections. AEs should be treated with the appropriate maximum supportive care, and dose reductions should be clearly documented in the electronic case report form (eCRF).

The time the study drug is held should not exceed 3 weeks. Once the dose of the study drug has been reduced, no dose re-escalation is permitted.

AEs requiring ABT-888 to be discontinued:
- Bone marrow findings consistent with AML/MDS
- Severe persistent anemia

Patients should not be allowed to remain in the study if they are taking ABT-888 as monotherapy and one of the toxicities above occurs.

Hematologic toxicity

Management of neutropenia and thrombocytopenia

Neutropenia and thrombocytopenia are recognized common adverse drug reactions reported for ABT-888. Treatment should be managed according to the following table:

CTCAE Grade	Definition	ABT-888 Dose
1-2>	ANC > 1.0 G/L or Platelet count > 50 G/L	Investigator judgement to continue treatment or allow dose interruption; dose interruptions should be for a maximum of 3 weeks; appropriate supportive treatment and causality investigation.
3-4	ANC <1.0 G/L or Platelet count < 50 G/L	Dose interruption until recovered to CTCAE Grade ≤1 for a maximum of 3 weeks. Upon recovery, ABT-888 dose should be reduced by one dose level. If repeat CTCAE Grade 3-4 occurrence, further dose reduce one ABT-888 dose level.

ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events

Use of hematopoietic agents

Use erythropoietin-stimulating agents per standard of care National Comprehensive Cancer Network (NCCN) and/or institutional guidelines, iron supplements, and/or transfusions as clinically indicated for management of anemia. Prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) highlight that there is a potential risk of shortening the time to tumor progression or disease-free survival. Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended. Aranesp, Epogen and Procrit may not alleviate fatigue or increase energy, and should not be used in patients with uncontrolled hypertension. The package inserts for these agents should be consulted.

If a patient develops febrile neutropenia, ABT-888 should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 hours of the last dose of ABT-888 unless absolutely necessary. Thus, G-CSF may be started Cycle 2, Day 15.

Platelet transfusions, if indicated, should be done according to local hospital guidelines.

Dose modifications for hematologic toxicity

Patients who have ABT-888/placebo held for hematologic toxicities should have blood counts and differentials checked at least weekly until recovery; these data should be recorded in eCRF as extra laboratory examinations. If counts do not improve to CTCAE Grade 1 or better despite drug cessation for 3 weeks, patients should be referred to a hematological oncologist for further assessment. A bone marrow analysis should be considered.

For AEs that are unrelated to the study drug, study drug may be withheld for up to 3 weeks at the discretion of the treating Investigator.

If the patient is receiving combination cisplatin plus ABT-888/placebo, then both drugs must be started at the same time for a new cycle to commence, when hematologic toxicities have improved to Grade 1 or better.

Management of anemia

Anemia is a common adverse drug reaction related to ABT-888. Management of anemia is in accordance with the following table:

CTCAE Grade	Definition	ABT-888 Dose
2	Hb <10 but ≥ 8 g/dL	Give appropriate supportive treatment and investigate causality. Investigator judgement to continue ABT-888 or interrupt dose for a maximum of 3 weeks. If repeat Hb < 10 but ≥ 8 g/dL, dose interrupt until Hb ≥ 10 g/dL for maximum of 3 weeks and upon recovery dose reduce by one dose level as a first step and then reduce by a second dose level as a second step upon recurrence of Grade 2 AE.
3	Hb <8 g/dL	Give appropriate supportive treatment and investigate causality. Interrupt ABT-888 until improved to Hb ≥ 10 g/dL. Upon recovery dose reduce ABT-888 by one dose level. If repeat Hgb < 8 g/dL, after one dose reduction, then discontinue ABT-888/placebo. .

BID = twice daily; Hb = hemoglobin

Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anemia may require blood transfusions. Any subsequently required dose interruptions related to development of anemia, or coexistent with newly developed neutropenia, and/or thrombocytopenia, will require ABT-888 dose reductions by one dose level as a first step and then reduce by a second dose level as a second step upon recurrence of Grade 2 AE.

If Hb drops to < 8 g/dL despite the dose reduction or more than one blood transfusion is required to recover Hb levels with no alternative explanation for the anemia, ABT-888 should be permanently discontinued.

Management of prolonged hematological toxicities while on study treatment

If a patient develops prolonged hematological toxicity such as:

- ≥ 2 week interruption/delay in velaparib due to CTCAE Grade ≥ 3 anemia (Hb <8 g/dL) and/or development of blood transfusion dependence
- ≥ 2 week interruption/delay in ABT-888 due to CTCAE Grade ≥3 neutropenia (ANC <1 x 10^9/L)
- ≥ 2 week interruption/delay in ABT-888 due to CTCAE Grade ≥ 3 thrombocytopenia and/or development of platelet transfusion dependence (Platelets <50 x 10^9/L)

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 3 weeks of dose interruption, the patient should be referred to a hematological oncologist for further investigations. Bone marrow for evaluation and cytogenetics should be considered at this stage according to standard hematological oncology practice. ABT-888 should be discontinued if blood counts do not recover to CTCAE Grade ≤1 within 3 weeks of dose interruption.

Management of MDS/AML

Patients who develop MDS/AML on treatment should discontinue ABT-888 treatment and be managed appropriately.

Management of seizures

Any event of seizure, regardless of grade or attribution, requires interruption of ABT-888/placebo and discussion with the Study Chair regarding the decision to resume treatment.

Management of other non-hematological toxicities

If ≥ Grade 3 non-hematological toxicity occurs, then interrupt ABT-888/placebo until recovery to Grade ≤ 1. Then resume ABT-888/placebo at same dose. If event returns to Grade ≥ 3, then interrupt ABT-888/placebo until recovery to Grade ≤ 1. Then reintroduce ABT-888/placebo at one lower dose level. If the event returns to Grade ≥ 3 then discontinue the ABT-888/placebo.

8.7 Dose Modifications for Cisplatin

Hematological toxicity	**Actions**
Grade 2 Thrombocytopenia	Hold cisplatin until recovery to Grade ≤ 1. Then resume cisplatin at same dose. If thrombocytopenia again returns to Grade 2, interrupt cisplatin until recovery to Grade ≤ 1. Then reintroduce cisplatin at one lower dose level. One further dose reduction is allowed for Grade 2 thrombocytopenia. If the event returns to Grade 2 then discontinue the cisplatin.
Grade ≥ 3 Thrombocytopenia	Hold cisplatin until recovery to Grade ≤ 1. Then resume cisplatin at same dose level. If thrombocytopenia again returns to Grade ≥ 3, interrupt cisplatin until recovery to Grade ≤ 1. Then reintroduce cisplatin at one lower dose level. One further dose reduction is allowed for Grade ≥ 3 thrombocytopenia. If the event returns to Grade ≥ 3 then discontinue the cisplatin.
Grade 3 Neutropenia	Interrupt cisplatin until recovery to Grade ≤ 1. Then resume cisplatin at same dose level. If ANC again returns to Grade 3, hold cisplatin until recovery to Grade ≤ 1 and then resume cisplatin at one lower dose level. One further dose reduction is allowed for Grade 3 neutropenia. If the event returns to Grade 3 then discontinue cisplatin.
Grade 4 Neutropenia	Interrupt cisplatin until recovery to Grade ≤ 1. Then resume cisplatin at one lower dose level. One further dose reduction is allowed for Grade 4 neutropenia. If the event returns to Grade 4 then discontinue cisplatin.
Grade ≥ 3 Febrile Neutropenia	Interrupt cisplatin until recovery to Grade ≤ 1. Then resume Cisplatin at one lower dose level. If again returns to Grade ≥ 3, discontinue patient from cisplatin.
Non-hematological toxicity	**Actions**
Grade ≥ 2 Ototoxicity or Nephrotoxicity	Interrupt cisplatin until recovery to Grade ≤ 1. Then resume cisplatin at one lower dose level. If the event returns to Grade ≥ 2, then discontinue the cisplatin. Decrease the cisplatin to one lower dose level.
Grade 2 Peripheral Neuropathy	Decrease the cisplatin to one lower dose level.
Grade 3 Peripheral Neuropathy	Interrupt cisplatin until recovery to Grade < 2. Then resume cisplatin at one lower dose level. If the event returns to Grade 3, then discontinue the cisplatin.
Grade 4 Peripheral Neuropathy	Discontinue cisplatin
Other Grade 3 non-hematological toxicity	Interrupt cisplatin until recovery to Grade ≤ 1. Then resume cisplatin at same dose. If event returns to Grade 3, then interrupt cisplatin until recovery to Grade ≤ 1. Then reintroduce

Hematological toxicity	Actions
Other Grade 4 non-hematological toxicity	cisplatin at one lower dose level. If the event returns to Grade 3, then discontinue the cisplatin. Interrupt cisplatin until recovery to Grade ≤ 1. Then reintroduce cisplatin at one lower dose level. If the event returns to Grade 4, then discontinue the cisplatin.

8.8 Dose Modifications Contacts

For treatment or dose modification questions, please contact **Dr. Eve Rodler at 916/734-3772 (S1416question@swog.org) or Dr. Priyanka Sharma at 913/588-6029 (S1416question@swog.org)**

8.9 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6 @			Off Treat F/U Prior to Prog £	Off Treat F/U After Prog √
REQUIRED STUDIES	PRE STUDY	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W		
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
PHYSICAL																					
History & Physical Exam	X	X Я			X			X			X			X			X			X	X
Weight and Performance Status	X	X Я			X			X			X			X			X				
Clinical Disease Assessment **					X			X			X			X			X			X	
Toxicity Notation					X			X			X			X			X				
Review Intake Calendar & Pill Count					X			X			X			X			X				
LABORATORY $																					
CBC, differential, platelets	X	X#			X			X			X			X			X				
Serum Chemistry (including Potassium, Magnesium)	X	X#			X			X			X			X			X				
Serum Creatinine	X	X#			X			X			X			X			X				
Bilirubin	X	X#			X			X			X			X			X				
ALT/AST	X	X#			X			X			X			X			X				
Pregnancy Test	X																				
SCANS $																					
CT scan chest/abd/pelvis for tumor measurement **	X										X									X	
Brain MRI (only for patients in brain metastases cohort)	X																			X	
MANDATORY SPECIMEN SUBMISSION																					
Tissue for Correlative Studies (see Sections 15.1 and 15.2)	X																				
Blood for BRCA testing (see Section 15.3)	X Б																				
Blood for CTC testing (see Section 15.4) ¥	X				X															X¥	

(CORRESPONDING FOOTNOTES ARE CONTINUED ON THE NEXT PAGE.)

		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6 @			Off Treat F/U Prior to Prog £	Off Treat F/U After Prog √
REQUIRED STUDIES	PRE STUDY	W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 13	W 14	W 15	W 16	W 17	W 18		
TREATMENT (see Section 7.0 for details)																					
ABT-888/Placebo †		X	X		X	X		X	X		X	X		X	X		X	X			
Cisplatin		X			X			X			X			X			X				

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://www.swog.org/sites/default/files/docs/2017-10/Best%20Practices%20upddate.pdf.

Footnotes:

√ After progression, follow-up will occur (with lab tests and scans performed at the discretion of the treating physician) every 6 months until 5 years after registration or until death, whichever occurs first.

Я If prestudy history and physical exam, weight and performance status are obtained within 21 Days prior to treatment, they do not need to be repeated for Cycle 1, Day 1.

\# Labs should be redrawn within 7 days prior to Cycle 1, Day 1.

† ABT-888/placebo is taken twice a day on Days 1-14 for all cycles with drug supply dispensed as per Section 3.1d. Patients with stable disease/PR/CR will continue both drugs until disease progression. If after 4 cycles of combination therapy a patient experiences an unacceptable toxicity, cisplatin can be discontinued and ABT-888/placebo will continue until progression taken twice a day on Days 1-21 continuously for 21 days of each 21 day cycle.

@ Protocol treatment and parameters will continue at these intervals until patient has met any of the criteria outlined in Section 7.6.

** Disease will be assessed clinically at each visit. Scans must be completed every 9 weeks for 54 weeks from registration and then every 18 weeks until progression, or more often as clinically indicated, using the same method used at baseline. If a scan is performed earlier than the next scheduled 9 week

scan, the next scan should occur 9 weeks from the actual date of the scan, not from the scheduled date. All sites of disease that existed at baseline must be evaluated at each assessment. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease. For all patients after the 5-year follow-up mark, patient visits and scans are at the physician's discretion.

£ If patient is taken off protocol treatment for any reason other than progression, he/she must continue to be followed every 9 weeks for progression for 54 weeks from registration, then every 18 weeks until progression.

¥ Circulatory Tumor Cell (CTC) specimens should be submitted at baseline, Cycle 2 Day 1 and at Progression (see Section 15.4).

$ The window for CT scans is +/- 3 days. Labs for toxicity assessment must be obtained within 3 days prior to the treatment cycle initiation.

Б Blood for BRCA testing is to be submitted after registration and before beginning protocol treatment, to be collected and shipped in the same day. See Section 15.3.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

Evaluation of disease will be done using two separate criteria in this study, RECIST 1.1 (Sections 10.1-10.3) and the assessment criteria from the RANO-BM group for intracranial disease for patients in the Brain Metastases Cohort (see Section 10.4).

10.1 Measurability of lesions

a. **Measurable disease**: Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

2. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

4. 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.

5. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default

measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

10.2 Objective status at each disease evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as ***target*** lesions at baseline. 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. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR):** Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable:** Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.2e).

   Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.
   1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.
   2. No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**. Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. Objective status notes:

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.

3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.

6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.

7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.3 Best Response

a. CR: At least one objective status of CR documented before progression or symptomatic deterioration.

b. PR: At least one objective status of PR or better documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 **Assessment Criteria for Brain Metastases Cohort**

a. **Measurable disease**: Measurable disease is defined as contrast enhancing lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of 1.0 cm, visible on two or more axial slices that are preferably ≤ 0.5 cm apart with 0-mm skip (and ideally ≤ 1.5 mm apart with 0-mm skip). In addition, although the longest diameter in the plane of measurement is to be recorded, the diameter perpendicular to the longest diameter in the plane of measurement should be at least 0.5 cm for the lesion to be considered measurable. If the MRI is performed with thicker slices, the size of the measurable lesion at baseline should be at least double the slice thickness.

b. **Non-measurable disease:** All other lesions, including lesions with longest dimension (LD) < 1.0 cm, lesions with borders that cannot be reproducibly measured, dural metastases, bony skull metastases, and leptomeningeal disease.

c. **Baseline Documentation of Target and Non-Target Lesions in the CNS:** When more than one measurable lesion in the CNS is present at baseline, all lesions up to a maximum of five CNS lesions should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesion[s] with the longest diameter), but in addition, should be those that lend themselves to reproducible repeated measurements.

d. **Objective Status and Best Response:** Patients in the brain metastases cohort will have non-CNS disease assessed and objective status determined according to RECIST 1.1 criteria, and CNS disease assessed and objective status determined per the RANO-BM criteria below for intracranial response. A determination of progression for PFS is defined as either an objective status of PD by RANO-BM for CNS or an objective status of progression by RECIST 1.1 for non-CNS, or both.

Evaluation of Target Lesions:

Complete response (CR): Disappearance of all CNS target lesions sustained for at least 4 weeks; no new lesions; no corticosteroids; stable or improved clinically.

Partial response (PR): At least a 30% decrease in the sum LD of CNS target lesions, taking as reference the baseline sum LD sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.

Progressive disease (PD): At least a 20% increase in the sum LD of CNS 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%, at least one lesion must increase by an absolute value of ≥ 0.5 cm to be considered progression.

Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD while on study.

Evaluation of Non-Target Lesions:
Non-target lesions should be assessed qualitatively at each of the time points specified in the protocol.
CR: Requires all of the following: disappearance of all enhancing CNS non-target lesions, no new CNS lesions.

e. **Non-CR/Non-PD:** Persistence of one or more non-target CNS lesion(s)
PD: Any of the following: unequivocal progression of existing enhancing non-target CNS lesions, new lesion(s) (except while on immunotherapy-based treatment), or unequivocal progression of existing tumor-related non-enhancing (T2/FLAIR) CNS lesions. In the case of immunotherapy-based treatment, new lesions alone may not constitute progressive disease

Summary of Criteria for Assessment of CNS Metastases

Criterion	CR	PR	SD	PD
Target lesions	None	≥ 30% decrease in sum LD relative to baseline	< 30% decrease relative to baseline but < 20% increase in sum LD relative to nadir	≥ 20% increase in sum LD relative to nadir*
Non-target lesions	None	Stable or improved	Stable or improved	Unequivocal PD*
New lesion(s) **	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	NA+
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse*
Requirement for response	All	All	All	Any+

Abbreviations: CNS, central nervous system; RANO, Response Assessment in Neuro-Oncology; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NA, not applicable; LD, longest dimension.

* Progression occurs when this criterion is met.

** New lesion = new lesion not present on prior scans and visible in at least 2 projections. If a new lesion is equivocal, for example because of its small size, continued therapy may be considered, and follow up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan showing the new lesion.

+ Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

10.5 Performance Status:

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.6 Time to Treatment Failure

From date of registration to date of first documentation of progression or symptomatic deterioration (as defined above), early discontinuation of treatment, or death due to any cause. Patients last known not to have failed treatment are censored at the date of last contact.

10.7 Time to Death

From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

10.8 Progression-Free Survival

From date of registration to date of first documentation of progression or symptomatic deterioration (as defined above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last contact.

11.0 STATISTICAL CONSIDERATIONS

11.1 Endpoints

The primary endpoint is progression-free survival (PFS) defined as time from registration (randomization) to progression or death due to any cause. Progression is defined as radiologic progression of disease by RECIST criteria **or** unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Progression in the brain metastases cohort is defined as the first detection of radiologic progression of intracranial, extracranial or both intracranial and extracranial disease.

Secondary endpoints include response rate (measurable disease only), clinical benefit rate, and overall survival. Overall survival is defined as time from registration to death due to any cause. Patients without the event are censored at the last contact. Patients will be followed for a minimum of 5 years after registration to determine overall survival results.

Patients who meet eligibility criteria for the trial will be enrolled and randomized to Arm 1 or Arm 2 for treatment. Patients will be stratified at time of randomization by line of therapy. At the start of the trial patients are not randomized by *BRCA* status but will be analyzed within their *BRCA* group after it is determined. Patients who enter the trial will undergo centralized *BRCA1/2* mutation testing and ultimately be assigned to the appropriate group (germline mutation confirmed positive or germline mutation confirmed negative). Because the testing takes several weeks, it is not possible to delay randomization until the test result is known. Interim assessments will be performed to assess the balance of the groups which incorporates information gained from *BRCA*1/2 mutation testing.

Classification of patients as germline *BRCA* or *BRCA*-like or non *BRCA*-like will be determined within a few weeks after randomization. We will monitor the number of patients in each of the three groups. If the observed accruals deviate strongly from the expected distribution across the three groups, it may be necessary to move to upfront testing of patients and to close groups that have fulfilled their accrual totals. Minor deviations from the expected numbers will be allowed since little impact on power would occur.

11.2 Accrual Goal

Cohort 1: The original expectation was that we would accrue 7 patients per month so that it would have taken 33 months to accrue 235 patients. It actually took 20 months to accrue the 235 patients. However, because there are smaller numbers in the two subgroups of greatest scientific interest than predicted, we are extending the sample size to 324. For the amended sample size of 324 we estimate 12 patients per month after re-opening accrual. The total duration of the accrual period would be 30 months allowing for the temporary suspension. Follow-up after the last patient enrolled is 15 additional months before the PFS analysis is performed, but all patients are followed for survival for a minimum of five years in order to assess OS. A total of 324 patients will be randomized 1:1 between the two arms with stratification on line of therapy. Originally the expected distribution was 63 *BRCA*-mutation patients, 86 *BRCA*-like non-carriers, and 86 non-carriers without *BRCA* characteristics. Using the data available from the interim analysis the final projection for the 324 patients is 44 *BRCA*-mutation patients, 99 *BRCA*-like non-carriers, and 142 non-carriers without *BRCA* characteristics. An additional 39 patients will not be able to be classified due to limited tumor tissue available, assay failure, or an inconclusive result from the assays. Extrapolating from prior studies, approximately 50% of primary sporadic TNBC patients are expected to have a BRCAness phenotype, but it could vary between 40-60%. Note that based on data available from interim analysis approximately 40% of the *BRCA* mutation negative patients are being classified as *BRCA*-like. We have four possible methods for classifying as *BRCA*-like.

After approximately 50% of the expected accruals, we will reassess the proportions allocated to each of the categories and determine if upfront stratification will be needed to prevent large discrepancies from the projected accruals in each category.

Progressive Brain Metastases Cohort (Cohort 2): In the cohort of patients with progressive brain metastases, the expectation is to accrue 2-3 patients per month so it will take about 24 months to accrue 98 patients. Follow-up after the last patient enrolled is 6 additional months before the PFS analysis is performed, but all patients are followed for survival for a minimum of 5 years in order to assess OS. A total of 98 patients will be randomized 1:1 between the two arms.

At the time of this sample size revision there are only three patients in the progressive brain metastases cohort. Therefore, we retain the overall accrual maximum of 333 patients even though the main cohort will accrue 324 patients. The brain metastases cohort will be closed when the main cohort completes accrual.

11.3 Primary Analyses

In the first cohort we will perform three separate analyses, followed by tests of interaction. Since this is a Phase II study, we do not adjust for multiple comparisons in order not to miss a significant signal. With the new sample sizes for the subgroups we recalculate power under the original assumptions. Note that we have determined that upfront testing for the various assays used for BRCA like classification is not practical due to the assay turn-around times and therefore it is not possible to close one or more subgroups and keep others open.

Primary analysis 1: Compare ABT-888 to no ABT-888 in the *BRCA* mutation-carriers (n=44)

A median PFS of 4 months is assumed for Arm 1 (cisplatin + placebo) that improves to 7 months for Arm 2 (cisplatin + ABT-888). Outcome data is expected to be available from 42 of the 44 registered patients. Assuming a hazard ratio (HR) of 1.75 for standard versus experimental, the study will have 69% power (1-sided α = 0.10) to detect if the experimental arm (2) is superior to the standard arm (1). A larger α is used due to the difficulty of enrolling patients with *BRCA* mutations as well as the likelihood of success with the experimental therapy. A stratified log-rank test will be used to compare PFS between the two arms in an ITT analysis where stratification is by line of therapy. Power drops from 80% to 69% under the new design considerations, but unfortunately a full increase in the sample size to restore 80% power is not possible.

Primary analysis 2: Compare ABT-888 to no ABT-888 in the *BRCA* mutation-negative BRCAness-like group (n=99).

A median PFS of 4 months is assumed for Arm 1 (cisplatin+ placebo) that improves to 7 months for Arm 2 (cisplatin + ABT-888). Outcome data is expected to be available from 95 of the 99 registered patients. Assuming a hazard ratio (HR) of 1.75 for standard versus experimental, the study will have 85% power (1-sided α = 0.05) to detect if the experimental arm (2) is superior to the standard arm (1). A stratified log-rank test will be used to compare PFS between the two arms in an ITT analysis.

Secondary analysis 1: Compare ABT-888 to no ABT-888 in the *BRCA* mutation-negative non-*BRCA*-like group (n=142)

Theoretically we would expect no difference by treatment (median PFS of 4 months in both arms). However, it is possible that the classification of *BRCA*-like status has error or that ABT-888 is efficacious anyway in this group. Outcome data is expected to be available from 136 of the 142 registered patients. A test of efficacy will be conducted at 1-sided α = 0.10 even though little or no effect is expected. A stratified log-rank test will be used to compare PFS between the two arms in an ITT analysis. Note: The CIRB requested this be labeled as a secondary analysis, rather than the third primary analysis as approved in the protocol reviewed by CTEP.

Progressive Brain Metastases Cohort

Primary analysis: Compare ABT-888 to no ABT-888 in patients with active brain metastases that are progressive after prior intracranial therapy (N=98).

A median PFS of 2 months is assumed for Arm 1 (cisplatin + placebo) that improves to 3.5 months for Arm 2 (cisplatin + ABT-888). Assuming a hazard ratio (HR) of 1.75 for standard versus experimental, the study will have 84% power (1-sided α=0.05) to detect if the experimental arm (2) is superior to the standard arm (1) with 89 PFS events. Outcome data is expected to be available from 93 of the 98 registered patients. A stratified log-rank test will be used to compare PFS between the two arms in an ITT analysis where stratification is by modified breast-GPA and prior systemic therapies.

11.4 Exploratory analyses of PFS

Interactions of group and treatment using PFS:

Exploratory interaction analysis 1: Test for an interaction of *BRCA*-like status by treatment. Treatment in the *BRCA*-like group (n=99) is expected to be effective (7 months to 4 months), but no effect is expected in the non-*BRCA*-like group (n=142). The study will have 78% power (1-sided α = 0.10) to detect this interaction.

Exploratory interaction analysis 2: Test for an interaction of a *BRCA* mutation versus *BRCA*-like status by treatment. Treatment in both the *BRCA*-like group (n=99) and the *BRCA* mutation group (n=44) is expected to be effective (7 months to 4 months), so no interaction is expected.

The patients who cannot be classified into subgroups will be included in a separate analysis comparing treatment. It is likely that these results will be intermediate to those for the three separate subgroups since they are likely comprised of all three groups, but just could not be categorized.

At the conclusion of these analyses, it should be clear if there is a positive signal for ABT-888 in both *BRCA*-mutated and *BRCA*-like patients, failing to reject the null of no ABT-888 effect in the non-BRCA-like cohort does not imply that ABT-888 has no effect in this subgroup. It is possible that a smaller effect exists but this trial is not sized sufficiently to detect such a difference. Progression will be determined by clinical symptoms and radiologic assessments, per RECIST. A stratified log-rank test will be used to compare PFS for Arm 1 (cisplatin + placebo) versus Arm 2 (cisplatin plus ABT-888), with additional analyses using Cox regression. It is assumed that the benefit of ABT-888 will be the same (on the log hazard rate scale) for *gBRCA* mutation-positive and for BRCA-like TNBC, but have no effect for non-*BRCA* like TNBC. These assumptions will be tested in appropriate tests of interaction. This secondary analysis will examine treatment effects for groups defined as *gBRCA* mutation-positive and BRCAness combined versus non-BRCAness, and will test the treatment by phenotype interaction.

Brain Metastases Cohort

Exploratory Analysis: Compare ABT-888 to no ABT-888 in the patients with progressive brain metastases with or without either a BRCA-mutation or BRCA-like phenotype.

For patients with BRCA-mutation or BRCA-like phenotype, it is assumed that a greater improvement in PFS would occur with the combination therapy that would result in an increase from a median PFS of 2 months for Arm 1 (cisplatin + placebo) to at least 4 months for Arm 2 (cisplatin + ABT-888), and corresponding HR ≥ 2.0. Because markers will be exploratory, analysis will only be conducted under a hypothesis testing framework if at least half of the patients enrolled (n ≥ 49) have evaluable specimen which indicate a BRCA-mutation or BRCA-like phenotype, and at least 80% power using a log-rank that with a 1-sided $\alpha = 0.10$. A larger α is used for the exploratory analysis due to the uncertainty of enrolling patients with evaluable specimen for BRCA status. A stratified log-rank test will be used to compare PFS between the two arms in an ITT analysis where stratification is by modified breast-GPA. If fewer than 49 brain metastases patients are enrolled with an identified BRCA-mutation or BRCA-like phenotype, the subgroup analysis will be estimation-only in order to explore the treatment effects in the biomarker—defined subgroup, reporting the observed HR and 95% confidence interval from a stratified Cox proportional hazard model.

Theoretically, we would expect no difference by treatment in BRCA mutation-negative non-BRCA-like subgroup. Analysis plans will be estimation-only for patients confirmed to be in this biomarker-defined subgroup, reporting the observed HR and 95% confidence interval from a stratified Cox proportional hazards model.

11.5 Overall Survival (OS)

The same analyses as in Sections 11.3 and 11.4 will be repeated using OS instead of PFS.

11.6 Response rate and clinical benefit rate

Response rate will be analyzed for patients with measurable disease. Patients who achieve complete or partial response will be classified as having a response. Clinical benefit will be assessed in all patients and will include those with complete or partial response and those with stable disease for 6 months. The primary analyses will be conducted using these binary responses using Fisher's exact test and logistic regression.

11.7 Interim analysis and timing of final analysis

Parent/Primary Cohort: Under the alternative hypothesis, about 207 events are expected overall in the three subgroups. Therefore, final analyses will be conducted at the expected total number of events or 2 years after the last randomized patient, whichever comes first.

Original protocol: We will monitor the three groups separately with respect to the percentage of expected failures. Ideally there will be a single time point for interim analyses where 50% of the expected total events have occurred. However, if any group has not yet reached 35% of the expected events or if one group has already reached 65% of the events, then separate interim analysis time points will be used. There are no planned interim efficacy analyses. If the groups are randomized as expected then 109 events would be reached after 2 years of accrual at about 67% of accrual. If the hazard ratio for ABT-888 versus no ABT-888 exceeds 1.0 (i.e. is in the wrong direction) in any one of the three groups, then we will recommend that no further patients will be randomized to that group. This recommendation will be made to the DSMC who will make the final recommendation about the trial. This would require an amendment since up-front testing would then be required before randomizing a patient. Currently, classification is done after a patient is enrolled and randomized.

Revised protocol: Due to the speed of accrual and delay in classification of patients into subgroups, a single interim analysis was performed after 235 patients were accrued. The DSMC recommended continuing the study as planned incorporating the new sample size into the protocol.

Original protocol: A similar futility analysis will be performed in the brain metastasis cohort when 50% of the expected 89 events have occurred, and will recommend closure if the hazard ratio for ABT-888 versus no ABT-888 exceeds 1.0.

Revised protocol: The DSMC recommended closure of this cohort at the same time as the main cohort completes accrual regardless of the total number of accrued patients.

11.8 Toxicity

Toxicity is assessed using criteria based on CTCAE Version 4. The two arms will be compared using Fisher's exact test for dichotomous classifications (e.g. Grades 3-5 versus Grades 0-2) for each toxicity. No adjustment for multiplicity is done since an important toxicity signal could be missed.

11.9 Data and Safety Monitoring Committee (DSMC)

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of the SWOG, 3 SWOG members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistics and Data Management Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

12.0 DISCIPLINE REVIEW

There will be no discipline review for this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than ten working days prior to planned start of treatment). **NOTE: No blinded starter supplies will be available for this study.** Initial patient-specific clinical supplies of ABT-888/placebo will be shipped from the Pharmaceutical Management Branch (PMB) to the registering investigator at the time of patient registration and should arrive within 7 to 10 days (see Section 3.1d).

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

13.3 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five-person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol Principle (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

13.4 CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

a. **IRB Approval:**

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB

Certification/Declaration of Exemption Form. In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating roster;

- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements
Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

b. **Protocol-Specific Requirements For S1416 Site Registration:**

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- For applicable NCTN studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations, access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component. Enrolling sites are responsible for ensuring that the appropriate agreements are in place with their RTI provider, and that appropriate IRB approvals are in place.

c. **Downloading Site Registration Documents:**

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select SWOG, and protocol number **S1416**;
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

d. **Submitting Regulatory Documents:**

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

e. **Checking Your Site's Registration Status:**

You can verify your site's registration status on the members' side of the CTSU website. Site registration status may be verified on the CTSU members' website.

- Click on Regulatory at the top of the screen;
- Click on Site Registration; and
- Enter the sites 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

13.5 Oncology Patient Enrollment Network (OPEN)Registration Requirements

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.
Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.6 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

Data submission schedule will be created by the stat center using the format below.

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the CTSU website (www.ctsu.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3a for details.

14.3 Data Submission Procedures

a. Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:
- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:
- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log

in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password and click on the accept link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

b. You may also access Rave® via the SWOG CRA Workbench via the SWOG website (www.swog.org).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to the CTSU Participation Table.

d. Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendar functionality.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF REGISTRATION:

Submit the following:

S1416 Onstudy Form

S1416 Baseline Abnormalities Form

S1416 Baseline Tumor Assessment Form

Documentation of previously confirmed deleterious BRCA1 or BRCA2 germline mutation

Pathology Report

Submit radiology reports from all scans performed to assess disease at baseline.

b. WITHIN 14 DAYS AFTER REGISTRATION:

Submit the following:

Tissue and blood specimens as outlined in Section 15.0.

c. WITHIN 7 DAYS AFTER EACH CYCLE OF TREATMENT:

Submit the following:

S1416 Treatment Form

S1416 Adverse Event Summary Form

d. WITHIN 14 DAYS AFTER EACH SCAN FOR DISEASE ASSESSMENT (EVERY 9 WEEKS UP UNTIL 54 WEEKS FROM REGISTRATION, THEN EVERY 18 WEEKS UNTIL PROGRESSION OR AS CLINICALLY INDICATED):

Submit the following:

Follow Up Tumor Assessment Form

Scan reports

e. WITHIN 14 DAYS OF DISCONTINUATION OF BLINDED TREATMENT:

Submit the following:

Off Treatment Notice

Final **S1416** Treatment Form

S1416 Adverse Event Form

f. WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

Submit the following:

Follow Up Tumor Assessment Form

Scan reports

Off Treatment Notice, final **S1416** Treatment Form and **S1416** Adverse Event Form and (if the patient was still on protocol treatment) or

Follow-Up Form (if the patient was off protocol treatment) documenting date, site and method for determining progression/relapse.

g. AFTER OFF TREATMENT EVERY 9 WEEKS UP UNTIL 54 WEEKS FROM REGISTRATION, THEN EVERY 18 WEEKS UNTIL PROGRESSION, THEN EVERY 6 MONTHS UNTIL 5 YEARS AFTER REGISTRATION:

Submit the following:

Follow Up Form

Late Effects Form (if prior treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] long term toxicity that has not been previously reported).

h. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death and a final **S1416** Treatment Form and **S1416** Adverse Event Form (if the patient was still on protocol treatment) or Follow-Up Form (if the patient was off protocol treatment) documenting death information.

15.0 SPECIAL INSTRUCTIONS

15.1 Primary Tumor Specimens (REQUIRED)

Primary tumor specimens (submitted to the SWOG Specimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201) **required** for patient:

a. Specimens must be submitted at the following times:

1. Baseline Submission - Formalin Fixed Paraffin Embedded (FFPE) Block or 20 unstained slides (eighteen (18) ten-micron uncharged slides and two (2) five-micron charged slides) from primary tumor. If unstained slides are being submitted, the following sequence for slide preparation should be followed: First, cut one (1) five-micron slide, followed by nine (9) ten-micron slides, followed by one (1) five-micron slide, followed by nine (9) ten-micron slides. NOTE: If archived primary tumor is not available, please contact Dr. Sharma (**S1416**question@swog.org).

b. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage https://www.swog.org/member-resources/biospecimen-resources), or via the link on the **S1416** protocol abstract page on the SWOG website (www.swog.org).

c. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

d. Any leftover tissue not consumed by testing will be banked for future use according to the patient's selection on the "Optional Biobanking for Possible Future Studies" section of the consent form.

15.2 Specimens from Metastatic Tissue

Specimens from metastatic tissue (or recurrence) (submitted to the SWOG Specimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201):

a. Specimens must be submitted at the following times:

Baseline Submission – Formalin Fixed Paraffin Embedded (FFPE) Block or 10 unstained slides (8-ten micron uncharged slides and 2- five micron charged slides) from archived metastatic tissue.

If archival metastatic tumor tissue is exhausted, then a new fresh tumor biopsy that is formalin-fixed and paraffin-embedded (FFPE) is highly recommended with patient's consent. Submission of the metastatic tissue is not required if no archival specimen is available and a new biopsy is not feasible.

b. Metastatic Tissue Biopsy Instructions:

If a pre-treatment metastatic tumor biopsy is performed, a local standard surgical consent form must be obtained. The biopsy can be image-guided or excisional and can be obtained as per local institutional guidelines. The use of imaging to facilitate biopsies will be decided by members of the Interventional Radiology team at the clinical site and may include ultrasound, CT scan, or MRI. Brain biopsies will be permitted if the patient has medical necessity for craniotomy for clinical care. Mediastinal, laparoscopic, gastrointestinal, or bronchial endoscopic biopsies can be obtained incidentally to a clinically necessary procedure and not for the sole purpose of the clinical trial. Sites are requested to follow the below standard instructions for metastatic tumor biopsy and preparation of paraffin embedded tissue block:

-Obtain four 16-gauge or 18-gauge core needle biopsy specimens.
-Place the fresh tissue in formalin. Do not exceed 24 hours fixation time.
-Fixed tissue must be paraffin embedded within 24 hours.
-Cut one H&E (hematoxylin and Eosin) stained section from the representative paraffin-embedded tissue block.

c. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

d. Specimen submission instructions can be accessed on the SWOG Specimen Submission webpage (https://www.swog.org/member-resources/biospecimen-resources), or via the link on the **S1416** protocol abstract page on the SWOG website (www.swog.org).

e. Any leftover tissue not consumed by testing will be banked for future use according to the patient's selection on the "Optional Biobanking for Possible Future Studies" section of the consent form.

15.3 BRCA 1 and BRCA 2 Testing (REQUIRED)

Specimens for Germline BRCA1 and BRCA2 testing (submitted to the University of Washington – King/Swisher Laboratory, Lab #223) **required** for all patients:

a. Specimens must be submitted at the timepoints listed below. Collection instructions are outlined in Section 15.3c and submission instructions are outlined in Section 15.3e. The genetic testing results for the patient will be provided back to the enrolling site in Rave® as a report uploaded in the Genetic Testing Results folder, and will include both "positive" and "negative" results for 12 genes (BRCA, BRCA2, ATM, BARD1, BRIP1, CHEK2, NBN, PALB2, PTEN, RAD51C, RAD51D, TP53). A positive result will only include "deleterious mutation". Mutations of uncertain significance will not be reported.

Note that treatment may begin prior to receiving results.

b. Specimens must be submitted at the following times (see Section 9.0):

1. Baseline Submission (after registration, collected and submitted on the same day) – 7mL whole blood in yellow top (ACD solution A) tube.

c. COLLECTION INSTRUCTIONS

ONLY COLLECT AND SHIP SAMPLES TO THE KING/SWISHER LABORATORY MONDAY THROUGH THURSDAY. DO NOT DRAW SAMPLES ON A FRIDAY OR THE DAY BEFORE A HOLIDAY. SAMPLES MUST BE SHIPPED ON THE SAME DAY OF COLLECTION.

1. No processing necessary. The filled tube must be maintained at ambient (15–30°C) temperature, avoiding extremes of heat and cold, at all times.

d. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

e. SHIPPING SAMPLES

1. SWOG Specimen Tracking System (STS)

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. Non- SWOG users may log into SpecTrack using their CTSU UserID and password on the SpecTrack login page located at: https://spectrack.crab.org (select the option "SWOG – SWOG – CTSU"). SpecTrack start-up instructions (both written and demo) are available after signing in to SpecTrack.

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

(NOTE: If a specimen had an incomplete submission, this must be documented in the Specimen Tracking System under “Comments.” If no specimen was available, this must be documented in the Specimen Tracking System by choosing “Notify that Specimen Cannot be Submitted”).

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page: https://spectrack.crab.org/Instructions; or contact the SWOG Statistics and Data Management Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

In the online specimen tracking system, the appropriate SWOG laboratory for submission of blood samples for SWOG Biospecimen Bank Submission and ***BRCA1 and BRCA2*** testing is identified as follows:

Lab #223: King/Swisher Laboratory
Phone: 206/616-4296
Contact: Dr. Elizabeth Swisher

2. Federal guidelines for the shipment of blood products:

   a. *The tube must be wrapped in an absorbent material.*

   b. The tube must then be placed in an AIRTIGHT container (like a resealable bag).

   c. Pack the resealable bag and tube in a Styrofoam shipping container.

   d. Pack the Styrofoam shipping container in a cardboard box.

   e. Mark the box "Biohazard".

15.4 Specimens for Circulating Tumor Cell-Next Generation Sequencing (CTC-by HD-CTC followed by CTC-NGS) **(REQUIRED)**:

a. Specimens must be submitted at the timepoints listed below. Collection instructions are outlined in Section 15.4c and submission instructions are outlined in Section 15.4e.

b. Specimens must be submitted at the following times (see Section 9.0):

   1. 1 tube of whole blood in a Streck Cell-Free DNA tube after registration (prior to treatment), Cycle 2 Day 1 and progression. The specimens must be shipped on the same day as collection.

c. Specimen Collection Instructions for CTC-NGS

ONLY COLLECT AND SHIP SAMPLES TO THE LABORATORY MONDAY THROUGH THURSDAY. DO NOT DRAW SAMPLES ON A FRIDAY OR THE DAY BEFORE A HOLIDAY. SAMPLES MUST BE SHIPPED ON THE SAME DAY OF COLLECTION.

- Materials required for blood collections are one (1) Streck Cell-Free DNA tube, Vacutainer® brand adapter, and needles.
- Blood samples can be obtained by venipucture using a Vacutainer brand adapter and needle, or from a port or other central venous catheter using appropriate access needles and techniques.
- If multiple tubes are being drawn, the Streck Cell-Free DNA tube must be last.
- If no other tubes are needed, then the first 2 mL of blood must be drawn into another tube (not Streck Cell-free DNA) and discarded. Then, proceed to draw blood into the Streck Cell-free DNA tube.
- Fill the Streck Cell-free DNA tube. Minimum blood volume is 8-9 mL.
- Invert Streck Cell-free DNA tube a minimum of eight (8) times to ensure proper mixing of the additives contained in the tube.
- Write the SWOG patient number, visit designation (*i.e.* baseline, C2D1, progression) and the date of collection on the tube.
- The filled tube must be maintained at ambient (15–30°C) temperature, avoiding extremes of heat and cold, at all times.

d. Specimen Collection Kits for CTC-NGS (sent to Kuhn Laboratory)

Supplies can be obtained by sending an e-mail to kuhnlab@usc.edu. Please indicate the part number and quantities. To facilitate the ordering process, the subject line of the e-mail should be "**S1416** [NCI site code]". Please provide full shipping address.

Part Number	Product Description	Quantity
42107	CTC-NGS shipping kit	1

CTC-NGS Shipping kit includes Standard71 shipping system, Streck Cell-free DNA tube and shipping instructions.

The hours of operation for the Kuhn Lab are Monday-Friday, 8:00 AM – 5:00PM PST. **Although the lab will attempt to ship supplies out as quickly as possible, orders should be placed approximately 10 days before supplies are needed.**

e. Shipping Instructions

ONLY COLLECT AND SHIP SAMPLES TO THE DESIGNATED STUDY LABORATORY MONDAY THROUGH THURSDAY, DO NOT DRAW SAMPLES ON A FRIDAY OR THE DAY BEFORE A HOLIDAY. SAMPLES MUST BE SHIPPED ON THE SAME DAY OF COLLECTION.

1. SWOG Specimen Tracking System (STS)

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. Non- SWOG users may log into SpecTrack using their CTSU UserID and password on the SpecTrack login page located at https://spectrack.crab.org (select the option "SWOG – SWOG – CTSU"). SpecTrack start-up instructions (both written and demo) are available after signing in to SpecTrack.

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an e-mail to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page: https://spectrack.crab.org/Instructions; or contact the SWOG Statistics and Data Management Center at 206/667-2267 to be routed to the Data Coordinator for further assistance.

In the online specimen tracking system, the appropriate SWOG laboratory for submission of blood samples **CTC-NGS** testing (**1 Streck Cell-Free DNA tube**) is identified as follows:

Lab #209: Kuhn-Hicks Laboratory
Phone: 213/740-9945
Contact: Xiomara Villasenor
E-mail: kuhnlab@usc.edu

NOTE: SpecTrack will prompt you to enter the CBC results for each of the CTC-NGS collection timepoints.

2. Guidelines for the shipment of CTC-NGS (sent to the Kuhn laboratory)

a. Instructions are available at: http://kuhn.usc.edu/SWOG1416shipping/
Ship on collection day (Monday to Thursday) and select appropriate courier overnight service for delivery by 10:30 am of the day after collection day
   - If FedEx: select Priority Overnight service
   - If UPS: select Next Day Air service

b. The filled Streck Cell-Free DNA blood collection tube must be inserted into the inner primary container along with a sachet of absorbent material. Place cap on securely to close.

c. The primary container must be placed into a secondary container. Place cap on securely to close.

d. Place the secondary container containing the primary container and the Streck Cell-Free DNA blood collection tube into one half of the white cassette.

e. Place the second half of the white cassette onto the other half fitting the plugs into the holes to close the cassette.

f. Place the white cassette into the protective silver shipping air bag. Place the Shipment Packing List (generated by SpecTrack) inside and close the bag.

g. Place the shipping air bag into the blue standard71.com cardboard box and close.

h. Generate the courier shipping label as instructed in (a). Insert label in the pouch attached to the outside of the blue cardboard box. Contact your local courier representative for pick-up.

i. Notify the receiving laboratory of the pending shipment by e-mail (kuhnlab@usc.edu) on collection day. The subject line should be "**S1416** [NCI site code]." Include the following information:

- Patient ID (6 digits) and Specimen # (7 digits, as provided by SpecTrack)
- Visit designation (Baseline, C2D1 or Progression)
- Date and time of blood collection
- Shipment tracking number

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Publication and Industry Contact

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

1. Agent may not be used outside the scope of this protocol, nor can Agent be transferred or licensed to any party not participating in the clinical study. Collaborator data for Agent is confidential and proprietary to Collaborator and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agent 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 investigational 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 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 which 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 investigational 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 exclusively 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 the Collaborator(s) for Phase III 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 the 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:

E-mail: ncicteppubs@mail.nih.gov

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

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol and patient-specific CDUS data will be submitted quarterly to CTEP by electronic means, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31 and October 31. The SWOG Statistics and Data Management Center will submit data using the CDUS that can be found on the CTEP web site (http://ctep.cancer.gov/reporting/cdus.html)

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event, as specified in Table 16.1.

In the rare event when internet connectivity is disrupted a 24-hour notification is made to NCI by telephone at 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Any supporting documentation requested by CTEP should be submitted in accordance with instructions provided by the CTEP-AERS system.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent used in this study is ABT-888. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] ABT-888/placebo.

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 CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

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. or Section 16.1f.

Expedited AE reporting timelines are defined as:

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

- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a CTEP IND:**

1) **Group-specific instructions**

Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. In addition, you may be asked to submit supporting clinical data to the Operations Offices in order to complete the evaluation of the event. If requested, the supporting data should be sent within **5 calendar days** by fax to 210-614-0006. Supporting clinical data submitted should include:

- Printed copy of the first page of the CTEP-AERS Report.
- Copies of clinical sourced documentation of the event.
- If applicable, and they have not yet been submitted to the SWOG Statistics and Data Management Center copies of Off Treatment Notice and/or Notice of Death.

2) The adverse events listed below also require expedited monitoring for this trial:

- Seizures – report all occurrences regardless of Grade attribution

3) The adverse events listed below do **not** require expedited reporting via CTEP-AERS:

- Neutropenia ≤ Grade 4

g. ***Reporting Secondary Malignancy, including AML/ALL/MDS***

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- 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.

Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

For more information see:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

2. Supporting documentation should be submitted to CTEP in accordance with instructions provided by the CTEP-AERS system. A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days by fax to 210-614-0006 or mail to the address below:
   - a copy of the pathology report confirming the AML/ALL /MDS diagnosis
   - (if available) a copy of the cytogenetics report

   SWOG
   ATTN: SAE Program
   4201 Medical Drive, Suite 250
   San Antonio, Texas 78229

   NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

h. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

1. **Pregnancy:** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Fetal Death:** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions** SOC.

3. **Death Neonatal:** Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

   A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm.

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18.0 APPENDIX

18.1 ABT-888/Placebo Intake Calendar

Cycle: ________ Start Date: ____________ Start Day (circle one): Sun M Tu W Th Fr Sat

Instructions for the participant:
This is a 21 day cycle calendar on which you are to record the number of ABT-888/Placebo capsules you take each day. ABT-888/Placebo should be taken twice daily at the same time of day for 14 days out of 21 days if taken with chemotherapy, or for 21 days continuously if taken after completing chemotherapy as monotherapy. You may take the medication with or without food. If you miss your scheduled dose of ABT-888/Placebo and less than 6 hours have passed since the scheduled dosing time, the dose may be taken.

- **Missed doses** are to be omitted rather than made up.
- If you **vomit** a dose, the dose should not be retaken.
- If you develop any side effects from the capsule, mark this on the calendar on the day you note the effect. Contact site personnel listed below.

Put the date in the box on the calendar and note the time of each dose for each day. Take medication as directed by study doctor. Line through the days medication is not taken.

Storage:
ABT-888/Placebo capsules should be stored at room temperature (not to exceed 25ºC) in their original container. Keep the medication in the bottles provided and do not transfer it to any other container.

If you have questions contact: ____________________ Telephone: _____________________

Special instructions:

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
AM: ________ PM: ________	AM: ________ PM: ________	AM: ________ PM: ________	AM: ________ PM: ________	AM: ________ PM: ________	AM: ________ PM: ________	AM: ________ PM: ________
AM: ________ PM: ________	AM: ________ PM: ________	AM: ________ PM: ________	AM: ________ PM: ________	AM: ________ PM: ________	AM: ________ PM: ________	AM: ________ PM: ________
AM: ________ PM: ________	AM: ________ PM: ________	AM: ________ PM: ________	AM: ________ PM: ________	AM: ________ PM: ________	AM: ________ PM: ________	AM: ________ PM: ________

Compliance confirmed by______________________________________
Research Staff Signature and Date

18.2 Emergency Unblinding Guidelines

a. **General Considerations**

The randomized regimen for this study includes ABT-888 or placebo. During the course of this study it may become necessary to identify (or unblind) a patient's treatment assignment. The circumstances that will warrant emergency unblinding and the procedure for emergency unblinding are described in this Appendix.

b. **Criteria for Emergency Unblinding**

In general, treatment assignments will not be emergency unblinded unless there is a compelling medical or ethical reason that the treatment should be identified. In most circumstances it will be appropriate to treat the patient or person who received ABT-888/placebo as though he or she received ABT-888, irrespective of the drug actually received. Therefore, emergency unblinding should seldom be necessary.

The following events MAY require emergency unblinding of treatment assignments in this study:

1. A compelling medical need as determined by a physician, e.g., existence of a condition for which knowledge of the patient's treatment assignment is necessary for the selection of appropriate care.

2. Administration of ABT-888/placebo to a person other than the patient.

c. **Procedure for Emergency Unblinding**

Emergency unblinding of treatment assignments for patients on this study will be performed by the Washington Poison Center (WPC), upon approval from a designated physician (either one of the WPC's resource physicians, Dr. Eve Rodler, or Dr. Priyanka Sharma). The procedure for emergency unblinding the treatment assignment for a patient on this study is as follows:

1. All requests for emergency unblinding must be made by the registering physician or his/her designee.

2. Call the WPC collect at 206/526-2121 from outside Washington State or toll free at 800/222-1222 from within Washington State. The WPC is accessible 24 hours per day, 365 days per year.

   The person calling the WPC must be prepared to provide the following information:

   Study number (**S1416**)
   SWOG Patient Number (e.g., "**S1416-XXX**")
   Patient Initials (LFM)
   Name and telephone number of the caller
   Reason emergency unblinding is thought to be required

3. The WPC will contact one of its resource physicians and provide the information received from the caller. If none of the WPC's resource physicians can be contacted, then the WPC will contact Dr. Eve Rodler or Dr. Priyanka Sharma. The contacted physician will evaluate the need for emergency unblinding and provide the WPC either approval to unblind or a recommendation for treatment, if any, while maintaining blinding. The WPC will then call the person who initiated the unblinding request and tell him/her either the treatment assignment or the resource physician's treatment recommendation.

4. If the WPC is unable to contact any of its resource physicians or Drs. Rodler or Sharma within three hours after receiving the request for emergency unblinding, then the WPC will notify the person who initiated the unblinding request that treatment assignment will not be unblinded at that time and treatment of the patient or person who received ABT-888/placebo should proceed as if the ABT-888/placebo is ABT-888. In such cases, the WPC will continue to attempt to contact the resource physicians, and when one of them is contacted, will proceed as in #3 above.

5. Any patient whose treatment assignment is emergency unblinded will receive no further ABT-888, but should continue all other protocol treatment if his/her medical condition permits.

6. Unblinding of treatment assignments for any reason must be documented on the Off Treatment Notice.

Questions regarding the unblinding may be directed to any of the following resource physicians:

Eve Rodler, M.D. (Medical Oncology)
UC Davis Comprehensive Cancer Center
4501 X Street, Ste. 3016
Sacramento, CA 95817
Phone: 916/734-5959
Fax: 916/734-7946
E-mail: erodler@ucdavis.edu

Priyanka Sharma, M.D. (Translational Medicine)
University of Kansas CC & Med Pavilion
2330 Shawnee Mission Parkway
Mail Stop 5003
Westwood, KS 66205
Phone: 913/588-6029
FAX: 913/588-4085
E-mail: psharma2@kumc.edu

Julie R. Gralow, MD
Seattle Cancer Care Alliance
825 Eastlake Ave E
MS G3-630
Seattle, WA 98109-1023
Phone: 206/288-7722
E-mail: pink@u.washington.edu

Washington Poison Center
Phone: 206/526-2121

18.3 New York Heart Association Criteria

Class	Cardiac Symptoms	Need for Limitations	Physical Ability Additional Rest*	To Work**
I	None	None	None	Full Time
II	Only moderate	Slight or occasional	Usually only slight	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.
** At accustomed occupation or usual tasks.

18.4 Patient Drug Information Handout and Wallet Card

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

[Note to investigators: This appendix consists of an "information sheet" to be handed to the patient at the time of enrollment. Use or modify the text as appropriate for the study agent, so that the patient is aware of the risks and can communicate with their regular prescriber(s) and pharmacist. A convenient wallet-sized information card is also included for the patient to clip out and retain at all times. If you choose to use them, please note that the information sheet and wallet card will require IRB approval before distribution to patients.]

The patient _____ is enrolled on a clinical trial using the experimental study drug **ABT-888 (veliparib)/placebo**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a prescriber need to know:

ABT-888 (veliparib)/placebo interacts with certain specific enzymes in the liver.

- The enzymes in question are ***CYP 1A1, 2D6, 2C19, and 3A4.*** ABT-888 (veliparib) is metabolized by these enzymes and may be affected by other drugs that inhibit or induce these enzymes.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

ABT-888 (veliparib)/placebo may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

ABT-888 (veliparib)/placebo must be used very carefully with other medicines that need certain **liver enzymes to be effective or to be cleared from your system.** Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of ***CYP 1A1, 2D6, 2C19, and 3A4*.**"

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is

_____ and he or she can be contacted at

_____.

May 2015

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **ABT-888 (veliparib)/placebo.** This clinical trial is sponsored by the NCI**.** **ABT-888 (veliparib)/placebo** may interact with drugs that are **processed by your liver**. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

ABT-888 (veliparib)/placebo interacts with **CYP 1A1, 2D6, 2C19, and 3A4,** and must be used very carefully with other medicines that interact with these enzymes and proteins.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **"strong inducers/inhibitors of CYP 1A1, 2D6, 2C19, and 3A4**"
- Before prescribing new medicines, your regular prescribers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is

  _____

  and can be contacted at _____.

18.5 Translational Medicine

a. **Introduction:**

The overarching hypothesis of the study is that the combination of platinum therapy and ABT-888 will be most active in breast cancers (BC) associated with germline (g) *BRCA* mutations and in *BRCA* wild-type triple negative breast cancer (TNBC) that express the BRCAness phenotype, but less active in the non-BRCA phenotype TNBC. Thus, the *gBRCA* testing and BRCAness phenotype assessment (which will be done using a multipronged biomarker approach) are integral biomarkers for this Phase II study (since the primary analysis depends on these assessments). The primary hypothesis tests whether ABT-888 is beneficial in the two populations, g*BRCA* mutation associated BC and in *BRCA* wild-type TNBC that express the BRCAness phenotype excluding those TNBC without the BRCAness phenotype. The secondary hypothesis then tests whether there is an interaction of ABT-888 and the *BRCA* phenotype (*gBRCA* positive and BRCAness type versus non-*BRCA* phenotype).

The following hypotheses will be addressed in the primary and secondary objectives of this trial:

- That cisplatin chemotherapy plus ABT-888 will be more effective than cisplatin chemotherapy alone in patients with *gBRCA* mutations and in patients with *gBRCA* wild-type metastatic TNBC that exhibit "BRCAness" phenotype (as assessed by *predetermined BRCAness phenotype markers)* but will not be effective in patients with *gBRCA* wild-type TNBC that lack *BRCAness* phenotype.
- Up to 50% of *gBRCA* wild-type metastatic TNBC will exhibit "BRCAness" phenotype (as assessed by pre-determined BRCAness markers).
- Pre-treatment metastatic tumor tissue may be a better tumor source than primary tumor to detect "real time" BRCAness phenotype in metastatic TNBC and that TM studies on pre-treatment tumor tissue may improve the performance of the already incorporated integral biomarkers in identifying TNBC patients likely to benefit from platinum-based therapy and ABT-888/placebo.

In order to address these hypotheses, we will perform several translational/correlative science investigations (Figure 1, Figure 2 and Table 1). These will include germline markers of homologous recombination repair deficiency and somatic markers of "BRCAness." The latter is a term coined by Ashworth and colleagues to describe cancers (mostly triple negative) that arise in patients with known wild-type germline BRCA1 and 2, yet behave as if they harbor defects in homologous recombination and DNA repair. *(1)* Therefore, we will collect both germline and somatic tumor tissue. The ***germline*** DNA will be used to determine germline *BRCA1/2* status and germline mutations in other genes involved in homologous recombination-Fanconi Anemia pathway.

Somatic tissue will be collected from both *gBRCA1/2* mutated and wild-type patients to determine "BRCAness" phenotype. We will mandate submission of at least archived, formalin-fixed, paraffin embedded (FFPE) primary cancer and/or metastatic tissue. Table 1 and Figure 1 list the integral BRCAness phenotype assays, with each assay described in detail later in this section.

b. **Objectives:**

Primary objective:

1. For patients with *gBRCA* mutation associated breast cancer or TNBC with a BRCAness phenotype, to compare the efficacy of cisplatin with or without ABT-888 on progression-free survival (PFS) *(gBRCA mutation status and predetermined BRCAness phenotype markers are integral to the study).*

Secondary objectives:

1. For patients with *gBRCA* mutation associated breast cancer or TNBC with a BRCAness phenotype, to compare the efficacy of cisplatin with or without ABT-888 on overall survival (OS) and overall response rate (ORR) *(gBRCA mutation status and predetermined BRCAness phenotype markers are integral to the study)*

2. To test the following molecular determinants (in metastatic and/or primary tumor tissue) of response to ABT-888 and cisplatin-based chemotherapy (*Integrated markers)*:

    a. Basal and Claudin low molecular breast cancer subtypes as assessed by PAM 50 assay
    b. Quantitative *BRCA1*mRNA expression
    c. Independent assessment of each individual BRCAness phenotype marker
    d. Novel BRCAness assays: if during the course of the study other novel and robust BRCAness assays become available we hope to evaluate the impact of the newer assay/s (independent of the pre-specified BRCAness markers). Before being incorporated into the protocol, a new marker will require approval by SWOG Leadership and the NCI in accordance with policies for use of biospecimens from NCTN clinical trials.

3. To determine the overlap of BRCAness phenotype (germline BRCA, BRCA-like, Non-BRCA-like) integral biomarkers with tissue PD-L1 status and to determine if veliparib benefit in patients with BRCA-like phenotype is maintained when adjusting for PD-L1 status.

4. To evaluate CTC-HRD status as a predictive biomarker of response to treatment with cisplatin plus ABT-888 (veliparib) versus cisplatin plus placebo.

5. To evaluate ctDNA HRR mutation status as a predictive marker of response to treatment with cisplatin plus ABT-888 (veliparib) versus cisplatin plus placebo.

Exploratory objectives:

1. Evaluation of markers of PARPi resistance (e.g.: tissue 53BP1 and *BRCA* reversion mutations).

2. To evaluate overlap among the various BRCAness markers.

3. To collect and bank the following specimens for future research:

    a. Germline DNA
    b. Cancer Tissue
    c. Cell-free DNA

c. Figures and tables

Figure 1: Trial schema with integral/integrated TM components

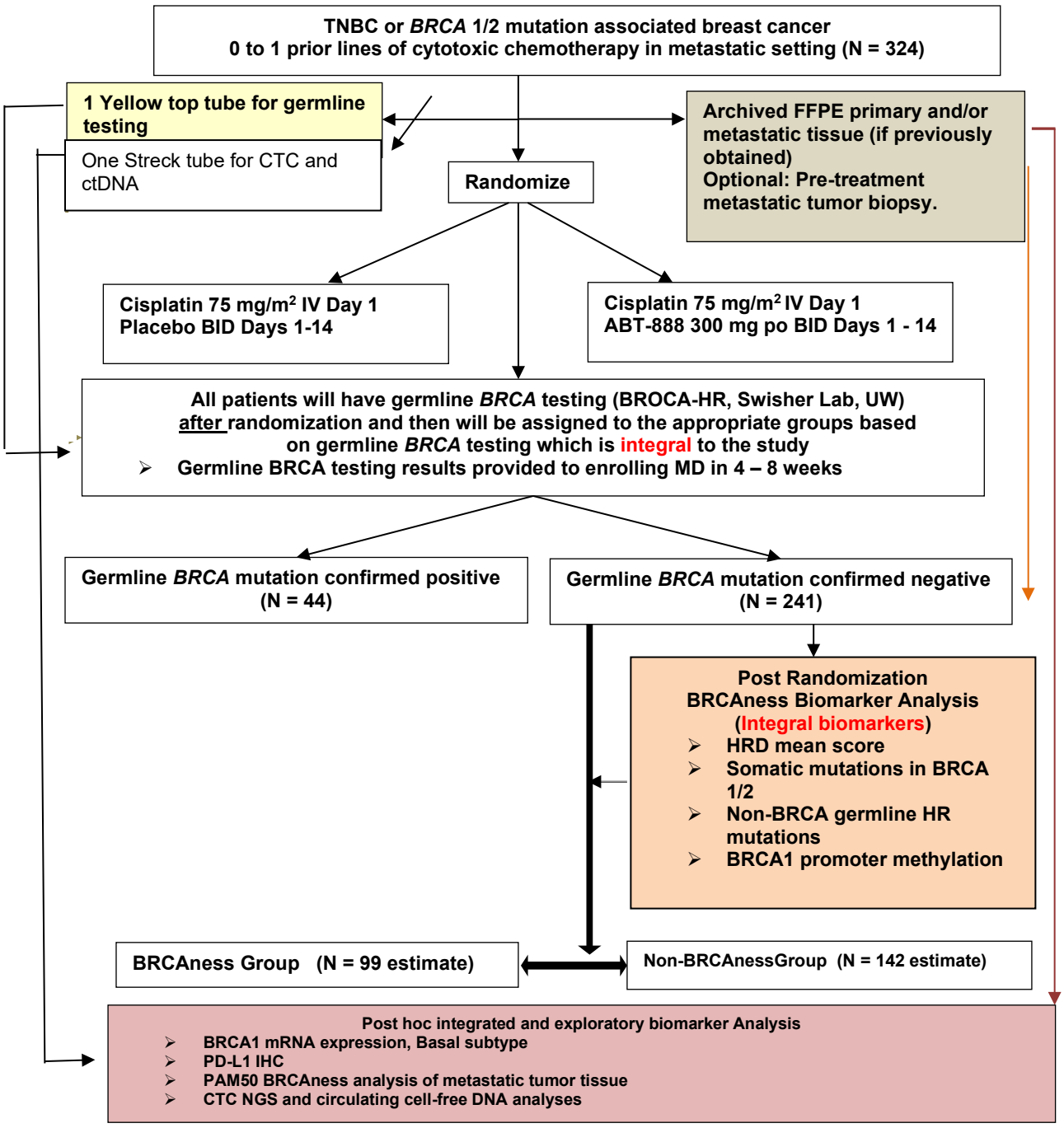
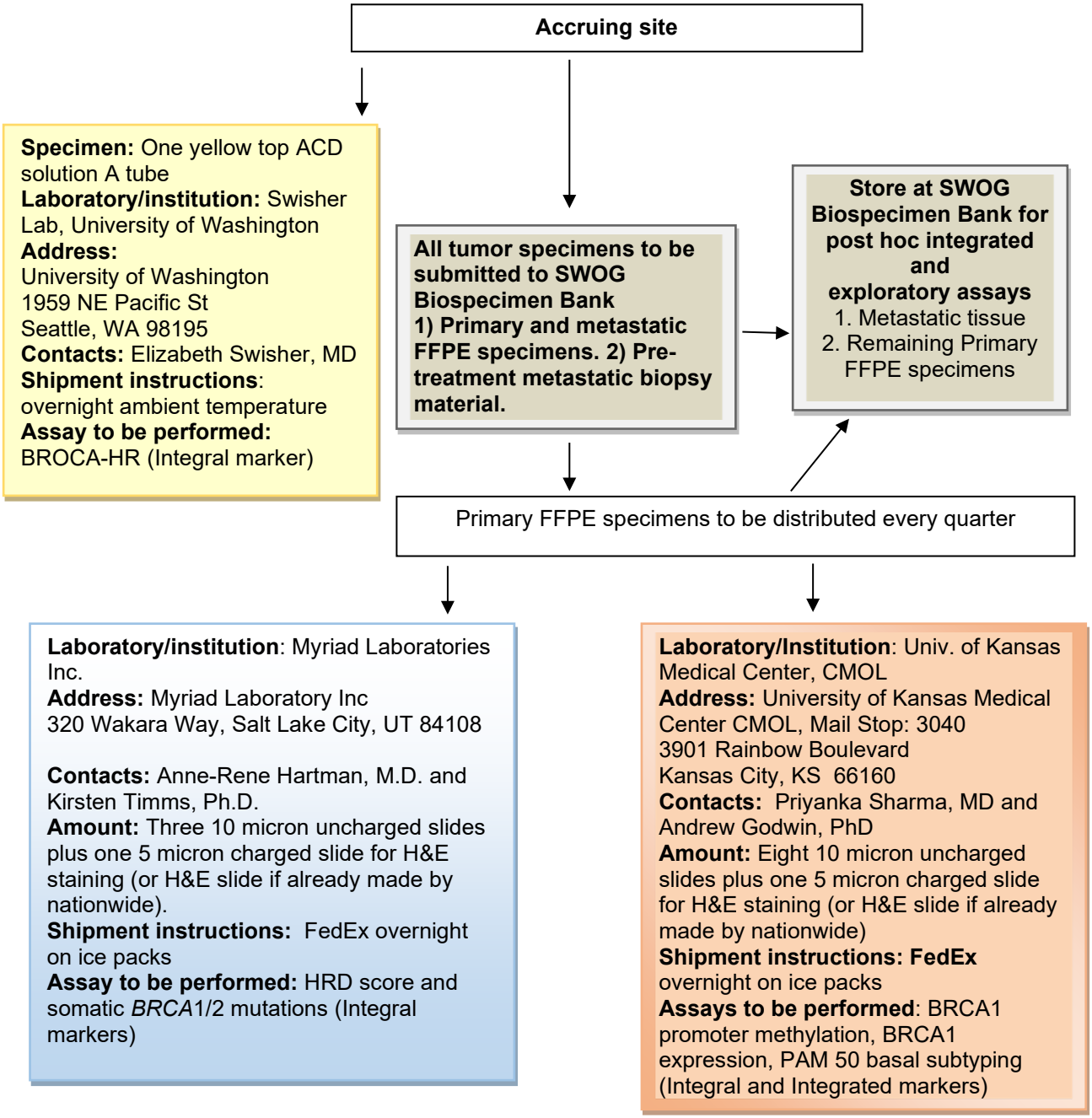


Table 1: Priority table for BRCAness phenotype markers

Marker	Material needed	BRCAness phenotype *	Priority order
HRD score	Tumor gDNA	High HRD score	1
BRCA1 Promoter methylation(PM)	Tumor gDNA	PM present	3
Somatic *BRCA 1/2* mutations	Tumor gDNA	Mutation/s present	2
Non-*BRCA* germline HR mutations	Germline DNA	Mutation/s present	4

*A positive result on ≥1 of the markers will place the subject in the BRCAness phenotype group

Figure 2: Specimen workflow figure for TM studies



d. **GERMLINE MARKERS OF HOMOLOGOUS RECOMBINATION DEFICIENCY**

1. **Germline *BRCA1* and *BRCA2* testing (BROCA-HR).**

Germline *BRCA* testing will be used as a stratification variable for this Phase II study. Germline (g) *BRCA1/2* status is essential for assigning patients to germline *BRCA* mutation-positive and negative groups. BROCA-HR test will be done for *gBRCA 1/2* testing. The patient will be entered into the trial and randomly assigned to ABT-888 or not. Upon availability of BROCA-HR result (which will be within 6-8 weeks of the patient's entry into the trial) patient will be assigned to *gBRCA* mutation confirmed positive or negative group. Thus, *gBRCA* testing will not delay randomization to treatment or initiation of treatment.

BRCA1 and *BRCA2* (*BRCA1/2*) are tumor suppressor genes, in which inherited loss-of-function mutations confer a high lifetime risk of breast and ovarian carcinoma. *(2) BRCA1/2* are key components of the BRCA-Fanconi anemia (FA) pathway, which is critical to homologous recombination (HR)-mediated DNA repair. Repair of platinum-induced interstrand crosslinks invokes *BRCA1*-mediated homologous recombination, and there is abundant clinical and in vitro evidence that *BRCA1*-deficient cells are hypersensitive to platinum agents. *(3,4,5,6,7,8)*

Randomized neoadjuvant and metastatic studies suggest that *BRCA1/2* mutation-associated breast cancers are very sensitive to platinum agents. *(9,10,11,12,13,14)* PARP enzymes recognize DNA damage and facilitate DNA repair to maintain genomic stability. Preclinical studies demonstrate that PARP inhibition in the presence of *BRCA* deficiency leads to synthetic lethality. *(15)* PARP inhibitors (i) have shown preclinical and clinical activity in targeting tumors with pre-existing DNA repair defects, in particular *BRCA1* and *BRCA2* deficient advanced breast and ovarian tumors. *(16,17,18,19,20,21,22,23,24)* A PARP inhibitor olaparib has recently been approved as monotherapy by the FDA as a first-in class drug to treat germline *BRCA* mutation associated advanced refractory ovarian cancers (https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-olaparib-germline-brca-mutated-metastatic-breast-cancer).

The above data provide a strong rationale for evaluation of platinum-based chemotherapy with or without a PARPi in breast cancer patients with *gBRCA1/2* mutations. Triple-negative breast cancers and *BRCA1* germline mutation-associated breast cancers share many histopathologic and molecular features. However, many additional genes involved in homologous recombination may be altered by mutation, rearrangement, DNA methylation or attenuated mRNA expression and can result in impairment of the HR pathway in TNBC. It is speculated that if other factors beyond germline *BRCA* mutations are comprehensively evaluated, 50-60% of TNBC will demonstrate HR deficiency or BRCAness. *(25,26,27)* The combination of platinum therapy and PARP inhibition may be most active in tumors with germline *BRCA1* deficiency and in *BRCA* wild-type tumors that harbor the BRCAness phenotype.

The main aim of this randomized Phase II study is to investigate whether the addition of a PARP inhibitor (ABT-888) to platinum-based therapy will improve progression free survival (PFS) for patients with germline *BRCA* mutation-associated breast cancers and sporadic triple negative breast cancers that express a BRCAness phenotype. Thus, *gBRCA1/2* testing for the entire study cohort is essential (integral biomarker) for identification of the *gBRCA* mutation positive and negative cohorts. Further delineation of

the BRCAness phenotype in the *gBRCA* mutation negative (sporadic) TNBC will be done utilizing *a priori* defined markers (as described above in Table 1 and later in the document).

2. **Laboratory conducting BROCA-HR assay:**

Elizabeth Swisher, MD
Professor, Dept Ob/Gyn
University of Washington
1959 NE Pacific St
Seattle, WA 98195
(206)543-3669

Laboratory: King/Swisher Lab
University of Washington
1959 NE Pacific St,
Health Science Building, K154
Seattle, WA 98195
(206)616-4296
CLIA ID No: 50D0631935
Expiration: 9/27/2019

3. **Description of the BROCA-HR assay:**

A targeted capture and massively parallel sequencing approach called BROCA will be applied to samples. For the proposed study, a more recent version of BROCA-HR with 40 genes (includes *BRCA1/2* as well as genes selected based on known involvement hereditary breast/ovarian cancer or Homologous recombination/ genomic stability) will be utilized. Library preparation has been fully automated to increase sample turnaround and lower cost. Paired-end libraries with 350bp inserts will be prepared from 1ug of constitutional DNA and hybridize to a custom pool of oligonucleotides targeting genomic regions as previously described using the SureSelectXT enrichment system on a Bravo liquid-handling instrument (Agilent). *(28)* Following capture, samples will be barcoded with 48 different indexed primers. The pooled samples are sequenced on a single lane of a HiSeq flowcell (Illumina) with 2x101bp paired end reads and a 7bp index read to allow for de-multiplexing and binning of individual samples. Single nucleotide variants and insertions and deletions will be detected as previously described with some updates in the bioinformatics pipeline. *(29,30)* Deletions and duplications of exons will be detected by a combination of depth of coverage and split read analysis as previously described, supplemented with additional alignments generated by SLOPE. *(31,32)* All germline loss of function mutations in cancer susceptibility genes will be confirmed with PCR amplification and Sanger sequencing.

4. **Description of the specimens, and anticipated methods for specimen acquisition and processing**:

Preferred Specimen: 7ml whole blood
Minimum Volume: 3.5 mL
Instructions: Collect in yellow top (ACD solution A) tube. Specimen to be shipped at ambient temperature for overnight delivery.
Specimen Stability: Room temperature: 3 days; Refrigerated: N/A; Frozen: N/A
Specimen processing: DNA will be extracted from peripheral blood mononuclear cells (PBMCs)
The results will be reported as deleterious germline *BRCA* mutation "present" or absent. Variants of uncertain significance will not be reported.

5. **The expected distribution of the biomarker in the study population:**

It is estimated that 20% of the study population will demonstrate deleterious germline *BRCA1/2* mutation. *(33,34)* Cutpoints will not be used for germline *BRCA* testing. Test results will be described as deleterious germline mutation "present" or "absent". In *gBRCA* mutation-positive patients median PFS of 4 months is assumed for Arm 1 (cisplatin) that improves to 7 months for Arm 2 (cisplatin + ABT-888).

6. **The accessibility of the biomarker assay results**:

Clinical *BRCA* testing report will be provided to the enrolling site for all patients. The genetic testing results for each patient will be provided via Rave® as a report uploaded in the Genetic Testing Results folder.

Genetic counseling services for sites with patients with positive results will be provided when needed (via telephone). Sites/providers in need of such service should contact Dr. Elizabeth Swisher at swishere@uw.edu. Note that counseling services are provided to sites to assist with how to manage patients in need of genetic counseling. The counseling provided is not intended to be provided directly to patients, and is not required of the site. Sites may refer patients to their preferred genetic counseling service.

7. **Data on the analytical performance of the assay:**

Accuracy and precision BROCA HR captures > 99% of known deleterious *BRCA1* and *2* Mutations. *(24)* Deleterious *BRCA1* and *BRCA2* mutations will be defined in the standard fashion to include protein truncating mutations (with the exception on the benign variant *BRCA2* K3326*), and missense mutations demonstrated experimentally to be damaging. Both "BIC", and "HGVS" nomenclatures will be used to report the deleterious mutations. Variants of uncertain significance will not be reported.
Turn-around time: 4-8 weeks
Failure rate: <1%. (35)

8. **Discrepancy between prior germline BRCA testing and trial testing:**

Although germline *BRCA* testing is recommended for a significant number of TNBC patients (all patients < 60 years of age) we expect that only 40-50% of patients will have had prior testing. We expect to find a deleterious *BRCA* mutation via the BROCA test in small percentage (< 2%) of patients who have had a prior negative *BRCA* test. This will be typically due to missed gene-disrupting large rearrangements. With the BROCA test, the chances of not detecting a previously known deleterious *BRCA* mutation are virtually nil (*centralized BRCA* testing has been done by BROCA-HR on >3000 cancer patients on clinical trials, and all previously known *BRCA* mutations were detected, personal communication Dr. Swisher).

e. **Germline testing for Non-*BRCA* genes (BROCA-HR)**

1. Background

Germline *BRCA1/2* mutations are the prototype molecular alterations that confer homologous recombination deficiency and sensitivity to PARPi. *(36,37)* PARPi also selectively kill cells in vitro that are deficient in other homologous recombination (HR) genes including RAD51D, NBN, ATM, and CHEK2. *(38,39)* Germline and somatic mutations in *BRCA1/2* and other *BRCA-FA* genes in ovarian carcinomas are associated with improved response to primary platinum therapy and longer overall survival. *(40)* Germline loss-of-function mutations in 12 such genes in ovarian cancer were evaluated using the BROCA test. Germline mutations were noted in >90% of the genes in the Fanconi anemia pathway with a prevalence of 23% in this series of ovarian cancer patients. *(41)* Utilizing the similar targeted genomic capture and next-generation sequencing platform a recent study evaluated inherited mutations in FA-HR genes in high risk African-American breast cancer patients. In this series of African-American patients 22% of harbored a damaging mutation in one of the FA-HR pathway genes. *(42)* In a large unselected TNBC population a recent study has reported a non-*BRCA* germline mutation prevalence rate of 4%. *(43)* Thus, 4-22% of TNBC patients may carry germline mutations in non-*BRCA* FA pathway gene and presence of these mutations has high likelihood of impacting response to PARPi therapy.

Accordingly, a panel of FA-HR pathway gene is incorporated in the BROCA-HR test. The following genes are included in the BROCA-HR test:

BROCA HR pathway: ATM, ATR, BABAM1, BAP1, BARD1, BLM, BRCA1, BRCA2 (FANCD1), BRIP1 (FANCJ), BRCC3, BRE, CHEK1, CHEK2, ERCC1, ERCC4 (FANCQ), FAM175A (abraxas), FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG (XRCCC9), FANCI, FANCL, FAMCM, GEN1, MRE11A, NBN, PALB2 (FANCO), RAD50, RAD51C (FANCO), RAD51D, RBBP8 (CtIP), SLX4 (FANCP), UIMC1 (RAP80), XRCC2,TP53 PI3K pathway: PTEN, PI3KCA

Non-*BRCA* Germline mutations in FA-HR genes will be used as a stratification variable for this phase II study. BROCA-HR testing which includes *BRCA1/2* and other FA-HR pathway genes will be done post randomization for all patients. Patients with non-*BRCA* deleterious mutations in FA-HR genes will be stratified to the BRCAness group. We estimate that 4-7% of the study population with WT *gBRCA1/2* will harbor deleterious germline mutations in non *BRCA* FA-HR genes. (44,45) Cutpoints will not be used for germline testing. Test results will be described as deleterious germline mutation "present" or "absent". Presence of germline *BRCA1/2* mutation will supersede the finding of germline mutation in non *BRCA* genes for group assignment (for example if a patient is found to have both a deleterious *BRCA* mutation and deleterious mutation in an additional FA-HR pathway gene, that patient will be placed in the *gBRCA* mutation positive group).

Laboratory conducting the BROCA-HR assay:

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Expiration: 9/27/2019

2. **Description of the BROCA-HR assay:**

A targeted capture and massively parallel sequencing approach called BROCA-HR will be applied to samples. For the proposed study, a more recent version of BROCA-HR with 40 genes (includes *BRCA1/2* as well as genes selected based on known involvement hereditary breast/ovarian cancer or Homologous recombination/ genomic stability) will be utilized. Library preparation has been fully automated to increase sample turnaround and lower cost. Paired-end libraries with 350bp inserts will be prepared from 1ug of constitutional DNA and hybridize to a custom pool of oligonucleotides targeting genomic regions as previously described using the SureSelectXT enrichment system on a Bravo liquid-handling instrument (Agilent). (46) Following capture, samples will be barcoded with 48 different indexed primers. The pooled samples are sequenced on a single lane of a HiSeq flowcell (Illumina) with 2x101bp paired end reads and a 7bp index read to allow for de-multiplexing and binning of individual samples. Single nucleotide variants and insertions and deletions will be detected as previously described with some updates in the bioinformatics pipeline. *(47,48)* Deletions and duplications of exons will be detected by a combination of depth of coverage and split read analysis as previously described, supplemented with additional alignments generated by SLOPE. *(49,50)* All germline loss of function mutations in cancer susceptibility genes will be confirmed with PCR amplification and Sanger sequencing.

3. **Description of the specimens and methods for specimen acquisition and processing:**

Specimen collected for germline *BRCA* testing will be utilized for testing of the non *BRCA* HR pathway genes and added specimen will not be needed.

4. **The accessibility of the biomarker assay results:**

Germline mutations for these additional genes involved in FA-HR pathway may impact response to DNA damaging therapy (like PARPi) in an affected individual with known breast cancer. Results of BRCA1, BRCA2 and other ten actionable genes in the BROCA-HR panel (ATM, BARD1, BRIP1, CHEK2, NBN, PALB2, PTEN, RAD51C, RAD51D, TP53) will be provided to the treating physician. Only deleterious mutations will be reported, and variants of uncertain significance will not be reported. Mutations in other FA-HR pathway genes included in this BROCA-HR panel which are not known to have clear evidence of increased cancer risk will not be provided to the treating physicians since this part of the test is "research use" only and not considered to be of clinical significance.

The genetic test result for all trial patients will be provided back to the ordering physician and will include both "positive" and "negative" results for 12 genes (BRCA1, BRCA2, ATM, BARD1, BRIP1, CHEK2, NBN, PALB2, PTEN, RAD51C, RAD51D, TP53). As stated above a positive result will only include "deleterious mutation". Mutations of uncertain significance will not be reported.

Providers will also have access to phone genetic counseling and advice regarding management guidelines for sites/providers with patients with deleterious mutations. This may specifically be needed for mutations in non BRCA genes. If a site/provider wishes to make use of this resource please contact Dr Swisher at swishere@uw.edu. For further questions you can also contact Dr. Sharma at: S1416question@swog.org. Please note that genetic counseling services are available to sites, not individual patients. The counseling provided is not intended to be provided directly to patients, and is not required of the site. Sites may refer patients to their preferred genetic counseling service.

5. **Data on the analytical performance of the assay:**

Accuracy and precision BROCA HR captures > 99% of known deleterious germline mutations in FA-HR pathway. *(51)*
Reportable range, reference ranges/intervals (normal values): Deleterious mutations will be defined in the standard fashion to include protein truncating mutations, and missense mutations demonstrated experimentally to be damaging. Both "BIC" and "HGVS" nomenclatures will be used to report the deleterious mutations. Variants of uncertain significance will not be reported.
Turn-around time: 12 weeks
Failure rate: < 1% (52)

f. **SOMATIC BRCAness PHENOTYPE MARKERS**

Formalin Fixed paraffin embedded primary tumor tissue (collected for routine clinical care) will be used for somatic BRCAness phenotype markers. If the primary tumor tissue is not available FFPE metastatic tumor tissue will be used for these assays.

1. **Homologous Recombination Deficiency (HRD) assay and somatic BRCA1/2 mutations**

Tumor Homologous Recombination Deficiency assay and somatic BRCA mutation testing will be used as a stratification variable for this Phase II study. Tumor HRD and somatic *BRCA* mutation testing will be done post randomization for all patients. In the germline *BRCA* mutation negative group (see Figure 1) patients with high HRD score or somatic BRCA mutations will be stratified to the BRCAness group. Tumor HRD and somatic BRCA mutation testing is done simultaneously as part of one single test.

In addition to BRCA1 and BRCA2, there are many additional homologous recombination-related genes that may be altered by mutation, rearrangement, DNA methylation or mRNA expression that are hypothesized to result in impairment of the homologous recombination pathway. A Homologous Recombination Deficiency (HRD) assay has been developed by Myriad Inc., which evaluates genomic patterns of loss of heterozygosity (LOH) “footprint” as an indicator of HR deficiency and thus allows for the detection of homologous recombination deficiency regardless of its etiology or mechanism. The assay is compatible with FFPE tumor tissue, requires 200-500 ng of tumor DNA and has high sensitivity for identification of *BRCA*-deficient tumors. *(53,54,55)*

The HRD assay has recently been evaluated in several TNBC clinical studies. (56,57,58) In a cohort of 77 TNBC/*BRCA* mutation carriers enrolled on a neoadjuvant study of gemcitabine, carboplatin and iniparib (a drug which was initially investigated as a PARP inhibitor however oxidative damage is now thought to be the mechanism of cytotoxicity), 74% of TNBC tumors had a high HRD score. The mean HRD score was higher for responders vs. non responders and there was no difference in the HRD scores between the BRCA-intact and mutant responders. The HRD score significantly correlated with pathologic response to platinum-based chemotherapy in this study (RCB 0/1 rate of 70% in patients with a high score vs. 20% in patients with a low score, p=0.0001). *(59)* High HRD score also predicted pathological complete response to neoadjuvant platinum-based chemotherapy in another neoadjuvant study. *(60)*

Correlative work from a Phase II metastatic platinum trial (TBCRC-009) has also recently demonstrated that high tumor HRD predicts response to treatment. *(61)*

A recent randomized Phase III trial (TNT) demonstrated that in unselected metastatic TNBC patients carboplatin was equal in efficacy to docetaxel in metastatic setting. *(62)* However, in *gBRCA* mutation associated TNBC carboplatin yielded a superior response rate and progression-free survival compared to docetaxel. In the TNT study high HRD score (done on primary tumor specimens) in *gBRCA* negative patients did not select for sensitivity to carboplatin over docetaxel. Further, correlative work from the TNT study where other BRCAness markers like *BRCA1* promoter methylation (PM) and HRD will be evaluated simultaneously are awaited and may explain the lack of association of response between high HRD score and platinum therapy. Our proposal does not rely on just HRD and utilizes four different markers to designate BRCAness in *gBRCA* negative patients (HRD score, somatic *BRCA* mutations, *BRCA1* PM and germline *BRCA* mutations in other FA-HR pathway genes). It is possible that the Myriad HRD assay does not identify all tumors with HR deficiency (and thus response to platinum and or/PARP inhibitors) in metastatic setting and thus may lead to inaccurate predictive results when used as an only test of BRCAness phenotype.

Tumor HR deficiency assays have not been evaluated as predictive biomarkers of response to PARPi in breast cancer yet, but recent encouraging data has come forth from the ovarian cancer literature. Correlative biomarker work from the ARIEL2 ovarian cancer study (Phase II study of single agent PARPi, Rucaparib) was recently presented. This trial recruited a significant proportion of *BRCA* wild-type tumors in order to identify biomarkers of response to PARPi in this population. 42% of the *BRCA* wild-type study population had tumor genomic LOH and presence of tumor genomic LOH was associated with response to single agent rucaparib in *BRCA* wild-type patients. *(63)* This data highly supports the concept of utilizing tumor LOH/genomic instability assay to select for PARPi therapy in the context of a clinical trial.

BRCA1 and *BRCA2* somatic mutations occur in approximately 4% of TNBC. *(64,65)* Ovarian cancer literature suggests that somatic *BRCA* mutation also confer sensitivity to PARPi. *(66)* Somatic *BRCA* mutations are identified in the process of Myriad HRD test, thus a separate test (or tumor material) will not be needed for BRCA1/2 somatic mutation testing.

Results of the HRD assay and somatic *BRCA* mutation testing will not be provided to the treating physicians or the patients.

2. **Laboratory conducting the assay:**

Myriad Laboratory Inc
320 Wakara Way, Salt Lake City, UT 84108
Attention: Anne-Rene Hartman M.D and Kirsten Timms PhD
CLIA ID No: 8/14/15
Expiration: 8/14/15

3. **Description of the assay:**

Extraction of DNA from FFPE tumors: A 5 micron H&E slide will be reviewed by a pathologist to facilitate enrichment of tumor derived DNA. Ten micron sections will be cut and regions of highest tumor cell density will be scraped from the slide. For DNA extraction, the Promega Maxwell 16 FFPE Plus LEV DNA purification kit (Promega, Madison, WI) will be used. Tissue will be incubated overnight at 56 degrees Celsius with proteinase K in a shaking heat block. After the overnight incubation undigested material is spun out and the Maxwell cartridges are loaded. gDNA will be eluted in 60 ul of low TE.

Hybridization capture and sequencing: A custom capture panel will be used targeting 54,091 SNPs. 50 – 200 ng of genomic DNA will be sheared to an average size of 150 base pairs on a Covaris E220 focused ultrasonicator. Sheared DNA end repair, A-base tailing, and adapter ligation reactions and indexed library amplification will be performed according to manufactures recommendations (Kapa Biosystems, cat. # KK8200). Kapa HiFi PCR will be performed for 6 cycles with the following cycling parameters: 98°C for 45 seconds; 8 cycles of 98°C for 15 seconds, 60°C for 30 seconds, 72°C for 30 seconds; 72°C for 1 minute. Genomic libraries will then pooled at an equal molar ratio and hybridized with the SureSelectxt2 capture library according to manufactures recommendations (Agilent Technologies, cat. # 5190-4867). Post hybridization amplification will then performed on pooled indexed libraries using Kapa HiFi PCR for 8 cycles with the following parameters: 98°C for 45 seconds; 8 cycles of 98°C for 15 seconds, 60°C for 30 seconds, 72°C for 30 seconds; 72°C for 1 minute. Libraries will be quantified on an Agilent 2200 Tape, normalized to 2nM, and denatured using 0.1 NaOH prior to sequencing. Sequencing will be performed on an Illumina HiSeq 2500 according to manufacturer's protocols (Illumina).

Tumor *BRCA1* and *BRCA2* mutation screening: Sequence reads generated on the HiSeq2500 are trimmed at both the start and end to remove low quality bases that could generate spurious variant calls. To call variants each read is aligned with the expected wild-type sequence of the exon. This alignment is a pairwise alignment performed by JAligner (http://jaligner.sourceforge.net/). Any differences represent variants. Variant calls from all reads for a sample are compiled in order to calculate the frequencies of all identified variants. Mutation Sequencing does not differentiate between germline and somatic mutations. Specifically, we are not assessing for inherited *BRCA1* and *2* mutations

SNP Analysis: A SNP sequence database for mapping sequence reads will be created by cutting from the whole genome (version 19) sequences of the SNPs with 400 bp flanks around the SNP positions. Each sequence read will be considered mapped if it matched to the database sequence with 7 or less mismatches. Sequence reads overlapping a SNP position will be used to count the SNP alleles. The resulting read counts will used to reconstruct allele specific copy number (ASCN) at each SNP location using an algorithm. *(67)*

4. **Quality of ASCN reconstruction:** To evaluate the quality of ASCN reconstruction, a quality metric, KS quality, was introduced. The specific definition of KS quality is based on Kolmogorov-Smirnov statistic. High quality ASCN reconstruction is expected to produce high KS quality. Through visual inspection of about hundred samples, a cutoff value 12.7 for KS quality has been established. ASCN reconstructions with KS quality below this cutoff are considered as failed. There are two major reasons for failures: (1) high noise level in the sequence data and (2) low tumor content in a sample.

5. **Calculation of HRD-LOH, HRD-TAI, HRD-LST, and HRD-Sum scores:**

   HRD-LOH score is defined as the number of LOH regions longer than 15 Mb but shorter than the whole chromosome. *(68,69)* HRD-TAI score is defined as the number of regions with allelic imbalance longer than 11 Mb that extend to one of the subtelomeres but do not cross the centromere. *(70)* A region will be counted only if it encompassed a certain minimum number of SNPs (on average approximately 1.8 Mb).

   HRD-LST score is the number of break points between regions longer than 10 Mb after filtering out regions shorter than 3 Mb. *(71)* HRD-LST score increases with ploidy both within *BRCA1/2* intact and deficient samples. Instead of using ploidy-specific cutoffs, the HRD-LST score was modified by adjusting it by ploidy: LSTm = LST – kP where P is ploidy and k is a constant. Based on multivariate logistic regression analysis with deficiency as an outcome and HRD-LST and P as predictors, k = 15.5 provided the best separation between intact and deficient samples.

6. **Scoring procedures and type of data to be acquired**:

   Type of data will be quantitative/ continuously distributed. HRD-Sum score is the sum of the HRD-LOH, HRD-TAI and HRD-LST scores (the number of LOH regions longer than 15 Mb but shorter than the length of a whole chromosome). *(72,73)* TAI Score (the number of telomeric regions imbalance which extend to the subtelomere but do not cross the centromere) and LST Score (the number of chromosomal breaks between adjacent regions longer than 10 Mb after filtering out regions shorter than 3 Mb). The HRD score ranges from 0-100. A high HRD score is defined as 42 or greater based on data generated by the manufacturer (Myriad). Patients with a high tumor HRD score (i.e., >42) will be stratified to the BRCAness group regardless of the tumor *BRCA* mutation results. Patients with tumor/somatic *BRCA* mutation will be stratified to BRCAness group regardless of the HRD score. Within the germline *BRCA* mutation-negative section of the study population it is estimated that 40% patients will demonstrate a high HRD score and 4% will demonstrate somatic *BRCA* mutations. *(74,75,76)*

7. **Description of the specimens and methods for specimen acquisition and processing:**

   Formalin fixed paraffin-embedded primary tumor tissue block.

   Minimum Volume: Three 10-micron uncharged slides for DNA isolation and, one 5-micron charged/uncharged slide for H&E staining

   Instructions: Specimens to be shipped on ice via overnight Fedex to the SWOG Biospecimen Bank.

Specimen processing: Specimens (slides or FFPE blocks) will be stored at the SWOG Biospecimen Bank at 4˚C till ready to be shipped to Myriad Inc for HRD analysis.

8. **Data on the analytical performance of the assay:**

Reportable range:
The reportable range of HRD assay is between 0-100.
Somatic (tumor) *BRCA* mutations will be reported as “present” or “absent”.
Turn-around time: 8-12 weeks
Failure rate: 10%

g. ***BRCA1* PROMOTER METHYLATION.**

1. **Introduction**:

Tumor *BRCA1* promoter methylation (PM) testing will be used as a stratification variable for this Phase II study. Tumor BRCA1 PM testing will be done post randomization for all patients in the germline BRCA mutation-negative group (see trial Schema) and patients with tumor BRCA1 PM will be stratified to the BRCAness group.

Hypermethylation of the BRCA1 promoter has been proposed as one of the mechanisms for functionally inactivating the BRCA1 gene in sporadic breast cancers and this epigenetic inactivation of BRCA1 is associated with a gene expression profile similar to that of inherited BRCA1 mutation-associated breast cancer. *(77,78,79)* BRCA1 PM is observed in 20-40% of sporadic TNBC and may be an important mechanism contributing to the loss of BRCA1 function in sporadic TNBC. (80,81,82,83,84)

Methylation-specific PCR (MSPCR) has been utilized to detect hypermethylation of the areas of interest in the CpG islands of the BRCA1 promoter by many investigators. (85,86,87) MSPCR is relatively inexpensive and can be performed on genomic DNA derived from formalin-fixed paraffin-embedded (FFPE) tissue, and can be being easily applied to clinical settings. We recently completed two pilot studies to examine the feasibility of detecting *BRCA1* PM and mRNA expression on FFPE tissue and to investigate the prognostic significance of *BRCA1* PM and expression in patients treated with chemotherapy for early stage TNBC. *(88,89)*

In the first study of 39 patients, *BRCA1* PM was detected in 30% of the specimens, was associated with lower *BRCA1* transcript levels (suggesting epigenetic silencing of *BRCA1* gene) and was associated with significantly worse DFS and OS in this cohort of anthracycline-based chemotherapy treated patients (Figure 2A and B). *(90)*

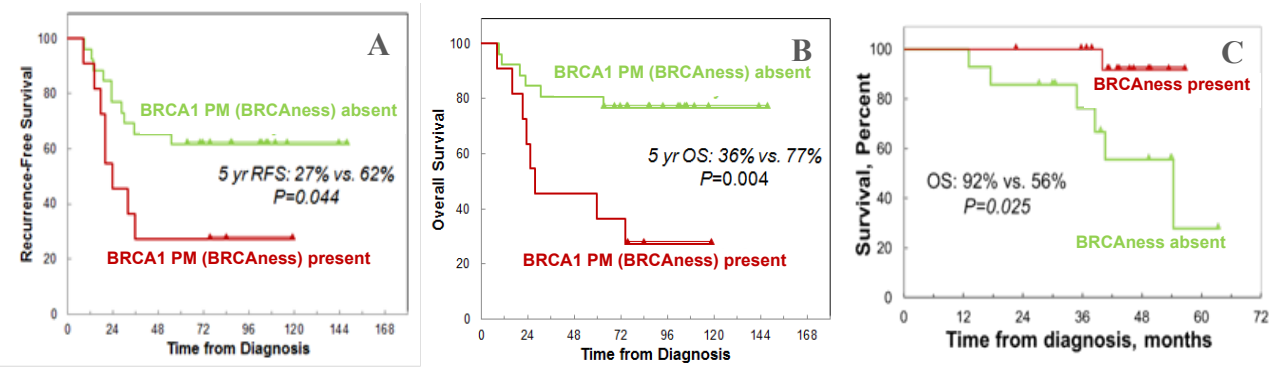

Figure 2: Kaplan-Meier Recurrence-free survival (A) and Overall Survival (B) curves from the anthracycline cohort and overall survival curve (C) from platinum cohort. Presence of BRCA1 PM was designated as "BRCAness present" in the anthracycline cohort.

In a second pilot study, tissue BRCA1 PM and BRCA1 expression and germline BRCA mutations were evaluated in 30 patients who received neoadjuvant platinum-based chemotherapy. BRCAness (defined by the presence of a germline BRCA1/2 mutation or BRCA1 PM or low BRCA1 mRNA expression) was present in 53% of patients and was associated with significantly better OS survival in this platinum-treated cohort (Figure 2C). (91)

In both of these studies we were able to successfully determine *BRCA1* promoter methylation status in 95% of the FFPE specimens using methylation-specific PCR assay. An ongoing correlative science study lead by SWOG (**S9313C**, Evaluation of BRCAness as Prognostic Marker in Triple-Negative Breast Cancer Patients Treated with Adjuvant Anthracycline-Based Chemotherapy, PI: Sharma) is also further evaluating prognostic value of tissue *BRCA1* PM (and other BRCAness markers) in 455 early stage TNBC patients. The results of this large study are expected in early 2016 and will also inform the analysis of the present proposal. Embedded within this study, the CMOL is validating a promoter methylation assay using next generation sequencing techniques in a subset of specimens. If proven more sensitive than the current approach then future analyses may incorporate this NGS assay. Bisulphite-treated DNA for the gel-based assays will be used for this validation.

In summary, *BRCA1* PM could serve as a clinically useful biomarker that could identify a significant proportion of early stage TNBC patients who likely would experience enhanced benefit from *BRCA1*-directed therapeutic approaches such as platinum compounds and/or PARP-inhibitors. Indeed, in vitro data suggests that epigenetic silencing of *BRCA1* via promoter methylation confers the same degree of sensitivity to PARP inhibitors as does *BRCA1* mutation. (92)

2. **Laboratory conducting the *BRCA1* PM assay:**

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Assistant Director Office: 913-945-6388
Laboratory: 913-945-6391
CLIA ID No: 17D2042936
Expiration: 06/17/2016

3. **Description of the assay:**

Methylation Specific PCR (MSP)
Genomic DNA (gDNA) will be isolated using commercially available kits (EpiTect Plus FFPE Bisulfite Kit, Qiagen). Purified converted DNA (100 ng) will be subjected to methylation-specific PCR (MSPCR) using the EpiTect® MSP Kit (Qiagen). The unmethylated template primers will be (forward) TTGGTTTTTGTGGTAATGGAAAAGTGT and (reverse) CAAAAAATCTCAACAAACTCACACCA, resulting in an 86 base pair PCR product. The methylated template primers will be (forward) TCGTGGTAACGGAAAAGCGC and (reverse) AAATCTCAACGAACTCACGCCG, resulting in a 75 base pair PCR product. These primers have been extensively characterized by previous groups. (43-49) PCR conditions will be as follows: 95°C for10 minutes, then 35 cycles of 94°C for 15 seconds, 55°C for 30 seconds, 72°C for 30 seconds, and a final extension at 72°C for 10 minutes. PCR products will be electrophoresed on a 2.5% agarose gel stained with ethidium bromide and visualized on a UVP Bioimaging system. Specificity of the reactions will be confirmed using the EpiTect® Control DNA set (Qiagen) with the same primers and PCR conditions. Gels images (e.g., Figure 1) will be visualized with UV light in a MultiImage Light Cabinet (Alpha Innotech Corp). The intensity of each band will be measured and analyzed using the AlphaView SA software (Cell Biosciences, Inc). These relative band intensities will be used to establish the quantitative ratio of the two products by comparing the unmethylated and methylated bands.

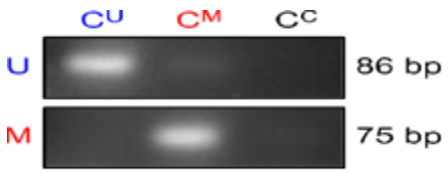

Figure 1: (B) Specificity controls for the MSP reaction. Unconverted genomic DNA (CC), universally unmethylated bisulfite-converted genomic DNA (CU) and universally methylated bisulfite-converted (CM) will be amplified with primers specific for bisulfite-converted unmethylated (U) or methylated (M) *BRCA1* promoter.

4. **Description of the specimens and methods for specimen acquisition and processing:**

Formalin fixed paraffin-embedded primary tumor tissue block.
Minimum Sample Requirement: Three 10 micron uncharged slides for DNA isolation and one 5 micron charged slide for H&E staining.

Instructions: Specimens to be shipped by overnight FedEx delivery to SWOG Biospecimen Bank Specimen processing: Specimens (slides or FFPE blocks) will be stored at the SWOG Biospecimen Bank at 4 ˚C until shipped to the University of Kansas Medical Center for the correlative studies.

5. **Scoring procedures and type of date to be acquired:**

Type of data will be Qualitative/non-ordered categorical. The results will be reported as BRCA1 promoter methylation “present” or “absent”.

6. **Expected distribution and cut points:** It is estimated that 30% of the germline *BRCA* mutation negative study population will demonstrate *BRCA1 PM*. *(93,94,95,96,97)* We do not expect any patients with germline *BRCA* mutations to have tissue *BRCA1* PM as several prior studies have previously demonstrated that germline *BRCA* mutations and *BRCA1* PM are mutually exclusive. *(98,99,100)*

Cutpoints will not be used for reporting *BRCA1* PM. Test results will be recorded as *BRCA1* PM “present” or “absent”. We will use band intensity ratios between unmethylated and methylated to determine the promoter methylation status. Commercially available positive and negative controls (EpiTect Control DNA set by Qiagen) will be used with each run as well as run-to-run clinical positive and negative samples. The band intensity ratio of clinical samples will be compared to commercial positive and negative controls to define the methylation status.

BRCA1 promoter methylation results will not be relayed back to the patients or the providers

7. **Data on the analytical performance of the assay:**

Accuracy and precision: The Clinical Laboratory Improvement Amendments (CLIA) to the code of federal regulations (42 CFR part 493) govern quality standards for laboratory testing of human specimens for the purpose of diagnosis, prevention, treatment of disease, or assessment of health. CLIA regulations require that each laboratory that introduces a lab-developed-test system must do the following before reporting patient test results: demonstrate that it can obtain performance specifications comparable to those established by the manufacturer for the following performance characteristics: a. accuracy; b. precision; c. reportable range of test results for the test system. The accuracy or overall concordance is defined as: (# of True positives + # of True negatives) / (# of True positives + # of False positives + # of False negatives + # of True negatives). The inner-laboratory comparison of tests results will be used to estimate assay accuracy. If the observed result agreed with the expected result the result is assumed to be "true" for the purposes of determining "true positives" and "true negatives". If the observed result disagreed with the expected result the result is assumed to be "false" for the purposes of determining "false positives" and "false negatives". The precision which includes repeatability (within-run imprecision) and reproducibility (run-to-run, day-to-day imprecision) will be achieved by consistent and expected test results from the tests on multiple runs throughout the validation period.

Turn-around time: 6-8 weeks
Failure rate: *<5%*

h. **Liquid Biopsy Integrated Markers: Circulating tumor cells (CTC) homologous recombination deficient (HRD) status and HR repair (HRR) gene mutation status.**

1. **Background:**

a. CTC-HRD

Various studies have correlated the homologous repair deficiency (HRD) phenotype with chromosome instability (CIN) measured by aggregate copy number alterations (CNA) in the genome *(101*). Large-scale transitions (LST), is a form of CNA defined as chromosomal breakages that generate chromosomal gains or losses of 10 Mb or more. LST (also known as 'genome scarring') correlates HRD associated with the presence of BRCA1/2 mutations in breast and ovarian cancer *(102,103*). Using the High Definition-Single Cell Analysis (HD-SCA) methodology (EPIC sciences, CTC platform) the tissue-based LST measure has been adopted for single circulating tumor cells (CTC) and the technical feasibility of determining LST number in single CTCs by next-generation sequencing (NGS) has been demonstrated *(104, 105)*.

Evaluation of LST along with morphometric parameters in prostate cancer CTCs using the commercial version of the HD-SCA (Epic Sciences) has recently been published *(106)*. In this study 10,240 CTCs in 367 pre-treatment blood samples obtained from 294 patients with metastatic castration-resistant prostate cancer were studied and a CTC with 9 or more LSTs was scored as a LST-high CTC. It was demonstrated that high LST in CTC was a marker of HRD/ CIN. At a cutoff of 3 or more LST-high CTCs per mL of blood, the sensitivity was 83%, specificity 100%, and PPV of 100%. Thus, an LST score of 9 or greater in >3 CTC cell/ml blood was deemed to be the appropriate threshold for denoting CTC HRD/CIN positive status. In this large study morphological analysis of CTC was also used to 'predict' which single CTCs (and thereby, which cases) are likely to exhibit CIN (or genomic evidence of HRD), followed by single cell NGS analysis to score LST. Using a clinical validation sets it was also demonstrated the above defined threshold for CIN in pretreatment CTCs strongly associated with poor overall survival in patients treated with androgen receptor signaling inhibitors and taxanes. In this study overall frequency of patients with ≥3 LST-high CTCs per mL of blood exceeded 40%. This threshold of CTC LST coupled with cell morphology metrics has also been assessed in a phase II prostate cancer study that compared aboraterone to abiraterone + veliparib. In this study, CTC- HRD/CIN positive status was noted in 48% of patients and correlated with better PSA responses with abiraterone + veliparib compared to abiraterone in patients with metastatic prostate cancer *(107)*.

For the analysis on the **S1416** samples, the technology and thresholds described above will be used to denote CTC-HRD status for the primary analysis. Alternative thresholds for CTC-HRD will be explored in secondary analyses.

Somatic HRR mutations and PARPi efficacy:

Emerging studies are now starting to demonstrate efficacy of PARPi in setting of somatic HRR gene mutations in ovarian and prostate cancer. TOPARP-B trial in prostate cancer and ARIEL 2 study in ovarian cancer demonstrated preliminary efficacy of PARPi in patient population beyond germline or somatic BRCA mutations *(108, 109)*. In breast cancer, a small Phase II study also suggested benefit of PARP inhibitor Talazolarib in breast cancer patients with non-BRCA somatic HRR genes mutations *(110)*. Lack of availability of adequate amount of tissue samples and assay failure pose challenges for HRD profiling when using tissue sample thus underscoring the need for a non-invasive, ctDNA alternative. For example, in **S1416** even in setting of mandatory tumor tissue submission, for 22% of patient population tissue based HRD could not be determined. Furthermore, CTC HRD assessment is also dependent on presence of CTC and is uninformative for patients who do not have any CTC. Thus, assessment of ctDNA based HRD is a valuable addition to the GuardantOMNITM, is a 500-gene liquid biopsy panel that annotates pathogenic SNV/Indels, identify structural rearrangements, gene-level homozygous deletions, loss-of-heterozygosity (LOH) and genome-wide LOH, CNV and de-novo fusions. GuardantOMNITM ctDNA tests performance has recently been studies in >620 prostate cancer patients and showed that

relative prevalence of ctDNA detected HRR alterations was consistent with those in tissue *(111)*. We plan to use GuardantOMNITM for assessment of ctDNA HRR gene mutations.

2. **Hypotheses**:

   a. Patients with CTC-HRD+ status will experience longer progression-free survival (PFS) in the presence of cisplatin plus ABT-888 (veliparib) treatment compared to treatment with cisplatin plus placebo.

   b. Patients with ctDNA HRR gene mutation (pathogenic/likely pathogenic) will experience longer progression-free survival (PFS) in the presence of cisplatin plus ABT-888 (veliparib) treatment compared to treatment with cisplatin plus placebo.

3. **Laboratories conducting the assays:**

CTC-HRD:
Convergent Science Institute in Cancer
University of Southern California (USC)
1002 Childs Way, MCB 350
Los Angeles, CA 90089-3502

and

Epic Sciences, Inc.
9381 Judicial Drive, Suite 200
San Diego, CA 92121

Both laboratory locations are operating equivalent experimental setups.

Allocation of work is as follows:

Convergent Science Institute in Cancer at USC: Custom cryostorage of slides as per protocol (already completed as part of previous objectives); QA/AC as per protocol. Data analysis of scanning and genomics data (lead).

Epic Sciences, Inc.: Staining and scanning of slides. Single cell genomics. Data analysis of scanning and genomic data (will be accomplished jointly with USC).

Although this work will be performed in a Research Use Only (RUO) format, a CLIA-CAP certified version of the high definition-single cell analysis (HD-SCA) has been commercialized by Epic Sciences (La Jolla, CA) and the reimbursable test for androgen receptor variant 7 is available.

ctDNA
Guardant Health, Inc
505 Penobscot Dr.
Redwood City, CA 94063

4. **Description of the specimens and previous methods for specimen acquisition and processing:**

CTC-HRD: In accordance with the previously approved **S1416** protocol: a) whole blood samples were previously collected in 10 mL cfDNA Streck tubes, b) shipped overnight to the Kuhn/Hicks lab at USC, c) upon receipt, plasma was separated/aliquoted and frozen and the cellular components spread on prepared microscope slides (within 48 hours of blood collection), and then d) slides were stored at -80°C for subsequent analysis (e.g.: immunofluorescent staining, cell enumeration, morphometric analysis and sequencing). As of December 12, 2020, the Kuhn-Hicks lab at USC had received, processed, and archived slides representing 798 draws from 331 unique patients, with a processing failure rate of <2%.

CTC-HRD: As indicated above, approximately 8 mL whole blood was previously collected in 10mL cfDNA Streck tubes, from 3 timepoints: prior to treatment, Cycle 2/ Day 1, and at time of progression will be utilized. At least two slides corresponding to the analysis of approximately 1 mL of blood will be analyzed. Given that 8 mL of blood was collected for each patient, only a small proportion of the total sample available will be utilized for the CTC-HRD analysis.

ctDNA: 2-4 mLs of frozen plasma (previously collected and stored) will be utilized.

5. **Description of the assays:**

a. **CTC-HRD assessment**

The HD-SCA® (high definition-single cell analysis) workflow (Figure 1) is developed as a direct analysis approach for rare cells to extract the maximum information from the cellular and acellular components of a blood draw. The cell-based component is designed to identify multiple subpopulations of cells in blood samples and capability to subject these cells to genomics and targeted proteomics characterization. It is based on semi-quantitative imaging approaches, including 4-color immunofluorescence (IF) and digital morphometry where DAPI is used to identify nucleated cells, CD45 to identify white blood cells (WBC), a pan-cytokeratin cocktail to identify cells of epithelial origin, and CD31 to exclude endothelial cells. The HD-SCA protocol also isolation and storage of plasma that can be processed for ctDNA sequencing.

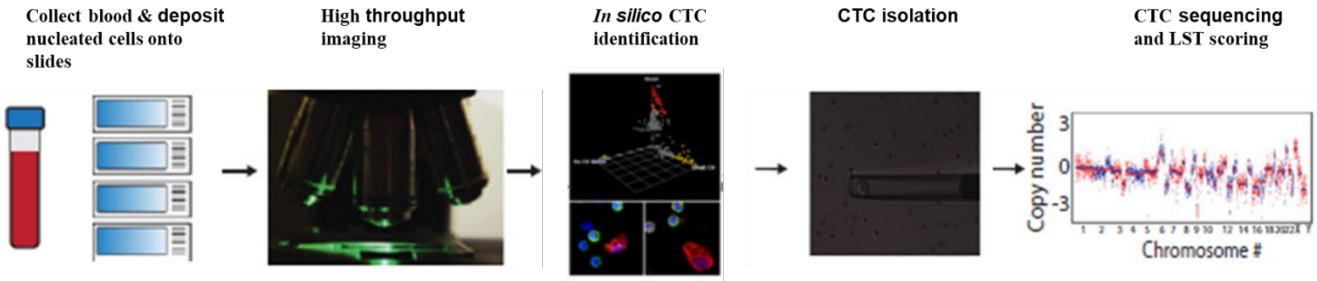

Figure 1: HD-SCA with specifics for CTC detection, imaging, and large-scale transitions (LST) scoring.

CTC-HRD:

CTC-HRD is a combination of CTC immunostaining and genomic assay. Semi-quantitative imaging approaches, including 4-color immunofluorescence (IF) and digital morphometry is utilized to identify CTCs (DAPI is used to identify nucleated cells, CD45 to identify white blood cells (WBC), a pan-cytokeratin cocktail to identify cells of epithelial origin, and CD31 to exclude endothelial cells). Identified CTCs will then be picked for low-pass sequencing. Previously published and widely used methodology will be employed for generating quantitative CNA data from single cells. *(112, 113, 114)*. Bioinformatic analysis will be as previously published *(115, 116).* (After sequencing and generation of genomic CNA profiles, each cell will be scored for large-scale transitions (LST) (CNA segments >10 Mbp). **A CTC with 9 or more LSTs will be scored as LST-high CTC. Patient samples with 3 or more LST-high CTCs per mL of blood will be denoted as CTC-HRD positive (CTC-HRD+).**

CTC Q/A and feasibility data from S1416:

Given the novelty of CTC-genomics for HRD assessment in breast cancer a feasibility pilot was desired. However, a TNBC metastatic 1-2nd line treated patient sample set where liquid biopsy samples were processed on the HD-SCA platform and single CTC could be subjected to sequencing could not be identified. Thus, a 30 sample Q/A endeavor utilizing random pretreatment S1416 samples was undertaken to establish feasibility. This was undertaken in the blinded fashion without knowledge of either treatment arm assignment, patient outcome or tissue HRD assignment. In this Q/A study 75% of the pretreatment samples demonstrated >3.0 CTC/ml and of the samples with >3 CTC/ml, 45% met the above-described CTC-HRD positive threshold.

b. **CtDNA**

GuardantOMNITM:

ctDNA NGS analysis will be performed at Guardant Health, Inc. (Redwood City, CA), a CLIA-certified, College of American Pathologists (CAP)-accredited, New York State Department of Health-approved laboratory.

The 2.145 Mb GuardantOMNI assay identifies single nucleotide variants (SNVs) and indels in 500 genes, copy number amplifications (106 genes), fusions (21 genes), MSI-High status, and tumor mutational burden (TMB) *(117, 118*). SNVs and indels are classified as somatic or germline using a statistical beta-binomial model *(119).* PlasmaTMB will be reported as mutations per Mb by the GuardantOMNI algorithm which includes all somatic synonymous and non-synonymous SNVs and indels excluding germline, CHIP, driver and resistance mutations, with statistical adjustment for sample-specific tumor shedding and molecular coverage. Samples with low tumor shedding (all somatic mutations <0.3% maximum somatic allele fraction) or low unique molecule coverage will be identified as plasmaTMB-unevaluable. Validation of plasmaTMB and MSI have been previously described *(120,121)*. Assuming optimal input material the anticipated assay failure rate is < 2%.

Product Features	GuardantOMNI™
Number of genes	500 genes
Total size	2.145 Mb
Optimal input material	5-30 ng cfDNA from ≥2mL plasma
Somatic variant detection	• Small Nucleotide Variants (SNVs, 496 genes) • Short insertions/deletions (Indels, 496 genes) • Copy Number Amplifications (CNAs, 106 genes) • Fusions (21 genes)
Tumor Mutational Burden (TMB)	TMB score (mut / Mb)
Microsatellite Instability (MSI)	MSI-High status
Homologous Recombination Repair Deficiency (HRD)	24 HRR genes (list provided in a separate document) • SNV/Indel Deleterious and Reversion Annotation • Copy number deletions (homozygous, loh, and indeterminate zygosity) • Fusions and long (multi-exon) deletions • Biallelic mutation annotation

Alteration Type	Reportable Range	95% Limit of Detection (LoD)	Specificity
SNVs (496 genes)	≥0.04%	0.15 – 0.6%*	>99%
Indels (496 genes)	≥0.1%	0.4 – 0.8%*	>99%
Activating Fusions (21 genes)	≥3 molecules	0.1 – 0.2%	>99%
Amplifications (106 genes)	≥2.18 copies	2.18 – 2.9 copies for 90% of genes	>99%
HRR Deletions (13 genes)	≤1.82 copies	8 – 30% tumor fraction**	>99%
HRR LoF Fusions (24 genes)	≥3 molecules	0.1 – 0.2%	>99%

* Range for 95% LoD include clinically actionable and non-clinically actionable variants, respectively.

** Range for 95% LoD is for homozygous and heterozygous deletions, respectively.

All metrics are based on 30 ng input using cfDNA clinical samples except for HRR deletions, which are based on in-silico simulations as described in Figure 1.

Specificity is based on false negative variant detection across a large cohort of normal samples.

ctDNA HRR mutation distribution:

The above 24 genes will comprise ctDNA HRR mutation panel. Patients with known germline BRCA1/2 mutations will be excluded from this analysis.

Based on the review of existing literature and interrogation of METABRIC and TCGA data sets, it is expected that 30% of patient samples will demonstrate ctDNA HRR mutations.

Results of CTC, CTC-HRD testing and ctDNA will not be provided to the treating physicians or the patients.

6. **Endpoints:**

a. Primary

The primary outcome in the clinical trial, progression-free survival (PFS), would be the primary outcome for these TM analyses.

b. Secondary

Overall survival and response rate would be secondary endpoints.

7. **Statistical Analyses:**

S1416 completed accrual with 335 in the primary cohort, of whom 322 are eligible. The trial results were reported at the virtual ASCO meeting in June 2020 and the primary manuscript is in preparation.

The protocol specified three separate comparisons as shown in the table below. Classification into HRD phenotype for the primary study assessment is based on tissue HRD. Some patients were not able to be classified due to missing tissue or blood, or failure of the tissue HRD assay/s.

The 257 patients with negative germline BRCA status will be used for statistical analysis. This includes 48 patients with who are germline negative, but have unknown tissue HRD status due to assay failure/lack of tumor tissue. Therefore, using pretreatment blood for HRD phenotype assessment provides a complementary means for assaying HRD in **S1416**.

Table 2. Analysis of PFS for the primary S1416 trial subgroups

Subgroup	Eligible N	Median PFS for placebo vs. ABT-888	HR (ABT-888 vs. placebo), 95% CI, and p-value
1: g*BRCA* mutation +ve	37	6.4 mos. vs. 6.2 mos.	0.66 (0.30-1.44); p=0.29
2: g*BRCA* mutation -ve HRD phenotype present	99	4.2 mos. vs. 5.9 mos.	0.53 (0.34-0.83); p=0.006
3: g*BRCA* mutation -ve HRD phenotype absent	110	3.0 mos. vs. 4.0 mos.	0.89 (0.60-1.32); p=0.89
Unclassified	75		

a. Primary Objective: To assess the impact of pre-treatment CTC-HRD status on PFS in patients treated with chemotherapy versus chemotherapy plus ABT-888 (veliparib) on **S1416**.

Classification into HRD phenotype for the primary study assessment is based on tissue HRD. In the current proposal we propose basing HRD phenotype on CTC-HRD status.

Of the 257 eligible patients who tested as germline BRCA negative, 252 (98%) contributed a baseline blood sample for CTC and ctDNA evaluation. We expect 75% of the patients would have detectable CTCs (n=189) at the threshold level of ≥3 cells/ml. Any value less than 3 cells/ml is considered below the level of detection and is called negative.

Patient samples with 3 or more LST-high CTCs per mL of blood will be denoted as CTC-HRD+. 50% of patients with detectable CTC are expected to have CTC-HRD+ status, thus this assay would evenly divide patients as HRD+ and HRD- (n~94 in each group).). In those with available blood specimens submitted, the overall treatment hazard ratio for veliparib versus placebo is 0.78 (95% CI 0.60-1.01) with median PFS of 4.3 months and 3.3 months for veliparib and placebo, respectively.

For the power calculations we assume 50% in each treatment group and 50% for each CTC-HRD group (positive or negative). For medians we assume 3.3 months for placebo treatment for both HRD+ and HRD- while for the veliparib arm we assume 3.3 months for HRD- and 6.1 months for HRD+ patients. This is consistent with the overall treatment effect ignoring HRD status under an exponential model.

i. gBRCA mutation negative, CTC-HRD positive patients would have improved PFS with ABT-888 (median 6.1 mos) than with placebo (3.3 mos) when combined with chemotherapy (HR=0.54). For the expected 95 total patients distributed equally by treatment arm with median follow-up of two years and two-sided α=0.05, there is 84% power to show a significant difference between treatment arms. Analysis is by log-rank testing and Cox regression.

ii. gBRCA mutation negative, CTC-HRD negative patients would not have improved PFS with ABT-888 (median 3.3 mos) than with placebo (3.3 mos) when combined with chemotherapy. We would have n=95 patients for this comparison. We would not formally test with a noninferiority design due to sample size requirements. We would not expect any statistically significant differences with log-rank testing and Cox regression.

iii. Prediction: Among gBRCA mutation negative patients, CTC-HRD positive patients would have improved PFS with ABT-888 (median 6.1 mos) than with placebo (3.3 mos) when combined with chemotherapy, while there would be no treatment effect for CTC-HRD negative patients with ABT-888 (median 3.3 mos) than with placebo (3.3 mos) when combined with chemotherapy. There would be 95 patients in both the

positive and negative groups. With median follow-up of two years and one-sided α=0.10 (consistent with the original hypotheses), there is 79% power to show a significant interaction between subgroup and treatment. Analysis is by Cox regression.

b. Secondary Objective: To evaluate pre-treatment ctDNA HRR mutations (HRRmut) as predictive marker of response to treatment with cisplatin plus ABT-888 (veliparib) versus cisplatin plus placebo.

We assume that n=247 (98%) of the patients who submitted blood (n=252) will have availability of ctDNA HRR mutations GuardantOMNITM test. We also assume that 30% will be positive for HRR mutations.

For the placebo arm we assume no difference in median PFS by HRRmut status (i.e.: 3.3 months for both).

For the veliparib arm we assume median PFS of 3.7 months for the 70% with negative HRRmut status and median PFS of 6.9 months for the 30% with positive HRRmut status. This is consistent with the observed veliparib median of 4.3 months overall based on an exponential model.

i. First, we show that treatment is effective in the subset positive for ctDNA HRRmut (n=74). Treatment with ABT-888 would result in improved PFS (median 6.9 mos) compared to placebo (3.3 mos) when both arms receive chemotherapy. One-half of the 74 patients are in each treatment arm. With median follow-up of two years and two-sided α=0.05, there is 88% power to show a significant difference between treatment arms. Again, analysis is by log-rank testing and Cox regression.

ii. For those without ctDNA HRRmut we expect very small improvement in PFS with ABT-888 (median 3.7 mos) than with placebo (3.3 mos) when combined with chemotherapy. For this comparison we would have 173 patients since 70% are expected to be negative. As expected this difference is not likely to be statistically significant (2-sided α=0.05) with a power of 11%. We will test this difference using a log-rank test followed by Cox regression.

iii. Prediction: HRRmut patients would have improved PFS with ABT-888 (median 6.9 mos) than with placebo (3.3 mos) when combined with chemotherapy, while there would be modest treatment effect for patients negative for HRR mutations with ABT-888 (median 3.7 mos) than with placebo (3.3 mos) when combined with chemotherapy. For the positive group there would be n=74 patients, while the negative group would have n=173. With a median follow-up of two year and one-sided α=0.10, there is 82% power to show a significant interaction between HRRmut subgroup and treatment. Analysis is by Cox regression.

c. Exploratory objectives:

i. We will assess the degree of overlap between CTC-HRD positivity and HRRmut positivity. It is possible that HRRmut positivity is a subset of CTC-HRD positivity. If there is some discrepancy then a combined classification could be more powerful.

ii. We will assess the overlap of tissue HRD status with HRD status of liquid biopsy components.

iii. To be called CTC-HRD positive there must be 3 or greater CTC cells/ml as a minimum threshold. It is possible that a higher value may be optimal. After the distribution of CTC-HRD is determined, two higher values will be selected that identify significant fractions of positive values to be useful. The survival analyses described above would be repeated with the two higher values to determine if either maximizes prediction of benefit of veliparib using the higher threshold. Any newly established cutpoint would need to be validated in another cohort of similar patients.

iv. CTC with 9 or more LSTs is to be designated as LST-high CTC. It is possible that a higher value may be more optimal. After distribution of LST is assessed we will evaluate alternate LST cutoffs. The survival analyses described above would be repeated with the alternate LST cut offs to determine if alternate cut offs maximizes prediction of benefit. Any newly established cutpoint would need to be validated in another cohort of similar patients.

j. **OTHER INTEGRATED BIOMARKERS**

1. PD-L1

a. Introduction

Since the initiation of **S1416**, immune checkpoint inhibitors have shown activity in treatment of patients with metastatic TNBC. In 2020, the U.S. Food and Drug Administration granted approval to pembrolizumab in combination with chemotherapy for patients with TNBC whose tumors express PD-L1 (CPS ≥10)). FDA also approved the PD-L1 IHC 22C3 pharmDx (Dako North America, Inc.) as a companion diagnostic for selecting patients with TNBC for pembrolizumab. This approval was based on the IKEYNOTE-355 trial which enrolled patients with metastatic TNBC who had not received prior chemotherapy for metastatic disease. *(122)* In the KEYNOTE-355 trial, 38% of patients demonstrated tumor PD-L1 positivity (CPS>10. Pembrolizumab plus chemotherapy is now considered standard of care first line treatment for patients with metastatic TNBC with PD-L1 positivity. *(123)*

Assessment the overlap between BRCA-like phenotype and PD-L1 positivity will be a vital component to inform the appropriate setting and patient population for a Phase III trial evaluating PARPi + cisplatin combination. The information about this overlap is not available from any other trials. The Impassion 130 trial demonstrated that that about 50% of patients with germline BRCA 1/2 mutation have PDL-1 positivity. (124) This proportion is not

much different than what is noted for unselected TNBC patients where 40% are noted to have PD-L1 positivity.

PD-L1 testing was not planned at the initiation of the trial given lack of information on efficacy of immune check point inhibitors in breast cancer at the time of development of **S1416**. There is some indirect evidence from another SWOG-led TM study (**S9313C**, PI: Priyanka Sharma) that shows that for patients with early stage TNBC there is some overlap between immune rich and HRD phenotype TNBC but that this overlap is not complete. For example, in **S9313C** there was no association between tumor infiltrating lymphocytes (TILs) and HRD status and only a modest association between an immune gene signature and HRD (unpublished data).

The hypothesis is that PD-L1 positivity in BRCA-like phenotype TNBC will be similar to what is noted for unselected TNBC (i.e., approximately 40-50%), and, similarly, that PD-L1 status will not change the effect of veliparib in **S1416** nor will it be prognostic.
PD-L1 status (by immunohistochemistry) will be assessed for all enrolled patients for whom gBRCA status and BRCA-like status is available and primary tumor tissue is available in the SWOG Biospecimen Repository (Estimated N=246) to allow for combined classification of patients by PD-L1 status and BRCA phenotypes.

b. Laboratory Conducting the Assay

Laboratory:
Biospecimen Resource Core Facility (BRCF) Histology Service/ Pathology Histology Resource
University of Kansas Medical Center
3901 Rainbow Boulevard
Hixson Building, Room G013
Kansas City, KS 66160

Andrew K Godwin, PhD Professor & Division Director, Genomic Diagnostics, Director, BRCF
Rashna Madan, MBBS, Professor, Assistant Director, BRCF & Department of Pathology & Laboratory Medicine
University of Kansas Medical Center
Kansas City, KS 66160

c. Required BioSpecimen samples

- Two (2) 4–5 microns thick, positively charged and unbaked slides plus

d. Description of the Assay

PD-L1 protein expression in TNBC is determined by using Combined Positive Score (CPS), which is the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.The specimen will be considered PD-L1 positive if CPS ≥ 10 (PD-L1 IHC 22C3 pharmDx Interpretation Manual – Triple-Negative Breast Cancer). Immunohistochemical staining for PD-L1 will be performed utilizing the PD-L1 IHC 22C3 pharmDx kit from Dako

Agilent, Santa Clara, CA using a standardized clinical protocol with appropriate positive and negative controls.

e. Endpoints

Primary endpoint: Determine the overlap of (integral) BRCA phenotype (germline BRCA, BRCA-like, Non-BRCA-like) with (integrated) PD-L1 status.

Secondary endpoint: Determine if veliparib benefit in BRCA-like patients is maintained when adjusting for PD-L1 status.

f. Statistical Plan

The analysis will include 246 patients classified previously by the integral markers into three groups: 37 germline BRCA positive patients; 99 BRCA-like patients; and 110 non-BRCA-like patients. Our primary question is whether the BRCA-positive phenotypes which includes 136 patients (gBRCA (n=37) and BRCA-like (n=99)) differ from the non-BRCA- like group with respect to PD-L1 status. Assuming that 90% can have PD-L1 determined will give results for 122 and 99 respectively for the two groups. We do not expect there to be an association of PD-L1 with the two groups (1. gBRCA and BRCA-like; (2) Not BRCA-like). A difference of 19% in PD-L1 positivity between the two groups can be detected with 80% power and 2-sided α=0.05. Chi-square testing is used. We will also assess any difference within germline BRCA and BRCA-like patients though power is limited to find a significant difference. Even with no significant difference among the BRCA phenotypes, it will still be informative for future trial design.

For the secondary outcome we wish to determine if PD-L1 might confound the effect of veliparib on PFS and OS. Separately, for the BRCA-like and non-BRCA-like groups we will fit a Cox model of randomized treatment on the survival outcomes with stratification for line of therapy. Then PD-L1 will be added to the Cox model to determine if it changes the effect of veliparib by 10% or more (definition of confounding). We predict it will not change the effect of veliparib nor will PD-L1 be prognostic.

2. ***BRCA1*** **EXPRESSION**

a. Introduction

Tumor quantitative BRCA1mRNA expression will be evaluated for its association with outcome under cisplatin therapy with or without ABT-888.

Retrospective biomarker studies in lung and ovarian cancer suggest that low BRCA1 expression may be associated with response to platinum chemotherapy. (125,126) We recently completed two pilot studies to examine the feasibility of detecting BRCA1 PM and mRNA expression on formalin-fixed paraffin-embedded (FFPE) tissue and to investigate the prognostic significance of BRCA1 PM and expression in patients treated with chemotherapy for early stage TNBC. (127,128) The data on BRCA1 PM has already been described in the previous section.

In the first study of 39 patients, treated with anthracycline-based adjuvant chemotherapy low BRCA1 expression was prognostic. Five-year RFS was 44% for patients with BRCA1 expression in the lowest three quartiles compared to 89% for patients with BRCA1 expression in the highest quartile (p=0.034, log rank test). While the same trend was maintained for OS (five-year OS 67% lowest three quartiles; 89% highest quartile), the trend was not statistically significant (p=0.099, log rank test). (129) In the second pilot study, tissue BRCA1 PM and BRCA1 expression and germline BRCA mutations were evaluated in 30 patients who received neoadjuvant platinum-based chemotherapy. BRCAness (defined by the presence of a germline BRCA1/2 mutation or BRCA1 PM or low BRCA1 mRNA expression) was present in 53% of patients and was associated with significantly better OS survival in this platinum-treated cohort. (130)

In both of these studies we were able to successfully determine BRCA1 mRNA expression in >90% of the FFPE specimens. An ongoing correlative science study lead by SWOG (S9313C, Evaluation of BRCAness as Prognostic Marker in Triple-Negative Breast Cancer Patients Treated with Adjuvant Anthracycline-Based Chemotherapy, PI: Sharma) is also further evaluating prognostic value of tissue BRCA1 mRNA in 455 early stage TNBC patients.

b. **Laboratory conducting the assay:**

Andrew K Godwin, PhD
Professor, Department of Pathology & Laboratory Medicine, University of Kansas Medical Center
Director, Molecular Oncology, University of Kansas Medical Center
University of Kansas Medical Center
Kansas City, KS 66160

Laboratory:
Clinical Molecular Oncology Laboratory (CMOL)
University of Kansas Medical Center
2601 Olathe Boulevard
Building 020, Room 4005
Kansas City, KS 66160

Mailing address:
University of Kansas Medical Center
CMOL, Mail Stop: 3040
3901 Rainbow Boulevard
Kansas City, KS 66160
Director Office: 913-945-6373
Assistant Director Office: 913-945-6388
Laboratory: 913-945-6391
CLIA ID No: 17D2042936
Expiration: 06/17/2016

c. **Description of the assay**

RNA isolation: Tumor-dense areas of the FFPE tissue sections will be macrodissected. There will not be any correction for tumor content in the sample. Minimum tumor content of 20% will be required. RNA will be isolated using commercially available kits.

***BRCA1* mRNA quantitative real-time PCR (qRT-PCR):** RNA will be reverse transcribed to cDNA which will be assayed in duplicate for *BRCA1* transcript levels as well as reference transcripts using specific primer and probe sets. Cycle threshold (Ct) values will be calculated for each endpoint, corrected for housekeeping gene expression and relative gene expression will be calculated using the ΔΔCt method, with normal breast tissue cDNA as calibrator. *(131)*

Scoring procedures: *BRCA1* expression will be reported as multiples of the median. *(132)* Expression is a continuous marker so it will be tested in two ways. First, low expression (first quartile) will be tested against higher values (upper 75%) in a Cox regression, adjusting for treatment. For the second method, log expression will be tested as a continuous variable in the Cox regression. We will be assessing BRCA1 expression both as a binary and continuous variable. Low BRCA1 expression is expected to be associated with response to DNA damaging therapy. Since the goal is to use BRCA1 expression as a predictive marker of response (and not resistance) to DNA damaging therapy, we want to compare the group with lowest expression to the rest of the study population. Thus, a binary split at 25% was chosen. Furthermore, **S9313C** is also using the binary split at 25%.

d. **Description of the specimens and methods for specimen acquisition and processing:** Formalin fixed paraffin-embedded primary tumor tissue block.

Minimum Sample Requirement: Two 10 micron uncharged slides for RNA isolation and one 5 micron charged slide for H&E staining.

Instructions: Specimens to be shipped by overnight FedEx delivery to SWOG Biospecimen Bank Specimen processing: Specimens (slides or FFPE blocks) will be stored at the SWOG Biospecimen Bank at 4˚C until shipped to the University of Kansas Medical Center for the correlative studies.

e. **Power Calculation**

We will be measuring BRCA1 expression in patients known to not have BRCA mutations. Then, 164 patients will have available PFS and BRCA1 expression data. To compare the bottom 25% to the upper 75%, we assume a median PFS of 4 months for the smaller group. The comparison also assumes 33 months of enrollment with 15 additional months after the last accrual. In the absence of a treatment effect, we can detect with 80% power (1-sided α=0.05) a difference in median PFS of 2.3 months or greater. If treatment is effective in the study, then the analyses need to test the interaction of treatment and the BRCA1 expression status as well. Power for dichotomized BRCA1 is

lower than that for continuous BRCA though the latter does not solve the cutpoint problem without additional work.

3. **PAM 50 BASAL SUBTYPE**

a. Introduction

It is thought that the triple-negative phenotype is a surrogate for the gene expression based basal like category. However, there is a lack of complete overlap between TNBC (defined on immunohistochemistry) and gene expression based basal-like category. Approximately 80% of triple-negative tumors are basal-like on gene expression and the remaining 20% consist of tumors of other subtypes suggesting that non-basal triple-negative tumors are a mixture of all other subtypes. Thus, the basal-like gene expression distinction appears to identify a relatively more homogenous subgroup compared to the triple-negative tumors (as identified on IHC). We intend to perform gene expression-based assays to identify samples that are basal-like, which may prove to be more precise when looking for correlates with PFS. In a recent neoadjuvant study 88% of non-metastatic TNBC were found to be of basal subtype and the presence of basal subtype did not predict for differential benefit from addition of carboplatin to AC/T chemotherapy. (Sikov WM, et al. [S4-05] However, the relationship between basal subtype, BRCAness phenotype and response to a PARPi has also not been studied.

b. Laboratory conducting the assay:

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Laboratory: 913-945-6391
CLIA ID No: 17D2042936
Expiration: 06/17/2016

c. Description of the assay

RNA isolation: Tumor-dense areas of the FFPE tissue sections will be macrodissected. There will not be any correction for tumor content in the sample. Minimum tumor content of 20% will be required. RNA will be isolated using commercially available kits. Amount of RNA needed: 200 – 300 ng.

The PAM50 assay is an in vitro assay which is performed on the NanoString nCounter Dx Analysis System using RNA isolated from FFPE breast tumor tissue. The algorithm uses a 50-gene expression profile to assign breast cancer to one of four PAM50 molecular subtypes determined by the tumor's molecular profile. Reagents (CodeSet containing the genes for the PAM50 gene signature and nCounter master kit) will be purchased from NanoString technology and assay will be run on the n-Counter (NanoString) system (which is housed in the clinical molecular oncology laboratory at the University of Kansas). Subtype calls will be generated using the nSolver™ Analysis Software (a free data analysis program that offers nCounter users the ability to QC, normalize, and analyze data). Tumor intrinsic subtypes will be performed for all patients who are germline BRCA negative.

d. Analysis Plan

Molecular classification results are expected in 95% of the study population. We expect 85% of our study population to be basal subtype on PAM50 subtyping. Primary study analysis 2 and 3 (germline BRCA negative patients) will be repeated on patients with basal subtype tumors. If 95% complete the assay and, of those 85% are basal, we should have 66 of the 82 patients with PFS data available to test this question in both subsets. This does assume that sharpening the criteria to include only basal disease does not change the distribution of BRCAness phenotype status. Again, we would not expect an effect of treatment in non-BRCA like basal patients. We would expect a treatment effect in BRCA-like patients, with 72% power (1-sided α=0.05) we could detect an increase in median PFS from 4 to 7 months due to Veliparib. To have 80% power, the median PFS would need to increase to 7.5 months.

Analytically, we would use a log-rank test on each of the two non-BRCA mutation groups who are identified as basal using the PAM50 test, followed by Cox regression to obtain he hazard ratio. The data would be then extended to the full sample. It is expected that there would be a slight change in the HR toward the null due to the contamination from the nonbasal tumors. The sample size is too small to show a significant interaction of Veliparib with basal/nonbasal status, but this model will be tested.

PAM 50 basal subtyping: The PAM50 assay is an in vitro assay which is performed on the NanoString nCounter Dx Analysis System using FFPE breast tumor tissue previously diagnosed as invasive breast carcinoma. The algorithm uses a 50-gene expression profile to assign breast cancer to one of four PAM50 molecular subtypes determined by the tumor's molecular profile. *(133*) This qualitative assay utilizes gene expression data, weighted together with clinical variables to generate a risk category and numerical score, to assess a patient's risk of distant recurrence of disease. *(134)*

e. Description of the specimens and methods for specimen acquisition and processing:

Formalin fixed paraffin-embedded primary tumor tissue block.
Minimum Sample Requirement: Three 10 micron uncharged slides for RNA isolation and one 5 micron charged slide for H&E staining.

Instructions: Specimens to be shipped by overnight FedEx delivery to SWOG Repository Specimen processing: Specimens (slides or FFPE blocks) will be stored at the SWOG Biospecimen Bank at 4˚C until shipped to the University of Kansas Medical Center for the correlative studies.

4. BRCANESS PHENOTYPE ASSESSMENT ON THE METASTATIC TUMOR

a. Introduction

Background: The Primary Translational Medicine objectives of **S1416** are focused around germline and somatic integral and integrated BRCAness markers which have been previously been reviewed and approved by CTEP and BIQSFP.

The overall design of this trial is to test whether adding ABT-888 (PARP inhibitor) to platinum-based chemotherapy will improve outcomes in patients with metastatic TNBC with germline BRCA mutation or somatic BRCAness phenotype (somatic markers to be done on archived FFPE primary tumor). However an important secondary aim is:

- Application of somatic BRCAness phenotype markers on metastatic tumor tissue (this was highly encouraged by CTEP) to improve the accuracy of identification of patients likely to benefit from platinum-based therapy and ABT-888.

Hypothesis: It is now increasingly being understood that primary tumor may not always reflect the biology in metastatic setting. Our hypothesis for this specific secondary integrated aim is that compared to archived primary tumor, metastatic tumor tissue may be a better source to detect "real time" BRCAness phenotype in metastatic TNBC and that translational medicine studies on metastatic tumor tissue may improve the performance of the already incorporated integral biomarkers in identifying TNBC patients likely to benefit from platinum-based therapy and ABT-888.

b. **Assays to be performed**

The integral and integrated somatic BRCAness markers which are already approved to be performed on the archived primary tumor tissue (BRCA1 Promoter methylation, BRCA1 mRNA expression, somatic BRCA mutation, tumor genomic instability) will be performed on the pre-treatment metastatic biopsies. In addition to the currently identified assays, if during the course of the study other novel and robust BRCAness assays become available we hope to incorporate them in the study. A new marker before being

incorporated will be will require approval from NCI CTEP or the NCI correlative science committee (depending on whether the trial is ongoing or closed) in accordance with policies for use of biospecimens from NCTN clinical trials.

In addition to answering TM objective of **S1416**, tumor tissue (primary and metastatic) collected as part of this study will also serve as a valuable source for future correlative studies aimed at molecular characterization of TNBC.

c. **Pre-Treatment metastatic biopsy:**

Since biomarker analysis on the pre-treatment tumor tissue is not being utilized for treatment assignment it was felt that mandating a pre-treatment biopsy may hider accrual to the study and also considered coercion by some institutional review boards. Thus, the following plan is going to be implemented for collection of metastatic tumor.

It is mandatory for investigators to attempt to obtain metastatic tumor tissue. When archived metastatic tissue is not available it will be highly recommended that pre-treatment metastatic biopsies be obtained unless in the opinion of the investigator image-guided biopsy poses undue risk.

Specifically, we request:

1) Archived metastatic tumor from previous clinical biopsy OR

2) If archived metastatic tumor is not available (biopsy of metastatic site not done, only FNA was done or previous biopsy material has been exhausted) pre-treatment metastatic biopsy will be **highly recommended**. If, in the opinion of the investigator, image guided biopsy poses undue risk to the patient (brain lesion, proximity to major blood vessel etc.) or may not provide adequate sample (pleural fluid, ascites, bone) please consult with the Study Chair. Eligibility in these situations would then be handled on case by case basis after discussion with Study Chair.

Adopting the above approach would allow patients who don't have adequate archived metastatic tissue available, but have easily accessible skin, chest wall, lung, liver or lymph node metastatic sites to undergo pre-treatment biopsy and participate on the trial. This approach would also allow patients with inaccessible lung/liver mets, or where biopsy would not provide adequate sample (pleural fluid, ascites, bone only disease) to participate by only having to submit a primary block. Since this is a study of TNBC we expect very low percentage of patients to present with bone only metastatic disease.

d. **Statistical considerations:**

End points
The primary endpoint is progression-free survival (PFS) defined as time from registration (randomization) to progression or death due to any cause. Progression is defined as radiologic progression of disease by RECIST criteria or unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided).

Secondary endpoints include response rate (measurable disease only), clinical benefit rate, and overall survival. Overall survival is defined as time from registration to death due to any cause. Patients without the event are censored at the last contact. Patients will be followed for a minimum of 5 years after registration to determine overall survival results.

Accrual Goal
We anticipate that metastatic archived tumor tissue will be submitted for 40% of patients and another 30-40% of patients will undergo pre-treatment metastatic biopsy. Thus, we will expect to have metastatic tumor for 70-80% of the study population. Metastatic tumor BRCAness phenotype assessment will be done for all germline BRCA negative patients with available metastatic tumor tissue. The trial plans to accrue 172 germline BRCA mutation negative patients. We are assuming availability of metastatic tumor for 70% of germline BRCA negative study population

Classification of patients as germline BRCA positive will take place during the course of the trial (real time testing). Metastatic tumor BRCA phenotype-like assessment will be done after completion of accrual to the study.

Statistical Analyses

Primary analysis 2: Compare ABT-888 to no ABT-888 in the BRCA mutation-negative BRCAness-like group (n=70% of 86).

A median PFS of 4 months is assumed for Arm 1 (cisplatin+ placebo) that improves to 7 months for Arm 2 (cisplatin + ABT-888). Outcome data is expected to be available from 82 of the 86 registered patients, but only 70% will have metastatic tissue so we assume the overall sample size is 57. Thus, we adjust the Type 1 error for this analysis to 10% instead of 5% (1-sided). Assuming a hazard ratio (HR) of 1.75 for standard versus experimental, the study will have 79% power (1-sided $\alpha = 0.10$) to detect if the experimental arm (2) is superior to the standard arm (1). A stratified log-rank test will be used to compare PFS between the two arms in an ITT analysis.

Primary analysis 3: Compare ABT-888 to no ABT-888 in the BRCA mutation-negative non-BRCA-like group (n=XX 70% of 86)

Theoretically we would expect no difference by treatment (median PFS of 4 months in both arms). However, it is possible that the classification of BRCA-like status has error or that ABT-888 is

efficacious anyway in this group. Outcome data is expected to be available from 82 of the 86 registered patients. A test of efficacy will be conducted at 1-sided $\alpha = 0.10$ even though little or no effect is expected. A stratified log-rank test will be used to compare PFS between the two arms in an ITT analysis.

5. NOVEL BRCAness ASSAYS

The purpose of this trial is to determine if the assays in our multipronged approach will be able to define a BRCAness phenotype and clinical response to PARP inhibition therapy. We anticipate that technical and biological advances will continue to progress as this study is conducted and at the end of the study, it is likely that other measures of BRCAness, and new technologies to define it, will be available.

In order for new BRCAness assays to be incorporated into the study as it progresses, protocol amendments will require approval from the NCI/CTEP in accordance with policies for use of biospecimens from NCTN clinical trials. At the end of the trial, proposals for retrospective studies of newer assays may be submitted to the Central Correlative Sciences Committee for review.

Circulating Tumor Cells

The overall goal of this translational medicine project is to identify patients treated with the PARPi who are refractory to the treatment. This section describes future plans to perform genomic and proteogenomic assays on isolated tumor cell DNA. This research will require review and approval in order to proceed. A correlative science study will be submitted to the NCI for review and approval prior to commencing research related to CTC's. One tube of blood, drawn into a Streck Cell-free DNA tube, will be sent to the Kuhn-Hicks lab (Los Angeles, CA) for divisions into aliquots for CTC identification and extraction for CNV analysis, as well as for plasma for circulating DNA analysis, and WBC for germ line DNA analysis (exploratory and when sufficient sample is available as not all blood samples will have the required 8 ml of blood). Thus, the Kuhn-Hicks laboratory will process the blood they receive for both cell analysis and cell-free DNA isolation. A single blood draw will be collected at baseline, Cycle 2 Day 1, and at progression.

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18.6 Modified Breast Graded Prognostic Assessment Index

The Modified Breast Graded Prognostic Assessment Index (modified breast-GPA) is calculated as the sum of the scores for the four factors as indicated in the following table:

Factor	0	0.5	1.0	1.5	2.0
Karnofsky PS	≤ 50	60	70 to 80	90 to 100	--
Subtype	TNBC	HR+/HER2-	HR-/HER2+	HR+/HER2+	--
Age, years	> 50	≤ 50	--	--	--
No. of brain metastases	> 3	1 to 3	--	--	--

18.7 SWOG Biospecimen Bank (BB) Instructions

Formalin-fixed paraffin-embedded (FFPE) tissue will be submitted to the SWOG BB (Solid Tissue Division) along with the appropriate pathology report(s). Submitting sites must label specimens with at least the SPID, block number, and indicate if the tissue is from a primary (P) or metastatic (M) site in addition to the standard labeling requirements. Sites will submit a FFPE block or 20 unstained slides from the primary tumor. Sites will also submit a FFPE block or 10 unstained slides from the archival metastatic tumor, or – if no archival metastatic FFPE is available – four FFPE core needle biopsies and an H&E-stained slide from the metastatic tumor biopsy may be submitted.

The Bank will store FFPE blocks/slides in a refrigerator (4°C) until distribution. Questions regarding specimen inventory at the Bank should be sent to BPCSWOG@nationwidechildrens.org.

After every 40 patients accrued in the Standard Cohort, the SWOG Statistics and Data Management Center will send a list of patients to the SWOG Biospecimen Bank so that specimens can be shipped to the laboratories performing the assays for classification. The repository will distribute primary FFPE slides and deidentified pathology reports, to both Myriad Laboratories and Drs. Sharma and Godwin at University of Kansas Medical Center, at the addresses below. If a block is received, the Bank will cut slides in the following sequence: one (5 µm) charged H&E stained slide and three (10 µm) uncharged unstained slides; one charged and H&E stained (5 µm) slide and eight (10 µm) uncharged unstained slides to distribute as indicated below:

1. Three (10 µm) unstained uncharged slides and one (5 µm) charged slide* for H&E staining from the primary tumor will be shipped to:

   Anne-Rene Hartman, MD and Kirsten Timms, PhD
   Myriad Laboratory Inc.
   320 Wakara Way,
   Salt Lake City, UT 84108

   The H&E stained slide will be returned to the SWOG BB for long-term storage.

2. Eight (10 µm) unstained uncharged slides and one (5 µm) charged slide* for H&E staining from the primary tumor will be shipped to:

   Priyanka Sharma, MD and Andrew Godwin, PhD
   University of Kansas Medical Center CMOL
   Mail Stop: 3040
   3901 Rainbow Boulevard
   Kansas City, KS 66160

   The H&E stained slide will be returned to the SWOG BB for long-term storage.

3. H&E slide (previously created and shipped to Myriad) will be returned to the SWOG Biospecimen Bank. The H&E slide plus two (2) 4–5 microns thick, positively charged and unbaked slides will be shipped to Foundation Medicine, Inc. at the following address.

   Foundation Medicine, Inc.
   Attn: Accessioning
   7010 Kit Creek Road
   Morrisville, NC 27560
   Phone: 888/988.3639

*Note: If a block is received at the SWOG Biospecimen Bank, then the Bank will cut and stain the charged slide prior to distribution. If slides are received, then an unstained slide will be sent.

Metastatic and all remaining primary FFPE will be stored at the SWOG BB for post hoc integrated/exploratory assays.