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GROUP CHAIR'S OFFICE

Charles D. Blanke, MD
CHAIR

3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239

503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE

4201 Medical Dr
Suite 250
San Antonio, TX 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER

1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1513**, "A Randomized Phase II Study of 2nd Line FOLFIRI versus Modified FOLFIRI with PARP inhibitor ABT-888 (Veliparib) (NSC-737664) In Metastatic Pancreatic Cancer" Study Chairs: Drs. E.G. Chiorean, P. A. Philip, and E. M. Swisher.

REVISION #2

Study Chair: Elena Gabriela Chiorean, M.D.
Phone number: 206/288-6248
E-mail: gchiorea@uw.edu

IRB Review Requirements

(√) Expedited review allowed

Protocol changes

- (√) Eligibility changes:
- (√) Informed Consent changes
- (√) Patient notification required: Notify patient at next visit and document this process in the patient chart

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 #1

This revision has been prepared in response to the Request for Rapid Amendment (RRA) received on May 24, 2018 from Dr. S. Percy Ivy (ivyp@ctep.nci.nih.gov), Dr. Jeffrey Moscow (jeffrey.moscow@nih.gov), and Dr. Meg Mooney (mooneym@ctep.nci.nih.gov). Specific protocol revisions to address risk mitigation plan are not applicable to this protocol as all patients have been previously removed from treatment and the study is permanently closed to accrual. For the same reason, the changes requested for inclusion criteria, exclusion criteria, and dose modifications

were not implemented in response to this RRA. The associated Action Letter is attached.

The above-referenced protocol and consent has been revised as follows.

1. [Title page](#): Version date has been updated.
2. [Section 3.1.c](#):
 - Added New Risk:
 - Rare But Serious: Leukemia secondary to oncology chemotherapy
 - Increase in Risk Attribution
 - Changed to Rare But Serious from Also Reported on ABT-888 Trials But With Insufficient Evidence for Attribution: Myelodysplastic syndrome; Treatment related secondary malignancy
 - Provided Further Clarification:
 - Blood and lymphatic system disorders - Other (bone marrow failure) is now reported as Bone marrow hypocellular.
 - Infections and infestations - Other (shingles) (CTCAE 4.0 language) is now reported as Shingles.
 - Injury, poisoning and procedural complications - Other (radiation proctitis) (CTCAE 4.0 language) is now reported as Radiation recall reaction (dermatologic).
 - Musculoskeletal and connective tissue disorder - Other (muscle spasms) (CTCAE 4.0 language) is now reported as Muscle cramp.
 - Renal and urinary disorders - Other (dysuria) (CTCAE 4.0 language) is now reported as Dysuria.
 - Skin and subcutaneous tissue disorders - Other (nail bed changes) (CTCAE 4.0 language) is now reported as Nail changes.
3. ICD:
 - Added:
 - Rare: Cancer of bone marrow caused by chemotherapy; A new cancer resulting from treatment of earlier cancer; Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Giovanna Kinahan – Merck
David McFadden – Merck
Tanja Obradovic – Merck

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SWOG

RANDOMIZED PHASE II STUDY OF 2ND LINE FOLFIRI VERSUS MODIFIED FOLFIRI WITH PARP
INHIBITOR ABT-888 (VELIPARIB) (NSC-737664) IN METASTATIC PANCREATIC CANCER

NCT#02890355

STUDY CHAIRS:

Elena Gabriela Chiorean, M.D.
(Medical Oncology)
University of Washington
825 Eastlake Ave E, G4830
Seattle, WA 98109
Phone: 206/288-6248
FAX: 206/288-2042
E-mail: gchiorea@uw.edu

Philip A. Philip, M.D., Ph.D., F.R.C.P.
Karmanos Cancer Center (Medical Oncology)
Wayne State University
4100 John R Street 4HWCRC
Detroit, MI 48201
Phone: 313/576-8728
FAX: 313-576-8729
E-mail: philipp@karmanos.org

Elizabeth M. Swisher, M.D. (Translational
University of Washington Medicine)
Box 356460
1959 NE Pacific Street
Seattle, WA 98195
Phone: 206/543-3580
FAX: 206/543-5230
E-mail: swishere@u.washington.edu

Florencia Jalikis, M.D. (Pathology)
University of Washington
Box 359791
325 Ninth Avenue
Seattle, WA 98104
Phone: 206-543-1140
Fax: 206-543-3644
Email: florj@uw.edu

AGENTS:

IND-Exempt Agents:
Fluorouracil (5-FU, Adrucil®) (NSC-19893)
Irinotecan (Camptosar®) (NSC-616348)
Leucovorin (NSC-3590)

NCI Supplied Investigational Agents (DCTD sponsored):
ABT-888 (Veliparib) (NSC-737664) (IND-129716)

BIOSTATISTICIANS:

Shannon McDonough, M.S.
Katherine A. Guthrie, Ph.D.
SWOG Statistical Center
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue N, M3-C102
P.O. Box 19024
Seattle, WA 98109-1024
Phone: 206/667-4623
FAX: 206/667-4408
E-mail: smcdonou@fredhutch.org
E-mail: kguthrie@fredhutch.org

ALLIANCE STUDY CHAIRS:

Michael J. Pishvaian, M.D., Ph.D.
Lombardi Comprehensive Cancer Center
Georgetown University
3800 Reservoir Rd NW
Washington, DC 20007
Phone: (202) 444-1212
Fax: (202) 444-9429
E-mail: pishvaim@georgetown.edu

ECOG STUDY CHAIRS:

Jordan Berlin, MD
Ingram Professor of Cancer Research
Phone: 615-343-41 28
Email: jordan.berlin@vanderbilt.edu

PARTICIPANTS

ALLIANCE/Alliance for Clinical Trials in Oncology
ECOG-ACRIN/ECOG-ACRIN Cancer Research Group
NRG/NRG Oncology
SWOG/SWOG

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
To submit site registration documents:	For patient enrollments:	Submit study data
<p>CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103</p> <p>Phone – 1-866-651-CTSU</p> <p>Fax – 215-569-0206</p> <p>Email: CTSURegulatory@ctsu.cocccg.org (for submitting regulatory documents only)</p>	<p>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.</p> <p>Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.</p>	<p>Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.</p>
<p>The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at 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 user log on with CTEP-IAM username and password.</p>		
<p>For clinical questions (i.e. patient eligibility or treatment-related) contact the SWOG Data Operations Center by phone or email: 206-652-2267 gquestion@crab.org</p>		
<p>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</p>		
<p>The CTSU Website is located at https://www.ctsu.org</p>		

1.0 OBJECTIVES

1.1 Primary Objective

- a. To evaluate the overall survival (OS) of metastatic pancreatic cancer patients treated with fluorouracil, irinotecan, leucovorin (modified FOLFIRI) and ABT-888 compared to a control arm of fluorouracil, irinotecan, and leucovorin (FOLFIRI).

1.2 Secondary Objectives

- a. To evaluate the frequency and severity of toxicity associated with each of the treatment arms in this patient population.
- b. To evaluate the progression-free survival (PFS) in each of the treatment arms in this patient population.
- c. To evaluate the overall response rate (confirmed and unconfirmed; complete response + partial response), disease control rate (confirmed and unconfirmed; complete response + partial response + stable disease), and duration of response in each of the treatment arms in this patient population.

1.3 Translational Objectives

- a. To evaluate if *BRCA1* and *BRCA2* mutations (somatic or germline) are associated with improved clinical outcomes [overall survival (OS), progression-free survival (PFS) and overall response rates (ORR)] in each treatment arm.
- b. To evaluate the impact of Homologous Recombination Deficiency (HRD) score on clinical outcomes in each treatment arm.
- c. To evaluate the impact of genomic alterations identified by the BROCA-HR assay, other than *BRCA1/2*, on clinical outcomes in each treatment arm
- d. To bank tissue for future translational medicine studies.

2.0 BACKGROUND

Pancreatic Cancer Overview

Approximately 277,000 new cases of pancreatic cancer are diagnosed each year in the world, among which roughly 49,000 each occur in the United States and Europe. (1,2,3) Despite modest improvements in detection, which may have contributed to its rise in incidence, the 5-year overall survival rate only increased from 5% to 6% in the past 3 decades. (4,5) While currently pancreatic cancer represents the 4th leading cause of cancer death in the United States (approximately 40,000 deaths annually), it is expected to become the 2nd cause of cancer related deaths in the US in the next decade. (6) More than 50% of pancreatic cancers are metastatic at diagnosis, where survival rates range from 7-11 months. (7,8) After progression from first line regimens such as gemcitabine plus nab-paclitaxel, or folinic acid (leucovorin), fluorouracil (5-FU) with irinotecan and oxaliplatin (FOLFIRINOX), second line regimens commonly used in practice are 5-FU with oxaliplatin (FOLFOX) or 5-FU with irinotecan (FOLFIRI), which both yield overall survival (OS) rates of approximately 6 months, and progression-free survival rates of 3 months. (9,10,11) In a randomized Phase II study using FOLFIRI versus FOLFOX chemotherapy, results were similar (PFS 8.3 vs 6 weeks, and OS 16.6 vs 14.9 weeks). (12) Most recently, the liposomal irinotecan agent MM-398 demonstrated OS rates of 6.1 months and progression-free survival (PFS) of 4.1 months in combination with 5-FU in the randomized Phase III Napoli -1 study. (13) While these results seem comparable to those with FOLFIRI, no randomized study to date has compared FOLFIRI with MM398 plus 5-FU in pancreatic cancer.

DNA Repair in Pancreatic Cancer

Pancreatic cancer is characterized by genomic instability. (14,15,16) Several DNA repair defects occur through mutations in DNA mismatch repair genes such as MLH1, MSH2 or MSH6 (3-15% incidence), tumor suppressor genes TP53 (tumor protein 53, 50% incidence), and the Fanconi anemia pathway genes BRCA1/2 (breast cancer genes 1,2) and PALB2 (partner and localizer of BRCA2), (7% incidence in sporadic pancreatic cancer, and up to 17% in familial cases), as well as FANCC (Fanconi anemia group C) and FANCG (Fanconi anemia group G) (5-10%). (17,18,19,20,21,22,23,24,25,26) Other key factors and pathways in DNA repair including ATM (ataxia-telangiectasia mutated)/Chk2 (checkpoint-like kinase 2), ATR (ataxia-telangiectasia and Rad3-related)/Chk1 (checkpoint kinase 1), Rad51, ERCC1 (excision repair cross-complementation group 1), and PTEN (phosphatase and tensin homolog), can be mutated or inactivated in pancreatic cancer. (27,28,29,30,31,32,33) Whereas among patients with familial pancreatic cancer syndrome, overall, the BRCA2 mutations have been reported in up to 17% of patients through retrospective analysis, a recent prospective cohort study of 306 patients with newly diagnosed pancreatic cancer identified pathogenic germline BRCA2 mutations in 3.6%, and BRCA1 mutations in 1% of patients. (34) Impaired DNA damage response pathways in pancreatic cancer create vulnerabilities that can be exploited therapeutically, and DNA-cross linking agents such as platinum and mitomycin C, topoisomerase inhibitors like irinotecan, and PARP inhibitors are of particular interest.

PARP Inhibitors and Pancreatic Cancer

Poly-(ADP-ribose) polymerases are nuclear enzymes activated by DNA single- (SSB) or double-strand breaks (DSB) which are able to synthesize poly(ADP-ribose) [pADPr] polymers leading to DNA repair. (35,36) Among the seventeen PARP family members identified, only three (PARP1, PARP2 and PARP3) have established roles in DNA repair. (37)

PARP1, the best characterized PARP enzyme, plays multiple roles in DNA repair pathways which have been extensively reviewed in the literature, and are summarized here: 1) base excision repair (BER) the repair of a single damaged base; 2) repair of DSB by recruitment of DNA repair proteins MRE11 and NSB1 to initiate homologous recombination (HR) and allowing one copy of a gene to serve as template for the second copy of the same gene to be restored; 3) prevents activation of the error-prone non-homologous end-joining recombination (NHEJ) DSB repair pathway; 4) alternative end-joining repair; 5) restarts replication forks; 6) modulates gene transcription; 7) regulates chromatin structure; 8) alters microRNA activity; and 9) affects energy metabolism. (38,39,40,41,42,43,44,45,46,47,48,49,50)

The development of PARP inhibitors has been exploited mostly in patients with breast and ovarian cancers, with known defects in the HR pathway such as BRCA1/2 or PALB2 mutations, given the synthetic lethality by treatment with a PARP inhibitor. (51,52) Molecular alterations besides those previously described in DNA repair pathways have been noted to benefit from PARP inhibition, such as HER2 overexpression, EGFR mutations, and PI3K pathway activation. (53,54,55) In addition to the benefit observed in tumors harboring HR deficiencies, PARP inhibitors have shown activity after pharmacologic induction of HR deficiency, such as with epidermal growth factor receptor inhibitors, and cyclin dependent kinase 1 (CDK1) blockade (which lead to BRCA1 translocation to the cytoplasm), and phosphatidylinositol 3-kinase (PI3K) inhibitors which decrease RAD51 and BRCA1/2 expression. (56,57,58,59)

PARP inhibitors have also shown activity in combination with DNA damaging agents such as cytotoxic chemotherapy and radiation therapy. (60,61) The high lethality of pancreatic cancer stems partially from its resistance to multiple cytotoxic agents. Since DNA damaging agents are the cornerstone treatment for this disease, blocking DNA repair may prevent chemo-resistance.

Topoisomerase inhibitors, such as irinotecan induce PARP cleavage. (62,63) In turn, PARP recognizes topoisomerase I cleavage complexes (Top1cc) resulting from treatment with camptothecin and irinotecan, and recruits tyrosyl-DNA phosphodiesterase 1 (TDP1), a key repair

enzyme for trapped Top1cc, and downstream base-excision repair (BER) proteins. (64) Combined treatment of irinotecan with PARP inhibitors results in persistent and increased DNA damage breaks and apoptosis compared to irinotecan alone. (65,66,67,68,69,70) These mechanisms explain the synergistic cytotoxicity observed between topoisomerase and PARP inhibitors in preclinical models. (71,72,73)

To date PARP inhibitors have demonstrated clinical activity as single agents in pancreatic cancers harboring BRCA1/2 or PALB2 mutations. Olaparib demonstrated 22% response rates and median PFS and OS rates of 4.6 and 9.8 months, respectively in patients who received at least 2 prior lines of therapy, while ABT-888 showed 31% 4 months+ stable disease rate, and a median PFS of approximately 2 months in refractory disease. (74,75,76) ABT-888 in combination with FOLFOX, gemcitabine/cisplatin, or FOLFIRI chemotherapy in first or second+ line setting demonstrated sustained responses in BRCA mutated or non-mutated patients, and response rates were 14-56%, and OS rates were up to 7.7 months. (77,78,79) The combination of FOLFIRI with ABT-888 has been tested in a Phase I trial among 92 patients with refractory solid tumors, including 13 patients with refractory pancreatic cancer irrespective of BRCA1/2 status. (80) Response and stable disease rates were 15% (n=2) and 46% (n=6), respectively, and the 6-month time-to-progression was 27%. Both responses were long lasting (308 and 749 days respectively), and occurred in non-BRCA mutated patients. Clearly the DNA-repair pathway should be further explored and genomic characterization beyond BRCA1/2/PALB2 status should be determined for a “personalized” approach in a larger patient population.

ABT-888 Clinical Experience

ABT-888 has been investigated as a single agent and in combination with various DNA-damaging agents in subjects with different cancer types. Overall, approximately 1,255 cancer subjects have been exposed to ABT-888 in company sponsored studies as of 24 March 2014. Additionally, in the Cancer Therapy Evaluation Program (CTEP) sponsored studies of ABT-888, approximately 1,687 adult subjects and 44 pediatric subjects have been exposed to ABT-888 as of 31 March 2014.

Company sponsored studies included the evaluation of ABT-888 in combination with temozolomide, whole brain radiation therapy, concurrent radiation therapy and temozolomide, carboplatin and gemcitabine, carboplatin and paclitaxel, and FOLFIRI in Phase I and Phase II clinical studies. The main toxicities associated with ABT-888 to date are mechanism based and are not clearly distinguished from those expected of the base regimens with which ABT-888 is combined. Hematological toxicities, such as thrombocytopenia and neutropenia, and gastrointestinal (GI) disturbances such as nausea and vomiting, are the main toxicities observed to date.

Study M10-977 was a Phase I, open-label dose escalation study evaluating the safety and tolerability of ABT-888 in combination with modified bimonthly FOLFIRI. (81) As of 14 March 2014, 96 subjects had been enrolled, enrollment was complete, and 6 patients remained on study. Although combining ABT-888 with standard FOLFIRI including a 5-FU bolus (400 mg/m²) was not tolerated, ABT-888 was dose escalated from 10 mg to 300 mg BID using a modified FOLFIRI regimen omitting the 5-FU bolus (irinotecan 150 mg/m², 5-FU 2400 mg/m², leucovorin 400 mg/m²). It is relevant to note that a CTEP-sponsored Phase I dose escalation study of ABT-888 in combination with FOLFOX independently reached the same conclusion that a 5-FU bolus is not tolerated with ABT-888. After 67 patients, the FOLFIRI dose was modified to irinotecan 180 mg/m², 5-FU 2400 mg/m² and a second dose escalation of ABT-888 starting at 100 mg BID was conducted. (82) Leucovorin was removed from this regimen as there was a US supply shortage and it was deemed unnecessary due to the absence of a 5-FU bolus. ABT-888 200 mg BID was tolerated in this higher irinotecan dose. As doses exceeding ABT-888 200 mg BID were not tolerated in the lower dose FOLFIRI regimen, further dose escalation was not pursued. The most common treatment-emergent adverse events, reported in ≥ 30% of all subjects, were diarrhea (57 subjects, 62.0%), nausea (55 subjects, 59.8%), vomiting (44 subjects, 47.8%), fatigue (43 subjects, 46.7%), alopecia (37 subjects, 40.2%), neutropenia (55 subjects, 60.9%), decreased appetite (30 subjects, 32.6%), and anemia (39 subjects, 42.4%). The most commonly reported treatment-emergent Grade 3 or 4 adverse events (rate > 5%) were neutropenia (33 subjects, 35.9%), anemia (9

subjects, 9.8%), diarrhea (5 subjects, 5.4%), dehydration (5 subjects, 5.4%) and hypokalemia (5 subjects, 5.4%). Two patients in the ABT-888 270 mg BID dose level experienced dose-limiting toxicities (one patient with Grade 3 severe gastritis and Grade 3 vomiting and another patient with Grade 4 neutropenia). The recommended Phase II dose combination was determined to be ABT-888 200 mg BID, irinotecan 180 mg/m², 5-FU 2400 mg/m², and leucovorin 400 mg/m². Although encouraging efficacy was noted in this study (17/96 PR, 42/96 SD), this was a heavily pre-treated population and thus efficacy comparisons with first-line FOLFIRI studies are not valid.

Additional details regarding clinical data can be found in the ABT-888 Investigator's Brochure. ⁽⁸³⁾

Rationale for FOLFIRI and PARP inhibitor ABT-888 in pancreatic adenocarcinoma

It is well known that PARP contributes in the repair from topoisomerase 1-associated DNA damage. Genetic PARP inactivation sensitizes cells to topoisomerase inhibitors and PARP inhibitors increase the cytotoxicity and DNA breaks from camptothecins in preclinical models. ^(84,85) Preclinical evidence suggests that MLH1 loss, RAD51 mutations, and ERCC1 loss may particularly enhance cytotoxicity from PARP inhibition plus irinotecan/SN38 combination. ^(86,87,88) While FOLFIRI is one of the standard second-line therapy options in pancreatic cancer, overall survival rates are only 6 months, and novel treatments are urgently needed. ⁽⁸⁹⁾ Given the key role of the DNA repair mechanisms in pancreatic cancer oncogenesis and progression, the preclinical synergism between topoisomerase I with PARP inhibitors, and the safety observed in Phase I trials, a randomized clinical trial of FOLFIRI with ABT-888 versus FOLFIRI alone for pancreatic cancer patients who progressed on prior chemotherapy has been proposed. ^(90,91) Tumor samples will be collected to perform a retrospective analysis of biomarkers to help inform the development of future Phase III clinical trials with this treatment combination, and with PARP inhibitors in general. No competing trials exist, per study team knowledge, with the combination of FOLFIRI and PARP inhibitors in second line therapy of pancreatic cancer, and given the high incidence of DNA repair pathways abnormalities in this tumor (up to 25%), this study expects to observe a meaningful improvement in the primary outcome, overall survival, and also to identify the patient population most likely to benefit from this targeted therapeutic approach with retrospective analysis of biomarkers.

Rationale for *BRCA1/2* Mutations, BROCA-HR and HRD Score Translational Medicine

DNA repair defects in pancreatic cancer (PC) involve DNA mismatch repair genes *MLH1*, *MSH2* and *MSH6* (3-15% incidence), tumor suppressor genes *TP53* (50%), *BRCA1/2* and *PALB2* (7% in sporadic and up to 17% in familial cases), other Fanconi anemia-homologous recombination (HR) genes *FANCC* and *FANCG* (5-10%), *ATM/Chk2*, *ATR/Chk1*, *Rad51*, *ERCC1*, and *PTEN*. ⁽⁷⁸⁻⁸⁷⁾ The marked susceptibility of patients with germline *BRCA* mutated (gBRCAm)-associated cancers has validated gBRCAm as a predictive biomarker for PARP inhibitors (PARPi) response. ⁽⁸⁸⁾ Several mechanisms lead to HR deficiency thus it is unlikely that a single test will detect all patients with the HRD (or *BRCAness*) phenotype. In addition to gene mutations, gene rearrangements, DNA methylation and mRNA expression can also affect the HR pathway. We hypothesize that assays that test capacity for homologous recombination (HR) DNA repair will identify subsets of PC patients with HRD. These biomarkers could guide future Phase III trials in PC, specifically with DNA-damaging agents and/or PARPi. The Myriad Genetics HRD test and the BROCA-HR assay (which includes *BRCA1/2* mutations analysis) have been evaluated in breast and ovarian cancer clinical trials using DNA damaging agents and/or PARPi, and have shown correlations with clinical outcomes. Given the current knowledge regarding the presence of germline or somatic *BRCA1/2* mutations, including in PC and benefit from PARPi, we consider the *BRCA1/2* testing as integrated biomarkers, while the HRD assay and remainder of the BROCA-HR assay to be exploratory biomarkers in **S1513**. ^(92,93)

HRD Assay

The homologous recombination deficiency (HRD) assay developed by Myriad Genetics (myChoice HRD™) combines genomic patterns of loss of heterozygosity (LOH) “footprint”, telomeric allelic imbalance (TAI), and large-scale state transitions (LST) scores as an indicator of HR deficiency

regardless of mechanism. (94,95,96) The HRD assay is a DNA-based, next generation sequencing assay that detects tumors with the HRD phenotype. The assay main components include the HRD score and somatic *BRCA1/2* mutations. Deleterious or suspected deleterious somatic mutations in *BRCA1/2* define a tumor as having the HRD phenotype (regardless of HRD score). The HRD score is the sum of its three individual components: 1) LOH score is the number of LOH regions of intermediate size (> 15 Mb and < whole chromosome), 2) LST score is the number of chromosome breaks points (translocations, inversions or deletions) in adjacent segments of DNA of at least 10Mb, 3) TAI score is the number of regions with allelic imbalance which extend to the subtelomere but do not cross the centromere. The HRD Score is the unweighted sum of LOH, TAI and LST measurements on a scale from 0-100. The three HRD components demonstrate significant correlation with each other (correlation coefficients 0.77 and 0.83). Although highly correlated, the three scores contain different information and combining them generates a more robust predictor of HRD. (97,98) Based on molecular data further tested in clinical trials, HRD positive tumors (breast and ovarian cancers) were those with an HRD score of ≥ 42 or a deleterious mutation in *BRCA1/2* gene. Although the primary clinical application of the HRD score will be to enrich for responders to HR targeted therapies, this was not the criteria for selecting the threshold. A threshold has not been yet described in PC. Response is highly dependent on the treatment regimen and activity of a specific drug. In contrast, a threshold based on the underlying biology of the tumor, i.e., HRD, should be independent of treatment effect. Establishing a predefined threshold value based on the biology of HRD, rather than a specific treatment outcome, allows the validation of the test to be conducted independent of the effect of a specific therapy.

The HRD assay is a next generation sequencing assay that targets ~54,000 SNPs which are evenly dispersed across the human genome. A by-product of this assay is the generation of 400 bp of sequence flanking each SNP location, resulting in a total of 21 Mb of genome sequencing data from each tumor sample analyzed. By cataloging the frequency of microsatellite repeat mutations and random somatic mutations within this 21 Mb of sequence data we are able to identify tumors with MSI or high somatic mutation burden due to underlying defects independent of MMR defects. In addition, the assay directly targets 43 genes known to be involved in DNA damage repair pathways and/or tumorigenesis, allowing the identification of both germline and somatic mutations within these genes (AKT1, ATM, ATR, BAP1, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, CTNNA1, ERCC4, FAM175A, FANCA, FANCD2, FANCE, FANCI, FANCL, KRAS, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PALB2, PIK3CA, PPP2R2A, PTEN, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54B, RAD54L, RPA1, TP53, TP53BP1, XRCC2, XRCC3). Finally, hypermethylation of the *BRCA1* promoter has been proposed as a mechanism for *BRCA1* epigenetic inactivation, and will be evaluated in this assay.

One hundred thirty four PC samples derived from resected pancreatic tumors were analyzed (Dr. Eileen O'Reilly collaboration). All samples were submitted as tumor cores from formalin fixed paraffin embedded (FFPE) tissue. Among 134 samples, 76 passed HRD analysis (failures were primarily to due to high non-tumor DNA content, > 70%). Approximately 7% of tumors carried *BRCA1/2/PALB2* deleterious mutations. Germline DNA was not available. Twenty other samples were analyzed from fine needle aspirate (FNA) specimens of patients with metastatic PC (Dr. E. Gabriela Chiorean collaboration). Fifteen samples provided sufficient DNA for HRD analysis. 80% of samples (12/15) passed HRD analysis. Failures were due to high non-tumor content. For this metastatic sample study, the HRD score ranged from 11 to 46. Among the 15 evaluable samples, 4 showed other deleterious mutations: 3 *RAD52* mutations, and 1 *BRCA2* mutation (HRD score 46). HRD score range for both studies was 0 - 53. The distribution of scores in samples with *BRCA1/2/PALB2* mutations was lower than observed in breast/ovarian cancer, suggesting the cut-off may need to be < 42 in PC.

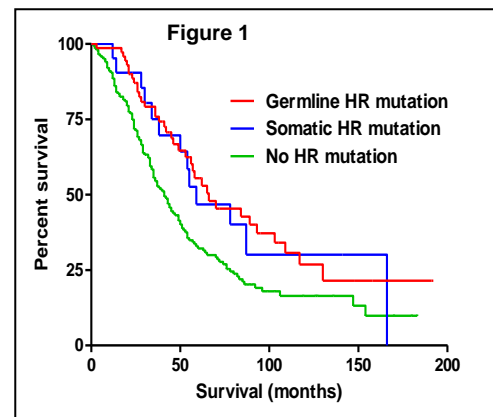
BROCA-HR Assay

BROCA-HR is a targeted capture and massively parallel sequencing assay designed to detect all mutation classes including gene rearrangements, copy number variations, and gene aberrations within the Fanconi Anemia-BRCA homologous recombination (HR), non-homologous end joining (NHEJ) DNA repair, and DNA mismatch repair pathways. BROCA-HR has been successfully used to characterize tumor samples from patients with breast and ovarian cancer, and provided useful

data of correlation with overall prognosis and prediction of response to platinum-based therapies. (99,100,101) In order to respond to PARPi, cancer cells seem to need to be deficient in HR but proficient in the alternative error prone non-homologous end joining (NHEJ) DNA repair pathway. (102,103) Thus, loss of HR is not, by itself, sufficient for PARPi sensitivity, and an accurate predictor of PARPi responsiveness could require assessment of many components of both the HR and NHEJ pathways. Recent evidence suggests that *BRCA1/2* deficient cancers exhibit global DNA alterations termed “genomic scarring” that are consistent with their reliance on the NHEJ pathway. (104,105,106) This genomic scar could serve as a downstream functional output to measure DNA repair capacity, indicative of both HR deficiency and NHEJ proficiency. Therefore, mutations in NHEJ and other pathways that could affect HR as well as genomic scarring will also be evaluated as exploratory biomarkers.

BROCA-HR and genomic scarring: preliminary data in breast and ovarian cancer

Using BROCA, Walsh et al demonstrated that nearly one-fourth of women with ovarian carcinoma have germline loss of function mutations in at least 12 genes. (107) After *BRCA1/2*, the most common genes mutated in women with ovarian cancer (which have also been reported in PC) are *BRIP1* (*FANCF*), *RAD51D*, *RAD51C* (*FANCO*), and *PALB2* (*FANCD2*). (108,109) Pennington et al applied BROCA to detect somatic mutations in tumor DNA from 363 women with ovarian carcinoma. (110) The presence of either a germline or somatic FA/HR mutation was highly predictive of an improved primary response to platinum chemotherapy ($p < 0.0005$) and longer overall survival ($p = 0.001$, [Figure 1](#)).



BROCA-HR includes additional DNA repair genes (75 total genes) as well as 3000 SNPs. The GOG3005 study in ovarian cancer uses BROCA-HR as an integrated assay to correlate with treatment response to chemotherapy and PARPi, and **S1416** utilizes blood BROCA-HR in breast cancer patients. Similar sequencing accuracy and sensitivity is obtained from FFPE, fresh blood and flash frozen specimens. BROCA-HR includes genes that are targets of both somatic and germline mutations. (111) The BROCA design is flexible and can be altered to include any genes of research interest. The current design for BROCA-HR includes the following genes (n=75):

- a. FA-BRCA HR pathway: ATM, ATR, BABAM1, BAP1, BARD1, BLM, BRCA1, BRCA2 (*FANCD1*), BRIP1 (*FANCF*), BRCC3, BRE, CHEK1, CHEK2, ERCC1, ERCC4 (*FANCG*), 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
- b. DNA mismatch repair *MLH1*, *MSH2* (and *EPCAM*), *MSH6*, *PMS2*
- c. Other DNA repair, surveillance genes, or modifier genes: *CDK12*, *CDH4*, *HELO*, *NEIL1*, *PPM1D*, *POLD1*, *POLE*, *RIF1*, *TP53*, *ID4*, *PAXIP1*, *POLQ*, *RINT1*, *TP53BP1*, *USP28*, *WRN*, *XRCC3*
- d. NER genes: *ERCC2*, *ERCC3*, *ERCC4*, *ERCC5*, *ERCC6*, *DDB1*, *XPA*, *XPC*
- e. NHEJ genes: *DCLRE1C*, *LIG4*, *PRKDC*, *TOBP1*, *XRCC4*, *XRCC5*, *XRCC6*
- f. PI3K pathway: *PTEN*, *PI3KCA*

A common characteristic of “genomic scarring” is large (> 15Mb) but sub-chromosomal deletions. Therefore, fine mapping of LOH is not necessary to identify the HRD genomic scar. We tested the theoretical ability of 3000 SNPs to define “genomic scarring” in existing TCGA ovarian cancer data (unpublished data, [Figure 2](#)). Indeed, using only 3000 SNPs can define cases with high LOH which

have better prognosis. Combining the BRCA mutational status and the LOH profile ([Figure 3](#)) provides additional prognostic information.

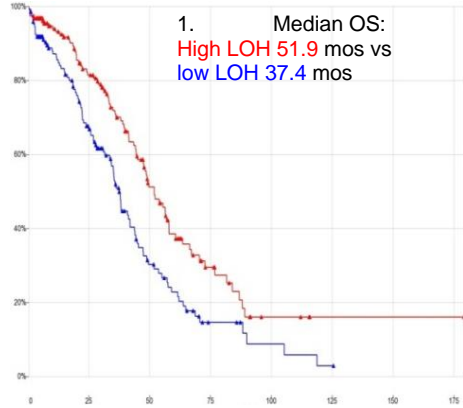


Figure 2 Using TCGA data we found that 3000 SNPs could be used to define high genomic LOH, which is associated with significantly longer survival.

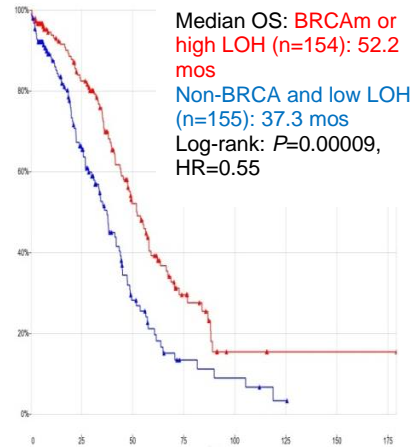


Figure 3 Using TCGA data, we evaluated the performance of 3000 SNPs defining high genomic LOH in combination with BRCAm status.

S1513 will assay 3000 SNPs with the same BROCA-HR mutational assay which will provide an LOH profile to assess genomic scarring as an exploratory biomarker. The mutation information from BROCA will then be combined biomarker as outlined in [Figure 4](#), with the prediction that HR proficient cancers would achieve no significant benefit from the addition of PARPi.

Figure 4		Genomic LOH-High	Genomic LOH-low
		HR mutation germline or somatic	HRD
No HR mutation	HRD	HR Proficient	

Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

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	1	0	0	2
Asian	3	5	0	0	8
Native Hawaiian or Other Pacific Islander	1	2	0	0	3
Black or African American	7	6	0	0	13
White	60	51	4	2	117
More Than One Race	0	0	0	0	0
Total	72	65	4	2	143

3.0 DRUG INFORMATION

Investigator Brochures

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

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

For this study, ABT-888 is investigational and is being provided under an IND held by the National Cancer Institute. The Investigator Brochure may be obtained by accessing PMB's Online Agent Ordering Processing (OAOP) application (http://ctep.cancer.gov/branches/pmb/agent_order_processing.htm).

3.1 ABT-888 (Veliparib) (NSC-737664) (IND-129716)

a. PHARMACOLOGY

Mechanism of Action: Poly(ADP-ribose) (PAR) polymerase (PARP) is a nuclear enzyme that recognizes DNA damage and enables DNA repair. Activation of PARP-1 and PARP-2 enzymes is an essential step in the recognition of DNA damage that results in the poly(ADP-ribosyl)ation of many nuclear target proteins, including those that facilitate DNA repair. PARP activity is needed for the repair of single-stranded DNA breaks and is also an important modulator of double-stranded break repair pathways. As a result, inhibition of PARP can enhance the effects of DNA-damaging agents including alkylators, platinum, topoisomerase poisons, and radiation therapy. The higher expression of PARP seen in cancer

cells compared to normal cells has been linked to drug resistance and the overall ability of cancer cells to sustain genotoxic stress.

ABT-888 is a small molecule (molecular weight=244.29) that is a potent PARP-1 and PARP-2 inhibitor. ABT-888 delays the repair of DNA damage induced by chemotherapeutic drugs. It increases the sensitivity of tumor cells to DNA-damaging agents *in vitro*; has demonstrated PARP inhibition in murine and human tumor cell lines xenographs *in vivo*; and in human peripheral blood mononuclear cells (PBMCs) *ex vivo*. In nonclinical tumor models, ABT-888 improved the antitumor activity significantly when administered at a schedule that overlapped the administration of DNA-damaging agents.

b. PHARMACOKINETICS

1. Absorption: After oral administration, ABT-888 absorption is relatively fast. Plasma concentrations peak at approximately 1 to 2 hours after dosing across dose levels. Food does not have a significant effect on ABT-888 bioavailability. Administration of ABT-888 with a high-fat meal results in a slight decrease in ABT-888 maximum plasma concentration (17%) and a delay of approximately one hour in ABT-888 reaching the maximum concentration. The effect on the area under the plasma concentration-time curve (AUC) is insignificant. The exposure of ABT-888 is closely proportional across doses of between 10 mg and 500 mg.
2. Distribution: ABT-888 binding to plasma proteins is low-to-moderate across species. Following a single dose of 10mg, 25mg and 50mg, the volume of distribution is large (134 ± 33 , 166 ± 26 , and 250 ± 122 liter, respectively). ABT-888 crosses the blood brain barrier.
3. Metabolism: ABT-888 is cleared primarily in the urine as intact parent drug with minor contributions from metabolism. The renal clearance and minimal metabolism observed in rats and dogs and the minimal metabolism observed *in vitro* in all species evaluated are consistent with the low molecular weight and good solubility of ABT-888. These data are supported by results from clinical studies which show that ABT-888 is cleared primarily as intact parent drug in urine.
4. Elimination: Renal excretion is a major pathway in ABT-888 elimination. In one clinical trial, after oral administration, the mean urinary recovery of unchanged ABT-888 was 72% and the total urinary recovery of ABT-888 (as parent compound and a metabolite) was 86%. The terminal half-life ($t_{1/2}$) of ABT-888 is about 6 hours, with minimal accumulation following multiple twice daily dosing.

c. ADVERSE EFFECTS

1. Adverse Effects:

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements'

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 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, 2018¹

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)
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	

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%)	
		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

HEPATOBIILIARY 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.

2. **Pregnancy and Lactation:** The potential for ABT-888 to cause teratogenic and developmental effects was evaluated in embryofetal toxicity studies in rats and rabbits and showed dose-dependent maternal and embryofetal toxicity that is considered a result of PARP inhibition. No human data regarding pregnancy are available. Based on ABT-888 mechanism of action and preclinical studies, pregnancy is to be avoided in all clinical trials. It is not known if ABT-888 is excreted in human milk.
3. **Drug Interactions:** ABT-888 is not a potent inhibitor of the major human cytochrome P450 proteins (CYPs) and does not significantly induce activities of major human CYP isoenzymes. Therefore there is a minimal potential for CYP-mediated drug-drug interactions at the anticipated therapeutic concentrations.

At therapeutically efficacious doses for combination therapy (e.g., 40 mg twice daily), ABT-888 has a low potential for clinical pharmacokinetic drug-drug interactions with transporters that have been assessed like P-

glycoprotein (p-gP), Breast Cancer Resistance Protein (BCRP) or kidney transporters. ABT-888 may inhibit some transports in the liver and the kidney at higher doses (e.g., 400 mg twice daily). Complete details are available in the Investigator's Brochure.

d. DOSING & ADMINISTRATION

See [Section 7.0](#) Treatment Plan.

e. HOW SUPPLIED

1. ABT-888 is an investigational agent supplied by AbbVie Pharmaceuticals and distributed by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.
2. ABT-888 capsules are available in 50 mg and 100 mg immediate release capsules. The inactive ingredients are microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, gelatin, sodium lauryl sulfate, and titanium dioxide. It may contain FD&C blue#1, FD&C yellow #6, or FD&C yellow #5.
3. ABT-888 will be packaged in bottles containing 64 capsules. Each bottle label will include all information as required by local regulations and must remain affixed to the bottle. All blank spaces on the label will be completed by site staff prior to dispensing to the subject.

f. STORAGE, PREPARATION & STABILITY

1. Store the original bottle at 15° to 25° C (59° to 77° F).
2. ABT-888 capsules may be repackaged from the supplied HDPE bottles into amber (or other low-actinic) child resistant pharmacy dispensing bottles. The expiration date is 30 days from the repackaging date (or the original retest date, whichever is earlier) when stored at 15°C to 25°C (59°F to 77°F).
3. Stability: Shelf-life stability studies for ABT-888 capsules are on-going.

g. DRUG ORDERING & ACCOUNTABILITY

1. Drug ordering: NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number (**S1513**) must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 and a CV. If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution. Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application <https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx>. Access to OAOP requires the establishment of a CTEP Identity and Access

Management (IAM) account <<https://eapps-ctep.nci.nih.gov/iam/>> and the maintenance of an “active” account status and a “current” password. For questions about drug orders, transfers, returns, or accountability, call 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

2. Drug Handling and Accountability

- a. 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 NCI Oral Drug Accountability Record Form available on the CTEP home page (<http://ctep.cancer.gov>).
- b. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF.

3. Drug return and/or disposition instruction

- a. ***Only undispensed clinical supplies should be returned to the PMB.*** *When it is necessary to return study drug (e.g., sealed bottles at study termination or, expired bottles recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Drug List available on the CTEP home page (<http://ctep.cancer.gov>) or by calling the PMB at 240/276-6575. Opened bottles with remaining capsules should be documented in the NCI Oral Drug Accountability Record Form (i.e., logged in as “returned by patient” and logged out as “destroyed on site”) and destroyed on-site in accordance with institutional policy.*
- b. *Drug expiration: If packaging does not have expiration date, check with drug ordering designee and/or PI at site to confirm receipt of ongoing stability testing letter from NCI. If packaging has expiration date, indicate drug expiration date on the DARF under Manufacturer and Lot # and use the drug lots with shorter expiration date first.*

4. Contact Information: Call the PMB at 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

3.2 Fluorouracil (5-FU, Adrucil®) (NSC-19893)

a. PHARMACOLOGY

Mechanism of Action: Fluorouracil is a pyrimidine analog antimetabolite that interferes with DNA and RNA synthesis in the S phase of cell division. After activation, the active metabolite F-UMP is incorporated into RNA to replace uracil and inhibit cell growth. The active metabolite, F-dUMP, inhibits thymidylate synthetase and depletes thymidine triphosphate.

b. PHARMACOKINETICS

1. Absorption: Rapid intravenous injection of fluorouracil results in high early levels of drug achieved both in plasma and bone marrow with a rapid fall afterwards. Prolonged infusions of fluorouracil show constant levels of the drug in plasma and significantly less in bone marrow.

2. Distribution: Fluorouracil distributes into tumors, intestinal mucosa, bone marrow, liver, third space fluids and other tissues. Fluorouracil diffuses readily across the blood-brain barrier and distributes into cerebrospinal fluid and brain tissue.
3. Metabolism: Fluorouracil is primarily metabolized in the liver via dihydropyrimidine dehydrogenase (DPD) to the active metabolites 5-fluorouridine monophosphate (F-UMP) and 5-fluoro-2'-deoxyuridine-5'-O-monophosphate (F-dUMP).
4. Elimination: The mean elimination half-life of fluorouracil from plasma is approximately 16 minutes, with a range of 8 to 20 minutes, and is dose dependent. Seven to 20% of fluorouracil is excreted unchanged in the urine.

c. ADVERSE EFFECTS

1. Possible Side Effects of Fluorouracil:

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

Common (> 20%): alopecia, hand-foot syndrome, maculopapular rash, photosensitivity, pruritis, diarrhea, nausea, vomiting, anorexia, esophagopharyngitis, stomatitis, indigestion, headache

Less common (4 to ≤ 20%): angina, coronary arteriosclerosis, thrombophlebitis, gastrointestinal ulcer, bleeding, anemia, leucopenia, agranulocytosis, pancytopenia, thrombocytopenia, cough, hoarseness, epistaxis, anaphylaxis, hypersensitivity reaction, confusion, nystagmus, visual changes, lacrimation, lacrimal duct stenosis, photophobia, dermatitis, acute cerebellar syndrome

Rare (≤ 3%): cardiotoxicity, secondary malignancy

2. Pregnancy and Lactation: Pregnancy Category D. Excretion in human breast milk is unknown and the manufacturer recommends against breastfeeding while receiving fluorouracil.
3. Drug Interactions: Fluorouracil is a strong inhibitor of CYP2C9. Refer to the current FDA-approved package insert for additional information. Due to potential drug interactions, a complete patient medication list, including fluorouracil, should be screened prior to initiation of and during treatment with fluorouracil. See [Section 8.0](#) Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

See [Section 7.0](#) Treatment Plan.

e. HOW SUPPLIED

Fluorouracil 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.

3.3 Irinotecan (Camptosar®) (NSC-616348)

a. PHARMACOLOGY

Mechanism of Action: Irinotecan and its metabolite SN-38 inhibit topoisomerase I. Topoisomerase I relieves torsional strain in the DNA helix during replication and RNA transcription by inducing single-strand breaks. By binding with the topoisomerase I—DNA complex, irinotecan or SN-38 prevents the relegation of the single-strand breaks. Irreversible DNA damage occurs when a DNA replication fork encounters the irinotecan or SN-38/topoisomerase I complexes resulting in double-strand DNA breaks. Camptothecins are highly S-phase specific in their activity due the requirement of DNA synthesis.

b. PHARMACOKINETICS

1. Absorption: N/A

2. Distribution: Protein binding of irinotecan is 30-70%, whereas SN-38 shows a higher protein binding of 95%. Both irinotecan and SN-38 are primarily bound to albumin. Volume of distribution of irinotecan is approximately 110-234 L/m².

3. Metabolism: Irinotecan is metabolized primarily in the liver by carboxylesterase to SN-38, and via hepatic cytochrome P450 (CYP) 3A4 to aminopentane carboxylic acid (APC). SN-38 is conjugated to form a glucuronide metabolite by the enzyme UDP-glucuronosyl transferase 1A1 (UGT1A1). Genetic polymorphisms exist in the enzyme UGT1A1, leading to different levels of exposure and toxicity among patients. In addition, both irinotecan and SN-38 undergo plasma hydrolysis between their active (lactone) and inactive forms (carboxylate). Finally, a small amount of irinotecan is metabolized by the intestinal wall.

4. Elimination: Approximately 10-25% of irinotecan is recovered unchanged in urine whereas only small amounts of SN-38 have been found. Clearance is approximately 13.5 L/hr/m². In addition, irinotecan has approximately 25% biliary excretion.

c. ADVERSE EFFECTS

1. Possible Side Effects of irinotecan:

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% to 100% of subjects treated with irinotecan include: diarrhea and cholinergic reaction (may be severe), constipation, nausea, vomiting, asthenia, infection, leukopenia, neutropenia, alopecia, anorexia, weight loss, anemia, fatigue, fever, pain, dizziness, cough, dyspnea, mucositis, rash, thrombocytopenia.

Adverse effects reported in 4% to 20% of subjects include: gastrointestinal perforation, hypersensitivity reaction, cardiovascular events, thromboembolic events, interstitial lung disease.

2. Pregnancy and Lactation: Pregnancy Category D. It is not known whether irinotecan or its derivatives are excreted in human milk.

3. Drug Interactions: Irinotecan and its active metabolite SN-38 may be substrates for CYP3A4, CYP2B6, OATP1B1/SCLO1B1, P-glycoprotein/ABCB1 and UGT1A1. Inducers or inhibitors may affect serum concentrations of irinotecan. Due to potential drug interactions, a complete patient medication list, including irinotecan, should be screened prior to initiation of and during treatment with irinotecan. Refer to the current FDA-approved package insert. See [Section 8.0](#) Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

See [Section 7.0](#) Treatment Plan.

e. HOW SUPPLIED

Irinotecan 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.

3.4 Leucovorin (NSC-3590)

a. PHARMACOLOGY

Mechanism of Action: During normal processes, thymidylate synthetase forms a noncovalent ternary complex with deoxyuridylate (dUMP) and the reduced folate cofactor of leucovorin 5-methyl-tetrahydrofolate (5MTHF). The reduced folate facilitates the association and disassociation of the complex and the formation of thymidylate (dTMP) and dihydrofolate. Fluorouracil inhibits thymidylate synthetase through the covalent binding of 5-fluorodeoxyuridine monophosphate (FdUMP) and 5MTHF. The binding of FdUMP is dependent upon the intracellular concentration of 5MTHF. Since l-leucovorin is metabolized to 5MTHF, it increases and stabilizes the binding of FdUMP to thymidylate synthetase, thus increasing the cytotoxic effects of fluorouracil.

b. PHARMACOKINETICS

1. Absorption: Oral bioavailability of leucovorin is concentration dependent and saturable at doses greater than 25 mg. Studies have produced bioavailabilities of 97%, 75% and 37% for doses of 25 mg, 50mg and 100mg respectively.
2. Distribution: Leucovorin is rapidly converted to 5-methyl-tetrahydrofolate (5MTHF) and widely distributed to tissues including the CNS. The time to peak concentration for oral, folate isomers and 5MTHF is 2 hours, 10 minutes and 1 hour respectively.
3. Metabolism: Leucovorin is metabolized by intestinal mucosa and hepatically to the active form 5MTHF.
4. Elimination: Leucovorin is primarily excreted unchanged in the urine and minimally in the feces. Leucovorin has a half-life elimination of approximately 4 to 8 hours.

c. ADVERSE EFFECTS

1. Refer to package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.

Adverse Events with Possible Relationship to Leucovorin		
Likely (>20%)	Less Likely (4 – ≤20%)	Rare but Serious (<3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Thrombocytosis	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
		Allergic reactions
		Anaphylactoid reactions
METABOLISM AND NUTRITION DISORDERS		
	Hypocalcemia	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Wheezing	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Rash	
	Pruritis	
	Erythema	
	Urticaria	

2. Pregnancy and Lactation: Pregnancy Category C. Excretion in human breast milk is unknown.
 3. Drug Interactions: Leucovorin may interact with antimetabolites, antifolates and anticonvulsants. Refer to the current FDA-approved package insert for additional information. Due to potential drug interactions, a complete patient medication list, including leucovorin, should be screened prior to initiation of and during treatment with leucovorin. See [Section 8.0](#) Toxicities to be Monitored and Dosage Modifications.
- d. **DOSING & ADMINISTRATION**
1. Dosing – See [Section 7.0](#) Treatment Plan
 2. Refer to the current FDA-approved package insert for drug administration.
- e. **PREPARATION, STORAGE & STABILITY**
- Refer to the current FDA-approved package insert for preparation, storage, stability and special handling information.
- f. **HOW SUPPLIED**
- Leucovorin is commercially available and will not be supplied. Refer to the current FDA-approved package insert for additional information.

4.0 STAGING CRITERIA

Staging criteria are not applicable to this study.

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 Data Operations Center in Seattle at 206/652-2267 or gquestion@crab.org prior to registration.

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 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Days 14, 28 or 42 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 histologically or cytologically documented pancreatic adenocarcinoma. Patients with pancreatic neuroendocrine tumors, lymphoma of the pancreas, or ampullary cancer are not eligible.
- b. Patients must have metastatic disease that is measurable, as defined in [Section 10.1](#). CT scans or MRIs of the chest, abdomen, and pelvis used to assess measurable disease must have been completed within 28 days prior to registration. CT Scans or MRIs used to assess non-measurable disease must have been completed within 42 days prior to registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form.
- c. Patients must not have history of brain metastases.

5.2 Prior/Concurrent Therapy Criteria

- a. Patients must have had one and only one prior regimen of systemic therapy for metastatic disease unless the patient meets the criteria in [Section 5.2c](#).
- b. Prior systemic therapy and chemoradiotherapy for treatment of resectable, borderline resectable or locally advanced unresectable disease is allowed and does not count toward prior therapy for metastatic disease.
- c. Patients who received systemic therapy with gemcitabine/nab-paclitaxel for resectable or borderline/locally advanced unresectable disease and progressed with metastatic disease within 3 months of the past dose of systemic therapy are eligible.
- d. Patients must have completed systemic therapy at least 14 days prior to registration, any surgical procedure must have been performed at least 14 days prior to registration, and radiation therapy must be completed at least 7 days prior to registration. Patients must have recovered from major side effects of prior therapies or procedures in the opinion of the local site investigator prior to registration.
- e. Patients must not have received prior irinotecan-based chemotherapy (e.g. FOLFIRINOX or FOLFIRI).
- f. Patients must not have received prior PARP inhibitor therapy including, but not limited to ABT-888, olaparib, rucaparib, and BMN637.

5.3 Clinical/Laboratory Criteria

- a. Patients must have a Zubrod Performance Status of 0-1 (see [Section 10.4](#)).
- b. Patients must be ≥ 18 years of age.
- c. Patients must have adequate hematologic function as evidenced by all of the following within 14 days prior to registration: ANC $\geq 1,500/\text{mcL}$; hemoglobin ≥ 9 g/dL; and platelets $\geq 100,000/\text{mcL}$.

- d. Patients must have adequate hepatic function as evidenced by all of the following within 14 days prior to registration: total bilirubin $\leq 1.5 \times$ Institutional Upper Limit of Normal (IULN); serum albumin ≥ 3.0 g/dL; and AST and ALT $\leq 2.5 \times$ IULN. Patients with liver metastases may have AST and ALT of $\leq 5.0 \times$ IULN.
- e. Patients must have adequate renal function as evidenced by the following within 14 days prior to registration: serum creatinine ≤ 2.0 mg/dL.
- f. Patients must have CA19-9 obtained within 14 days prior to registration. If CA19-9 is normal, then CEA must be tested within 14 days prior to registration.
- g. Patients must have BUN, alkaline phosphatase, sodium, potassium, calcium, glucose, chloride, and carbon dioxide levels obtained within 14 days prior to registration.
- h. Patients must not have any clinically significant and uncontrolled major medical condition(s) including, but not limited to uncontrolled nausea/vomiting/diarrhea; active uncontrolled infection; symptomatic congestive heart failure (NYHA Class \geq II) (see [Section 18.2](#)); unstable angina pectoris or cardiac arrhythmia; psychiatric illness/social situation that would limit compliance with study requirements.
- i. Patients must not have active seizure or history of seizure.
- j. Patients must be able to swallow whole capsule.
- k. Patients must have a complete physical examination and medical history within 28 days prior to registration.
- l. Patients must not have known Gilbert's Syndrome.
- m. Patients must not have known hypersensitivity to irinotecan, fluorouracil, or leucovorin.
- n. Patients of childbearing potential must have a negative pregnancy test within 28 days prior to registration and must not be nursing due to the risk of fetal or nursing infant harm. Women/men of reproductive potential must have agreed to use an effective contraceptive method during the study and for 6 months following completion of 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.

5.4 Specimen Submission Criteria

- a. Patients must be willing and able to undergo a biopsy after signed consent and prior to registration. Patients must have tumor tissue and blood samples available and be willing to submit tumor and blood samples as described in [Section 15.1](#).

NOTE: Core biopsy required. FNA is not an acceptable substitute for core biopsy
- b. If archival tumor is available for submission, patients must be willing to submit tumor sample as described in [Section 15.1b](#).

- c. Patients must be offered the opportunity to participate in specimen banking for future use (see [Section 15.2](#)).

5.5 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 13.4](#) 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.

6.0 STRATIFICATION FACTORS

Patients will be randomized using a dynamic balancing algorithm with stratification based on prior systemic treatment for metastatic disease: yes vs no.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Chiorean at 206/288-6248 or Dr. Philip at 313/576-8746. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at <http://swog.org> (then click on "Policies and Manuals" under the "About" menu and choose Policy 38).

7.1 Pre-Medication

Antiemetics may be given at the discretion of the treating physician, but aprepitant may not be given prior to FOLFIRI/mFOLFIRI.

It is recommended that atropine, 0.25 – 1.0 mg IV or SC (subcutaneously) or similar anticholinergic medication be used as needed or during irinotecan administration to prevent cholinergic symptoms (e.g., hot flashes, abdominal cramping, diarrhea, lacrimation).

7.2 Treatment – Arm 1: ABT-888 + mFOLFIRI

Patients assigned to Arm 1 will receive the following treatment (outpatient setting) until meeting one of the criteria in [Section 7.6](#). NOTE: Patients on this arm will receive modified FOLFIRI which does not include the bolus fluorouracil.

a. Arm A

Agent	Dose	Route	Day	Schedule
ABT-888	400 mg (200 mg per dose)	PO BID**	1-7	Every 12 hours. Given 1 hr ± 30 min prior to irinotecan on Day 3
Irinotecan	180 mg/m ²	IV over 90-120 min	3	Given concurrently with leucovorin ^α
Leucovorin	400 mg/m ²	IV over 90-120 min	3	Given concurrently with irinotecan ^α
Fluorouracil	2,400 mg/m ²	IV over 46 hr ^β	3-5	Given after Irinotecan and leucovorin

* Note: One cycle = 14 days

** Morning and evening dose should be approximately 12 hours apart, with or without food in the same calendar day. Patients will take two 100 mg capsules in the morning and two 100 mg capsules in the evening for a total daily dose of 400 mg. It is recommended that if a patient misses a scheduled dose and less than 6 hours have passed since scheduled dosing time, the dose should be immediately taken. It is recommended that if more than 6 hours have passed since the scheduled dosing time, the patient should not take the missed dose, but should wait for the next regularly scheduled dose. If the patient vomits within 15 minutes of taking drug, another dose is to be taken. The dose may only be repeated once. If more than 15 minutes has passed from the time of oral dosing then no additional doses will be taken. **NOTE: Patients should be instructed to take Day 3 dose at treating institution and not at home. ABT-888 should be taken 1 hour (± 30 minutes) before irinotecan on Day 3.**

α Irinotecan and leucovorin are administered via separated lines concurrently, or per institutional guidelines they may be administered sequentially.

β Fluorouracil will be administered as a continuous intravenous infusion delivered by an infusion pump via a central venous infusion port placed subcutaneously. The specific chemotherapy port and infusion pump to be used are at the discretion of the treating physician.

7.3 Treatment – Arm 2: FOLFIRI

Patients assigned to Arm 2 will receive the following treatment (outpatient setting) until meeting one of the criteria in [Section 7.6](#).

Agent	Dose	Route	Day	Schedule*
Irinotecan	180 mg/m ²	IV over 90-120 min	1	Given concurrently with leucovorin **
Leucovorin	400 mg/m ²	IV over 90-120 min	1	Given concurrently with irinotecan **
Fluorouracil (bolus)	400 mg/m ²	IV over 15 min	1	Given after irinotecan and leucovorin
Fluorouracil β	2,400 mg/m ²	IV over 46 hr α	1-3	Given after fluorouracil bolus

* Note: One cycle = 14 days

** Irinotecan and leucovorin are administered via separated lines concurrently, or per institutional guidelines they may be administered sequentially.

α Fluorouracil will be administered as a continuous intravenous infusion delivered by an infusion pump via a central venous infusion port placed subcutaneously. The specific chemotherapy port and infusion pump to be used are at the discretion of the treating physician.

β Fluorouracil bolus may be administered per institutional guidelines.

7.4 Drug Compliance Documentation

Drug compliance will be recorded by patients in the Intake Calendar (see [Section 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. Note that the Intake Calendar is provided only as a tool for tracking patient compliance. Sites may utilize institutional pill diaries or other source documentation in place of the Intake Calendar at the discretion of the treating physician.

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 14.4b](#), the **S1513** Treatment Form, and the **S1513** Adverse Event Form). A cycle is defined as 14 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.
- c. Treatment delay for any reason > 4 weeks.
- d. The patients may withdraw from the study at any time for any reason.
- e. Pregnancy or breastfeeding.

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 3 years after registration, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 Dose Modifications

- a. If patient experiences adverse events that result in the dose modification (including dose delay, reduction, or discontinuation) of ABT-888, or FOLFIRI during a cycle, the patient will complete the planned activities of the cycle as scheduled per [Section 9.0](#) until resuming protocol therapy. If dose interruption is needed, the patient will continue to have study visits as planned. The timing of dose resumption should be at the discretion of the treating physician as long as it is within 4 weeks.
- b. Dose interruptions for events that are clearly not related to the protocol therapy (e.g., underlying cancer, planned surgical procedures, or acute viral illnesses) should not necessitate a dose reduction.
- c. Patients may be treated with antibiotic therapy if they develop severe neutropenia. A new cycle of treatment may not begin until the ANC is $\geq 1,500/\text{mcL}$, the platelet count is $\geq 75,000/\text{mcL}$, and any treatment-related gastrointestinal toxicity has resolved to \leq Grade 1. White blood cell growth factors, including biosimilars, must be used per ASCO guidelines (<http://jco.ascopubs.org/content/24/19/3187.full>) and NCCN Guidelines $\text{\textcircled{R}}$ Myeloid Growth Factors.

(http://nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf).

- d. No dose re-escalations are permitted. If the patient experiences toxicity requiring a dose reduction, the dose will remain lowered for subsequent cycles.
- e. Where several toxicities with different grades or severity occur at the same time, the dose modification applied should be the greatest reduction applicable.
- f. For toxicities that are considered by the treating physician to be unlikely to develop into serious or life-threatening events (e.g., alopecia, altered taste, etc.), treatment will be continued at the same dose without reduction or interruption. In addition, no dose reductions or interruptions will be required for anemia (non-hemolytic) as it can be satisfactorily managed by transfusions.
- g. The maximum dose delay for any reason is 4 weeks. If the treatment is delayed for > 4 weeks, patients must be removed from protocol therapy.
- h. Dose omitted during a cycle will not be made up.

8.3 Dose Modification for ABT-888

a. Guidelines

1. **Any event of seizure, regardless of grade or attribution, requires interruption of ABT-888 and discussion with one of the Study Chairs regarding the decision to resume treatment.**
2. ABT-888 will be held until the toxicity(ies) (Grade 3 or 4) recover to ≤ Grade 1 or baseline grade if present at registration. Upon resuming ABT-888 treatment, the dose is to be reduced one dose level as shown. Unless otherwise specified, treatment should continue unmodified for toxicities < Grade 3
3. If a patient begins ABT-888 on Day 1, but subsequently experiences an event requiring delay of the modified FOLFIRI dosing on Day 3, the patient is to stop ABT-888 dosing immediately. Upon resolution of the event, the patient may restart the current cycle by repeating Day 1 and Day 2. For such delays, a new ABT-888 supply will be dispensed to restart the cycle at Day 1.
4. For the purposes of this study, only three dose reductions of ABT-888 are allowed. All dose reductions are permanent. If a dose reduction is required beyond dose level -3, patients should discontinue all protocol therapy. If an intolerable toxicity does not develop, treatment with additional cycles of protocol therapy may be continued indefinitely as long as patient has not met any of the criteria in [Section 7.6](#).
5. ABT-888 may exacerbate neutropenia and thrombocytopenia associated with modified FOLFIRI. ABT-888 dose should be reduced one dose level, as appropriate. **Patients should not receive ABT-888 while fluorouracil infusion and irinotecan are suspended. Skipped doses of ABT-888 during Days 3-7 of each cycle are not made up.**

b. Dose Levels for Treatment Modifications

Agent	Starting Dose	Level -1	Level -2	Level -3
ABT-888	200 mg BID (400 mg daily total)	150 mg BID (300 mg daily total)	100 mg BID (200 mg daily total)	50 mg BID (100 mg daily total)

c. Neutrophil Count Decreased

Hold treatment for up to four weeks until recovery to at least Grade 1 (ANC \geq 1,500/mcL). If patient has not recovered to \leq Grade 1 in four weeks, discontinue treatment. Follow drug specific modifications below for subsequent cycles. In addition, it is recommended that pegfilgrastim 6 mg subcutaneously, be administered with each subsequent dose, on the day of fluorouracil pump discontinuation.

Toxicity Grade	Modification
3-4	1 dose level reduction. At 4 th occurrence, discontinue all protocol treatment.

d. Platelet Count Decreased

Hold treatment for up to four weeks until recovery to at least Grade 1 (PLT \geq 75,000/mcL). If patient has not recovered to \leq Grade 1 in four weeks, discontinue treatment. Follow drug specific modifications below for subsequent cycles.

Toxicity Grade	Modification
3-4	1 st occurrence, maintain dose. For subsequent occurrences, continue ABT-888 at 1 dose level reduction. At 5 th occurrence, discontinue all protocol treatment.

e. Nausea/Vomiting

Toxicity Grade	Modification
3-4	Hold treatment for up to four weeks until recovery to at least Grade 1. Continue ABT-888 at 1 dose level reduction. At 4 th occurrence, discontinue all protocol treatment.

f. Diarrhea

Patients should be instructed in the use of loperamide as treatment for diarrhea. No ABT-888 dose modifications are required for diarrhea. Patients should not receive ABT-888 while fluorouracil infusion and irinotecan are suspended. Skipped doses are not made up.

g. Mucositis

No ABT-888 dose modifications are required for mucositis. Patients should not receive ABT-888 while fluorouracil infusion and irinotecan are suspended. Skipped doses are not made up.

h. Other Non-Hematologic Toxicities

For all other \geq Grade 3 non-hematologic toxicities not described above, hold ABT-888 and monitor at least weekly. If toxicity resolves to \leq Grade 1 within four weeks, protocol therapy may be resumed. ABT-888 may be reduced at the treating physician's discretion.

8.4 Dose Modification for FOLFIRI

a. Guidelines

Dose modifications for the current cycle and reduction for subsequent cycles should be carried out as shown below. Dose adjustments of irinotecan and fluorouracil infusion may be made independently based on the specific types of toxicities observed as discussed in [Sections 8.4c-i](#). For the purposes of this study, only three dose reductions of FOLFIRI are allowed. If a dose reduction is required beyond dose level -3 for irinotecan, discontinue irinotecan, but continue ABT-888, fluorouracil, and leucovorin. If a dose reduction is required beyond dose level -3 for continuous infusion fluorouracil, discontinue all protocol therapy.

Patients should not receive ABT-888 while fluorouracil infusion and irinotecan are suspended. Skipped doses of ABT-888 during Days 3-7 of each cycle are not made up.

Note: The fluorouracil bolus can only be skipped or discontinued.

b. Dose Levels for Treatment Modifications

Agent	Starting Dose	Level -1	Level -2	Level -3
Fluorouracil (bolus)*	400 mg/m ²	Discontinue	N/A	N/A
Fluorouracil	2,400 mg/m ²	1920 mg/m ²	1600 mg/m ²	1360 mg/m ²
Irinotecan	180 mg/m ²	150 mg/m ²	120 mg/m ²	100 mg/m ²
Leucovorin**	400 mg/m ²	No dose adjustments allowed		

* Fluorouracil bolus is only given in Arm 2.

** Leucovorin is always administered at 400 mg/m² IV prior to fluorouracil. If fluorouracil 46-48 hour infusion needs to be skipped, leucovorin must also be skipped.

α Patients known to be homozygous for UGT1A1*28 are recommended to start irinotecan with a 30% dose reduction.

c. Neutrophil Count Decreased

Toxicity Grade Modification:

3-4 Hold treatment for up to four weeks until recovery to at least Grade 1. If patient has not recovered to \leq Grade 1 in four weeks, permanently discontinue treatment. If patient recovers to \leq Grade 1, one dose level reduction of fluorouracil and irinotecan. At 4th occurrence, discontinue all protocol treatment. NOTE: For patients in Arm 2, discontinue bolus fluorouracil at first occurrence.

d. Platelet Count Decreased

Toxicity Grade Modification:

3-4 Hold treatment for up to four weeks until recovery to at least Grade 1. If patient has not recovered to \leq Grade 1 in four weeks, discontinue treatment. If patient recovers to \leq Grade 1, one dose level reduction of fluorouracil. At 4th occurrence, discontinue all protocol treatment. For the first occurrence, maintain irinotecan dose level and for subsequent occurrences 1 dose level reduction up to 2 steps down. NOTE: For patients in Arm 2, discontinue bolus fluorouracil at first occurrence.

e. Diarrhea

Patients should be instructed in the use of loperamide as treatment for diarrhea. Patient should not be retreated with irinotecan until recovery from diarrhea has occurred.

Toxicity Grade Modification

3-4 Hold treatment. Check weekly. When resolves to \leq Grade 1, continue at next lowest dose level. If patient recovers to \leq Grade 1, one dose level reduction of fluorouracil and irinotecan. At 4th occurrence, discontinue all protocol treatment. NOTE: For patients in Arm 2, discontinue bolus fluorouracil at first occurrence.

f. Mucositis

Toxicity Grade Modification: Fluorouracil and irinotecan

2-4 Hold treatment. Check weekly. When resolves to \leq Grade 1, continue at next lowest dose level. NOTE: For patients in Arm 2, discontinue bolus fluorouracil at first occurrence.

g. Hand-Foot Skin Reaction

Toxicity Grade Modification:

3-4	Hold treatment. Check weekly. When resolves to \leq Grade 1, continue irinotecan at next lowest dose level. Reduce fluorouracil infusion by 1 dose level.
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h. Nausea/Vomiting

Toxicity Grade Modification

3-4	Hold treatment. Check weekly. When resolves to \leq Grade 1, continue at 1 dose level reduction of fluorouracil and irinotecan up to 3 steps down. At 4 th occurrence, discontinue all protocol treatment. NOTE: For patients in Arm 2, discontinue bolus fluorouracil at first occurrence treatment
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i. Other non-hematologic toxicities

All treatment related non-hematological toxicities \geq Grade 3 (with the exception of hair loss) must resolve to Grade 1 prior to starting next cycle of therapy. Treatment should continue unmodified for toxicities $<$ Grade 3.

Toxicity Grade Modification: Fluorouracil and irinotecan

3	Hold all drugs until resolution to \leq Grade 1. Then resume treatment at the next lower dose level. Fluorouracil bolus should be discontinued in Arm 2.
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4	Discontinue all protocol treatment
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8.5 Dose Modifications Contacts

For treatment or dose modification questions, please contact Dr. Chiorean at 206/288-6248 or Dr. Philip at 313/576-8746.

8.6 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in [Section 16.1](#) 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

9.1 Arm 1: ABT-888 + mFOLFIRI

Σ

REQUIRED STUDIES	PRE STUDY	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Ω	%
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	FU prior to prog	FU after prog
PHYSICAL													
History and Physical Exam ◊	X	X		X		X		X		X		X	X
Weight and Performance Status	X	X		X		X		X		X			
Disease Assessment	X									X			
Toxicity Notation	X	X		X		X		X		X		X	
Baseline Abnormalities	X												
LABORATORY ^{π d}													
CBC/Differential/Platelets	X	X		X		X		X		X			
CA19-9/CEA \$	X	X				X				X			
AST/ALT, total bilirubin, serum albumin, serum creatinine	X	X		X		X		X		X			
Chemistry **	X	X		X		X		X		X			
Pregnancy test △	X	X △										X △	
X-RAYS AND SCANS ^c													
CT/MRI for disease assessment	X									X		X	
SPECIMEN SUBMISSION													
Tissue block or slides for TM (required) δ	X												
Archival tissue slides for TM (required) δ	X												
Blood for TM (required) δ	X												
Tissue for banking (optional) δ	X												
TREATMENT													
ABT-888 ζ		X		X		X		X		X			
Irinotecan φ		X		X		X		X		X			
Leucovorin ω		X		X		X		X		X			
Fluorouracil ξ		X		X		X		X		X			

Click here for [footnotes](#).

9.2 Arm 2: FOLFIRB

REQUIRED STUDIES	PRE STUDY	Σ										Ω Follow up prior to prog	%		
		Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5					
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10				
PHYSICAL															
History and Physical Exam	X	X		X		X		X		X		X		X	X
Weight and Performance Status	X	X		X		X		X		X		X			
Disease Assessment	X									X					
Toxicity Notation	X	X		X		X		X		X		X		X	
Baseline Abnormalities	X														
LABORATORY ^{tr d}															
CBC/Differential/Platelets	X	X		X		X		X		X		X			
CA19-9/CEA \$	X	X				X				X					
AST/ALT, total bilirubin, serum albumin, serum creatinine	X	X		X		X		X		X		X			
Chemistry **	X	X		X		X		X		X		X			
X-RAYS AND SCANS ^c															
CT/MRI for disease assessment	X									X				X	
SPECIMEN SUBMISSION															
Tissue block or slides for TM (required) δ	X														
Archival tissue slides for TM (required) δ	X														
Blood for TM (required) δ	X														
Tissue for banking (optional) δ	X														
TREATMENT															
Irinotecan β		X		X		X		X		X		X			
Leucovorin β		X		X		X		X		X		X			
Fluorouracil bolus α		X		X		X		X		X		X			
Fluorouracil γ		X		X		X		X		X		X			

Click here for [footnotes](#).

Footnotes:

- ∑ Protocol treatment and physical, laboratory, and scan parameters will continue at these intervals indicated in the Cycle 2-5 columns until progression of disease or until patient has met any of the guidelines in [Section 7.6](#).
- Ω After off treatment prior to disease progression, scans for disease assessment and physical assessments (with lab tests performed at the discretion of the treating investigator) should take place every 8 weeks until progression.
- % After off treatment following disease progression, physical assessments (with lab tests performed at the discretion of the treating investigator) should take place once every 3 months for three years from the time of registration.
- ζ Oral capsule taken twice daily on Days 1-7 of every cycle. Day 3 dose should be taken at treating institution 1 hour (\pm 30 minutes) prior to irinotecan (see [Section 7.2](#)).
- φ Infusion to be given on Day 3 of every cycle (see [Section 7.2](#)).
- £ Infusion to be given starting on Day 3 over 46-48 hours (see [Section 7.2](#)).
- α Bolus to be given on Day 1 prior to 46 hour infusion (see [Section 7.3](#)).
- β Infusion to be given on Day 1 of every cycle (see [Section 7.3](#)).
- γ Infusion to be given starting on Day 1 over 46-48 hours (see [Section 7.3](#)).
- δ See [Section 15.0](#) for more information.
- ** BUN, alkaline phosphatase, sodium, potassium, calcium, glucose, albumin, chloride, carbon dioxide/bicarbonate
- π Labs do not need to be repeated if pre-study labs were done within 7 days prior to Cycle 1 Day 1.
- \$ CA19-9 should be repeated every 4 weeks if abnormal at baseline. If CA19-9 normal at baseline, CEA must be tested and if CEA is abnormal, should be repeated every 4 weeks.
- △ Women of childbearing potential must have a negative serum or urine pregnancy test at screening within 28 days prior to registration. If randomized to Arm 1, serum or urine pregnancy tests are required within 72 hours prior to the first dose of study treatment. At discontinuation, a pregnancy test must be done within 4 weeks after the last dose of study drug. A pregnancy test should be done at any time there are clinical concerns for possible pregnancy.
- ◇ History prior to each treatment initiation to include a menstrual, sexual, and contraceptive use history, including date of last menstrual period (for women of childbearing potential) which will help determine the need for pregnancy testing. Similar questions regarding contraceptive use to be asked to men who are sexually active with women of childbearing potential.
- c CT or MRI, of chest, abdomen, and pelvis for disease assessment must be performed every 8 weeks while on study treatment.
- d Labs are to be drawn on Day 1 of each cycle. If the labs are satisfactory, they do not need to be repeated on Day 3 prior to FOLFIRI. If the labs drawn on Day 1 are not satisfactory for FOLFIRI therapy, the local investigator may repeat them prior to Day 3, as clinically indicated.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

This study will use the RECIST 1.1 guidelines. (112)

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.

10.3 Best Response

This is calculated from the sequence of objective statuses.

- a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

- b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart 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.
- h. Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 Performance Status:

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

<u>POINT</u>	<u>DESCRIPTION</u>
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.

10.5 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.

10.6 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.

10.7 Duration of Response (DoR)

From date of first documentation of response (CR or PR) to date of first documentation of progression or symptomatic deterioration (as defined above), or death due to any cause among patients, who achieve a response (CR or PR). Patients last known to be alive without report of progression are censored at date of last contact.

11.0 STATISTICAL CONSIDERATIONS

11.1 Sample Size and Accrual Goals

The primary objective of the study is to compare overall survival (OS) between the 2 treatment arms. We estimate the median OS of patients treated with FOLFIRI to be 6 months in this population. (113,114) Assuming that the addition of ABT-888 offers an increase in OS to 9 months (HR 1.5), we will need 128 eligible patients, based on a 1:1 randomization, a one-sided type 1 error of 10% and 80% power. Allowing for an approximately 10% ineligibility rate, accrual will be to a total of 143 patients. We expect 28 months of accrual and 10 months of follow-up. Our accrual rate estimate is based on the observed accrual to SWOG study **S1115**.

11.2 Analysis of Primary Endpoint

The primary analysis of OS will be conducted in all eligible patients according to the intent-to-treat principle, using the log-rank test with stratification by prior systemic treatment for metastatic disease. Distributions of overall survival in Arms 1 and 2 will be estimated using the method of Kaplan-Meier. The final analysis will take place upon the observation of approximately 110 deaths.

11.3 Interim Analysis

An interim futility analysis of progression-free survival (PFS) by treatment arm will be performed by testing an alternative hypothesis of a 1.5 HR at $p < 0.05$ when approximately 35% of the expected PFS events in the control arm have been observed. We expect this analysis to occur when approximately 50% of the study sample has been accrued. Unless there are toxicity concerns or extenuating circumstances, the study will not close during this interim assessment. If this alternative hypothesis is rejected at $p < 0.05$ then the study may be closed to further accrual and the experimental agent declared of no interest for further development. If we fail to reject this hypothesis, the study will complete accrual.

11.4 Secondary Endpoints

Secondary endpoints include toxicity, PFS, overall response rate, disease control rate, and duration of response (DoR). The chi-square test will be used to compare toxicity, response rates, and disease control rates and a stratified log-rank test will be used to compare PFS between treatment arms. The distribution of PFS and DoR (among patients who achieve CR/PR) in each treatment arm will be estimated using the Kaplan-Meier method. The overall response rate (confirmed and unconfirmed, complete and partial) in each treatment arm will be assessed in the subset of patients with measurable disease. At least 64 eligible patients in each arm are sufficient to estimate the disease response rate to within 13% (95% confidence interval).

Patients receiving at least one dose of any drug on any arm will be included in the assessment of adverse events. Adverse event monitoring is conducted by the study chairs, disease committee chair, Adverse Event Coordinator and study statistician on an ongoing basis, with notification to the DSMC and CTEP should any concerns arise. Any events reported through the CTEP-AERS system are reported immediately, and reports are sent to the above group for all other AEs on a monthly basis. At least 64 eligible patients in each arm are sufficient to estimate the probability of a particular toxicity to within 13% (95%

confidence interval). Any toxicity occurring with at least a 5% probability is likely (96% chance) to be seen at least once.

11.5 Translational Endpoints

We assume that 90% of eligible patients will submit tissue and 80% of these will be successfully assayed. With 128 eligible patients enrolled on S1513, it is estimated that for each arm, 46 patients (n=92 total) will be included in analyses. The overall prevalence of each biomarker can be estimated to within 10% (95% confidence interval).

- a. The primary translational objective is to evaluate if *BRCA1* and *BRCA2* mutations (somatic or germline) are associated with improved clinical outcomes (OS, PFS, and ORR) in each treatment arm. Prevalences of *BRCA1* and *BRCA2* mutations in this patient population are estimated to be approximately 1-2% and 5-7%, respectively.
- b. Secondly, we will evaluate the impact of HRD positivity on clinical outcomes in each treatment arm. Although the HRD score threshold for positivity has yet to be determined in this disease, we will first dichotomize the score at its observed median value (represented as 50% prevalence in the tables below), and estimate the associations between that binary predictor and clinical outcomes. We will also assess the associations of HRD score as a continuous variable with clinical outcomes.
- c. Additionally, we will evaluate the impact of other exploratory genomic alterations (other than *BRCA1/2* mutations) identified by the BROCA-HR assay on clinical outcomes in each treatment arm.

We will evaluate if each potential biomarker is associated with the clinical outcomes of overall survival (OS), progression-free survival (PFS), and response rate (ORR) separately by treatment arm. The associations between each potential biomarker and both OS and PFS will be explored via Kaplan-Meier curves and Cox regression. We assume the baseline median OS is 6 months, 46 patients enrolled over 28 months and an additional 10 months of follow-up. The following table shows approximate power to detect OS hazard ratios of 2.5, 3, and 3.5, corresponding to median OS of 15, 18, and 21 months in the biomarker-positive subgroup, using a two-sided alpha of 0.1, for a range of biomarker frequencies.

Biomarker Prevalence	Power		
	<i>HR</i> =2.5	<i>HR</i> = 3	<i>HR</i> = 3.5
5%	30%	35%	39%
10%	45%	54%	60%
25%	73%	83%	89%
50%	86%	93%	97%

Assuming a baseline median PFS of 3 months, the following table shows approximate power to detect PFS hazard ratios of 2.5, 3, and 3.5, corresponding to median PFS of 7.5, 9, and 10.5 months in the biomarker-positive subgroup, using a two-sided alpha of 0.1, for a range of biomarker frequencies.

Biomarker Prevalence	Power		
	<i>HR</i> = 2.5	<i>HR</i> = 3	<i>HR</i> = 3.5
5%	35%	43%	50%
10%	54%	65%	73%
25%	82%	91%	95%
50%	91%	97%	99%

Assuming a null ORR of 10%, the following table describes the approximate power to detect differences in response rate of 25%, 30%, and 35% (corresponding to ORR of 35%, 40%, and 45%) in the biomarker-positive sub-group, using a two-sided 0.1 level test of proportions across a range of biomarker frequencies.

Biomarker Prevalence	Power		
	$\Delta = 25\%$	$\Delta = 30\%$	$\Delta = 35\%$
10%	20%	30%	39%
25%	44%	56%	67%
50%	50%	64%	76%

We also plan to estimate an HRD score threshold for positivity in this population by applying receiver operating characteristic curves, classifying patients by overall disease response. The precision of this estimate will depend not only on the number of patients with available data but also on the prevalence of disease response.

11.6 Data and Safety Monitoring

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 Statistical 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

Discipline review is not applicable in this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than five working days prior to planned start of treatment).

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a NCTN 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.

a. CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed **Statement of Investigator Form** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed **Supplemental Investigator Data Form** (IDF)
- a completed **Financial Disclosure Form** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>.

For questions, please contact the **CTEP Investigator Registration Help Desk** by email at <pmbregpend@ctep.nci.nih.gov>.

b. CTEP Associate Registration Procedures

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the **CTEP Associate Registration Help Desk** by email at <ctepreghelp@ctep.nci.nih.gov>.

c. CTSU Registration Procedures

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials at <https://www.ctsu.org>. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

1. Downloading Site Registration Documents:

Site registration forms may be downloaded from the **S1513** protocol page located on the CTSU members' website.

- Go to <https://www.ctsu.org> and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the By Lead Organization folder to expand
- Click on the SWOG link to expand, then select trial protocol **S1513**
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

2. Requirements for **S1513** Site Registration:

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

3. Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206

E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

4. Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to <https://www.ctsu.org> and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab

Enter your 5-character CTEP Institution Code and click on Go

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < <https://eapps-ctep.nci.nih.gov/iam/index.jsp> >) and a 'Registrar' role on either the LPO or participating organization roster.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

- a. Institution CTEP ID



- b. Protocol Number
- c. Registration Step
- d. Treating Investigator
- e. Credit Investigator
- f. Patient Initials
- g. Patient's Date of Birth
- h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)
- i. Country of Residence
- j. ZIP Code
- k. Gender (select one):
 - Female Gender
 - Male Gender
- l. Ethnicity (select one):
 - Hispanic or Latino
 - Not Hispanic or Latino
 - Unknown
- m. Method of Payment (select one):
 - Private Insurance
 - Medicare
 - Medicare and Private Insurance
 - Medicaid
 - Medicaid and Medicare
 - Military or Veterans Sponsored NOS
 - Military Sponsored (Including Champus & Tricare)
 - Veterans Sponsored
 - Self Pay (No Insurance)
 - No Means of Payment (No Insurance)
 - Other
 - Unknown
- n. Race (select all that apply):
 - American Indian or Alaska Native
 - Asian
 - Black or African American
 - Native Hawaiian or other Pacific Islander
 - White
 - Unknown

13.4 Registration Procedures

- a. All site staff will use OPEN to enroll patients to this study. OPEN is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at <https://open.ctsu.org>, from the OPEN tab on the CTSU members' side of the website at <https://www.ctsu.org>, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

- b. Prior to accessing OPEN site staff should verify the following:
 - All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to [Section 5.0](#) to verify eligibility.
 - All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).
 - c. The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.
 - d. Further instructional information is provided on the OPEN tab on the CTSU members' side of the website at <https://www.ctsu.org> or at <https://open.ctsu.org>. For any additional questions contact the CTSU Help Desk at 888/823-5923 or ctscontact@westat.com.
- 13.5 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

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 SWOG website (www.swog.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. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, you must have an active CTEP-IAM account (check at <https://eapps-ctep.nci.nih.gov/iam/index.jsp>) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in 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 users must log into the Select Login (<https://login.imedidata.com/selectlogin>) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users 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.

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

- b. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG web site (<http://swog.org>) and logon to the Members Area using your SWOG Roster ID Number and password. After you have logged on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

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.

14.4 Data Submission Overview and Timepoints

- a. DAY OF BLOOD DRAW (before or within 5 days after registration prior to treatment):

Submit the following:

Blood specimen as outlined in [Section 15.1c](#).

- b. WITHIN 7 DAYS OF REGISTRATION:

Submit the following:

S1513 Onstudy Form

S1513 Baseline Abnormalities Form

Baseline Tumor Assessment Form (RECIST 1.1)

Pathology Reports: Initial diagnosis, metastatic (if done), and fresh biopsy (NOTE: Upload reports via the Source Documentation: Baseline form in Rave®.)

Submit radiology reports from all scans performed to assess disease at baseline. (NOTE: Upload reports via the Source Documentation: Baseline form in Rave®.)

c. WITHIN 28 DAYS OF REGISTRATION:

Tissue specimens as outlined in [Sections 15.1](#) and [15.2](#).

d. WITHIN 14 DAYS AFTER EACH CYCLE OF TREATMENT:

Submit the following:

S1513 Treatment Form

S1513 Adverse Event Form

e. WITHIN 14 DAYS AFTER EACH CA19-9 OR CEA TEST (every 4 weeks):

Submit the following:

S1513 CA19-9 (CEA) Form

f. WITHIN 14 DAYS AFTER EACH DISEASE ASSESSMENT (INCLUDING BOTH ON TREATMENT AND OFF TREATMENT PRIOR TO DISEASE PROGRESSION):

Submit the following:

Follow Up Tumor Assessment Form (RECIST 1.1)

Radiology reports from all scans performed to assess disease (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®.)

g. WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT:

Submit the following:

Off Treatment Notice

S1513 Treatment Form

S1513 Adverse Event Form

h. WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

Submit the following:

Follow-up Tumor Assessment Form (RECIST 1.1)

Off Treatment Notice (if the patient was still on protocol treatment)

Final **S1513** Treatment Form (if the patient was still on protocol treatment)

Final **S1513** Adverse Event Form

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

Radiology Reports (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®.)

i. AFTER OFF ALL PROTOCOL TREATMENT, EVERY 3 MONTHS UNTIL 3 YEARS FROM REGISTRATION:

Submit the following:

Follow Up Form

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

j. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death **and final S1513** Treatment Form and 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 Translational Medicine

Specimens for HRD and BROCA-HR (submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201):

Note: If patient consented to banking, see additional requirements in [Section 15.2](#).

a. Tissue specimens from pre-treatment biopsy for translational medicine (required for patient) must be submitted within 28 days of registration:

1. One 5-micron charged slide*.
2. Nine to fourteen 10-micron unstained, uncharged slides*. The tissue should not be cover-slipped and should not be baked.

*Sites may submit block in lieu of specific slides listed above.

NOTE: Pre-treatment biopsy may be from either the primary or metastatic tumor site. Core biopsy required. FNA is not an acceptable substitute for core biopsy. A local standard surgical consent form must be obtained. The biopsy 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.

b. Archival tissue from the time of initial diagnosis specimens for translational medicine (required, if available) must be submitted within 28 days of registration:

1. Two 10-micron unstained archival tumor (FFPE) slides. NOTE: Archival tissue from initial diagnosis.

- c. Blood specimen for translational medicine (required for patient) must be submitted within 5 days of registration (prior to beginning treatment):
 - 1. 7mL whole blood collected in yellow top (ACD solution A) tube at baseline. The filled tube must be maintained at ambient (15-30°C) temperature, avoiding extremes of heat and cold, at all times. If Yellow Top, ACD, tubes are not available, EDTA tubes are allowed and will be accepted. **ONLY COLLECT AND SHIP SAMPLES TO THE SWOG SPECIMEN REPOSITORY MONDAY THROUGH THURSDAY. DO NOT COLLECT SAMPLES ON FRIDAY OR THE DAY BEFORE A HOLIDAY. THIS SPECIMEN MUST BE SHIPPED THE DAY OF COLLECTION FOR OVERNIGHT DELIVERY TO LAB #201 AT AMBIENT TEMPERATURE.**
- d. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (<http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp>). Please note that all tissue specimens should be accompanied by a pathology report.
- e. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.
- f. Any leftover specimens 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 for Banking

Specimens for banking (submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201) (optional for patient):

- a. With patient's consent, pre-treatment biopsy specimens must be submitted within 28 days of registration (see [Section 9.0](#)):
 - 1. Tumor block or fifteen 10 micron unstained tumor sections (FFPE) from primary or metastatic tumor site.
NOTE: If tissue block is submitted for [Section 15.1](#), this additional tissue is not required.
- b. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (<http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp>). Please note that all tissue specimens should be accompanied by a pathology report.
- c. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

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

1. Agent(s) may not be used outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: <http://ctep.cancer.gov>.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other 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 electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (<http://ctep.cancer.gov/reporting/cdus.html>).

Note: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS.

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(s) as part of the trial. Reporting requirements are provided in [Table 16.1](#). The investigational agent(s) used in Arm 1 of 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/Intervention¹ ABT-888 (Arm 1)

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)				
<p>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)</p> <p>An adverse event is considered serious if it results in ANY of the following outcomes:</p> <ol style="list-style-type: none"> 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). 				
<p>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.</p>				
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	
<p>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.</p> <p>Expedited AE reporting timelines are defined as:</p> <ul style="list-style-type: none"> ○ “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. 				
<p>¹Serious 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:</p> <p>Expedited 24-hour notification followed by complete report within 5 calendar days for:</p> <ul style="list-style-type: none"> • All Grade 4, and Grade 5 AEs <p>Expedited 10 calendar day reports for:</p> <ul style="list-style-type: none"> • Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization • Grade 3 adverse events 				
<p>May 5, 2011</p>				

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 Data Operations Center copies of Off Treatment Notice and/or Notice of Death.

g. **Expedited reporting for commercial agents**

Commercial reporting requirements are provided in [Table 16.2](#). The commercial agent(s) used in Arms 1 and 2 of this study are fluorouracil, irinotecan, and leucovorin. 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 Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.2. Expedited reporting requirements for adverse events experienced by patients on study Arm 2 who have received the commercial drug(s) listed in 16.1g above within 30 days of the last administration of the commercial agent(s).

ATTRIBUTION	Grade 4		Grade 5 ^a	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			CTEP-AERS	CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS	CTEP-AERS

CTEP-AERS: Indicates an expedited report is to be submitted via CTEP-AERS within 10 calendar days of learning of the event^b.

^a This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

^b Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210-614-0006.

h. **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. Any supporting documentation should be submitted to CTEP per NCI guidelines for AE reporting located at:
http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/aeguidelines.pdf.

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.

i. **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 Intake Calendar
- 18.2 Patient Drug Information Handout and Wallet Card
- 18.3 New York Heart Association Criteria
- 18.4 Translational Medicine: HRD and BROCA-HR

18.1 Intake Calendar – ABT-888 (Veliparib) SWOG Study: **S1513**

Cycle: _____ Start Date: _____ Start Day (circle one): Sun M Tu W Th Fr Sat						
<p>Instructions for the participant: This is a 14 day cycle calendar on which you are to record the number of ABT-888 tablets you take each day. ABT-888 should be taken twice daily at the same time of day \pm 2 hours, unless otherwise instructed, with or without food. ABT-888 capsules should be swallowed whole; do not chew them prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact.</p> <ul style="list-style-type: none"> • Missed doses are to be omitted rather than made up if more than 6 hours have passed from the original dose time. • If you vomit a dose within 15 minutes, a replacement dose can be taken. If more than 15 minutes have passed since the dose, you should not take another dose. • If you develop any side effects from the tablet, mark this on the calendar on the day you note the effect. Contact site personnel listed below. • On Day 3 of each cycle, ABT-888 must be taken at your treating institution 1 hour (\pm 30 minutes) before starting irinotecan. <p>Put the date in the box on the calendar for and note the times of dose for each day. Take medication as directed by study doctor. Line through the days medication is not taken.</p> <p>Storage: ABT-888 capsules should be stored at room temperature (not to exceed 25°C) in their original container. Keep the medication in the bottles provided and do not transfer it to any other container.</p> <p>Site Personnel: The patient number should be recorded on the bottle label in the spaces provided by site personnel at the time of assignment to patient. Site personnel must ensure that patients clearly understand the guidelines for self-medication. Patients should be given a sufficient supply to last until their next study visit. Unused drug and/or empty bottles should be returned to the site at the next study visit.</p>						
If you have questions contact: _____ Telephone: _____						
<p>Special instructions:</p>						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
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Time: _____	Time: _____	Time: _____	Time: _____	Time: _____	Time: _____	Time: _____
Time: _____	Time: _____	Time: _____	Time: _____	Time: _____	Time: _____	Time: _____
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Time: _____	Time: _____	Time: _____	Time: _____	Time: _____	Time: _____	Time: _____
Time: _____	Time: _____	Time: _____	Time: _____	Time: _____	Time: _____	Time: _____

18.2 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)**. 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) interacts with certain transporter proteins that help move drugs in and out of cells.

- The proteins in question are **OCT2, MATE1, MATE2K, and P-gp**. ABT-888 (veliparib) is a substrate of P-gp, OCT2, and MATE1/2K and may be affected by other drugs that inhibit these protein transporters. ABT-888 is an inhibitor of OATP1B1, OATP1B3, MATE1/2K, OAT1/3 and OCT1 and may affect transport of other drugs in and out of cells.

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

ABT-888 (veliparib) 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:

Use caution when administering ABT-888 (veliparib) with other medicines that need certain **transport protein 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 **P-gp, OCT2, and MATE1/2K**.”

- 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 can be contacted at _____.

<p style="text-align: center;">STUDY DRUG INFORMATION WALLET CARD</p> <p style="text-align: center;">STUDY DRUG INFORMATION WALLET CARD</p> <p>You are enrolled on a clinical trial using the experimental study drug ABT-888 (veliparib). This clinical trial is sponsored by the NCI. ABT-888 (veliparib) may interact with drugs that need certain transport proteins in your body. Because of this, it is very important to:</p> <ul style="list-style-type: none">➤ 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.	<p>Use caution as ABT-888 (veliparib) may interact with medicines that stop transport proteins MATE1/2K, OCT2, and P-gp to process further in the body.</p> <ul style="list-style-type: none">➤ 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 P-gp, MATE1/2K, and OCT2.”➤ 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 _____ <p>and can be contacted at _____.</p>
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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 Translational Medicine: HRD and BROCA-HR

Purpose	Specimens	Sites to Ship to	Laboratory Performing Testing	Funding
BROCA-HR (including BRCA1 & BRCA2)	<ul style="list-style-type: none"> Archival tissue: two 10-micron slides Pre-treatment tissue: four 10-micron slides 7mL whole blood (Bank to process PBMCs for DNA) 	SWOG Specimen Repository – Solid Tissue, Myeloma, and Lymphoma Division #201	King/Swisher Lab University of Washington 1959 NE Pacific St, Health Science Building, K154 Seattle, WA 98195 Phone: 206/616-4296	BIQSFP to fund biopsy and tumor BRCA1 and BRCA2 analysis Pharmaceutical Company (Abbvie) to fund the exploratory BROCA-HR assays (BROCA-HR excluding BRCA1 and BRCA2)
HRD	Pre-treatment tissue: <ul style="list-style-type: none"> One 5-micron H&E charged slide Five to ten 10-micron slides 	Specimen Repository – Solid Tissue, Myeloma, and Lymphoma Division #201	Myriad Laboratory Inc. 320 Wakara Way Salt Lake City, UT 84108	Pharmaceutical Company (Myriad)

a. HRD Assay

Tumor Homologous Recombination Deficiency (HRD) assay and somatic BRCA mutation testing will be 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 three different types of genomic “scarring” (LOH (the number of regions of loss of heterozygosity (LOH) that are longer than 15 Mb but shorter than a whole chromosome), TAI (the number of regions of allelic imbalance that start at the subtelomere and do not cross the centromere), and LST (the number of breakpoints between different regions which are both longer than 10 Mb)). High levels of these genomic “scars” are 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 50-200 ng of tumor DNA and has high sensitivity for identification of *BRCA*-deficient tumors. (1,2,3)

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

Laboratory conducting the assay:

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



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 be 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 be 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 TapeStation, 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.

- b. BROCA-HR Assay including *BRCA1* and *BRCA2* Testing

***BRCA1* and *BRCA2* testing**

BRCA1 and *BRCA2* (*BRCA1/2*) are tumor suppressor genes, in which inherited loss-of-function mutations confer a higher lifetime risk of breast and ovarian carcinoma, as well as an increased risk of pancreatic adenocarcinoma (standardized incidence ratios (SIR) 3.5-5.8 for *BRCA2*, and SIR 4.1 for *BRCA1* mutations, respectively). (4,5,6,7) *BRCA1/2* are key components of the *BRCA*-Fanconi anemia (FA) pathway, which is critical to homologous recombination (HR)-mediated DNA repair.

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. (8) 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, ovarian, and pancreatic tumors. (9,10,11,12,13,14,15,16,17,18)

In addition to BRCA1/2 mutations, many 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. It is speculated that if other factors beyond germline BRCA mutations are comprehensively evaluated, 20-25% of pancreatic cancers will demonstrate HR deficiency (HRD phenotype) or BRCAness. (19,20)

Preclinical evidence suggests that MLH1 loss, RAD51 mutations, and ERCC1 loss may particularly enhance cytotoxicity from PARP inhibition plus irinotecan/SN38 combination. (21,22,23) It is not yet known whether BRCA1/2 mutations will sensitize pancreatic cancer to treatment with irinotecan and PARP inhibitors.

The secondary aim of this randomized Phase II study is to investigate whether the addition of a PARP inhibitor (ABT-888) to irinotecan-based therapy (mFOLFIRI) will improve response, progression free survival (PFS), and overall survival (OS) for patients with germline or somatic BRCA1/2 mutation-associated pancreatic cancers. Thus, gBRCA1/2 and somatic tumor BRCA1/2 testing for the entire study cohort is an essential integrated biomarker.

Exploratory translational aims will assess whether BRCAness or HRD phenotype (by BROCA-HR and the HRD assay described previously in [Section 18.4a](#)) correlate with response, PFS and OS in each treatment arm.

The current design for BROCA-HR includes the following genes (n=75):

- a. FA-BRCA HR pathway: ATM, ATR, BABAM1, BAP1, BARD1, BLM, BRCA1, BRCA2 (FANCD1), BRIP1 (FANCI), BRCC3, BRE, CHEK1, CHEK2, ERCC1, ERCC4 (FANCD2), 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
- b. DNA mismatch repair MLH1, MSH2 (and EPCAM), MSH6, PMS2
- c. Other DNA repair, surveillance genes, or modifier genes: CDK12, CDH4, HELQ, NEIL1, PPM1D, POLD1, POLE, RIF1, TP53, ID4, PAXIP1, POLQ, RINT1, TP53BP1, USP28, WRN, XRCC3
- d. NER genes: ERCC2, ERCC3, ERCC4, ERCC5, ERCC6, DDB1, XPA, XPC
- e. NHEJ genes: DCLRE1C, LIG4, PRKDC, TOBP1, XRCC4, XRCC5, XRCC6
- f. PI3K pathway: PTEN, PI3KCA

A common characteristic of “genomic scarring” is large (>15Mb) but sub-chromosomal deletions. Therefore, fine mapping of loss of heterozygosity (LOH) is not necessary to identify the HRD genomic scar. We tested the theoretical ability of 3000 SNPs to define “genomic scarring” in existing TCGA ovarian cancer data (unpublished data). Indeed, using only 3000 SNPs can define cases with high LOH which have better prognosis. Combining the BROCA-HR mutational status and the LOH profile provides additional prognostic information. **S1513** will assay 3000 SNPs with the same BROCA-HR mutational assay which will provide an LOH profile to assess genomic scarring as an exploratory biomarker. We will then combine the mutation information from BROCA combined biomarker as outlined in Figure 18.4b, with the prediction that HR proficient cancers would achieve no significant benefit from the addition of PARPi.

	Genomic LOH-High	Genomic LOH-low
HR mutation germline or somatic	HRD	HRD
No HR mutation	HRD	HR Proficient

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

Specimen collected for germline and somatic *BRCA1/2* testing will be utilized for testing of the non-*BRCA* BROCA-HR genes including genomic LOH “scarring” phenotype and added specimen will not be needed.

- FFPE Slides archival tumor: 2 consecutive unstained 10 micron slides, minimum 20% tumor
- FFPE Slides pre-treatment tumor: 4 consecutive unstained 10 micron slides, minimum 20% tumor
- 7mL whole blood

Tumor Tissue: DNA will be extracted from FFPE tumor tissue containing at least 20% tumor nuclei. A targeted capture and massively parallel sequencing approach called BROCA will be applied to samples. Library preparation has been fully automated to increase sample turnaround and lower cost. Paired-end libraries with 350bp inserts will be prepared from 1µg 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). (96) 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. (24,25) 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. (26,27) All loss of function mutations in cancer susceptibility genes will be confirmed with PCR amplification and Sanger sequencing.

Tumor specimens should be shipped at room temperature to the SWOG repository (Nationwide). Specimens will be stored at the SWOG repository at room temperature until ready to be shipped to King/Swisher Laboratory for analysis.

Blood: 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 targeted capture and parallel sequencing BROCA-HR described above will be used

The results will be reported as deleterious somatic and/or germline *BRCA* mutation “present” or absent. Variants of uncertain significance will not be reported.

The expected distribution of the biomarker in the study population:

It is estimated that 7-10% of the study population will demonstrate deleterious germline or somatic *BRCA1/2* mutations. Cutpoints will not be used for *BRCA* testing. Test results will be described as deleterious germline or somatic mutation “present” or “absent”. In *gBRCA* or somatic *BRCA* mutation-positive patients median PFS of 3 months is assumed for Arm 2 (FOLFIRI) that improves to 5 months for Arm 1 (mFOLFIRI + ABT-888).

It is estimated that 20-25% of the study population will demonstrate germline or somatic alterations in other BROCA-HR panel genes or evidence of “genomic scarring” by SNPs analysis.

The accessibility of the biomarker assay results:

Clinically significant germline *BRCA* and BROCA-HR testing reports will be provided to the treating physician. Genetic counselling and discussion of results with patient are the responsibility of the treating physician.

Data on the analytical performance of the assay for BRCA1/2 mutations:

Accuracy and precision BROCA HR captures > 99% of known deleterious *BRCA1* and *2* Mutations. (28) 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%. (29)

Data on the analytical performance of the assay for BROCA-HR:

Accuracy and precision BROCA HR captures > 99% of known deleterious germline mutations in the FA-*BRCA* HR, DNA mismatch repair, NER, NHEJ pathways, and surveillance and modifier genes of interest previously listed. (126)

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%. (30)

Discrepancy between prior germline BRCA testing and trial testing:

Although germline *BRCA* testing may have been previously performed for some pancreatic cancer patients with strong family history of breast/ovarian cancer syndrome or family history of pancreatic cancer, we expect that <10% 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).

BROCA-HR testing which includes *BRCA1/2* will be done post randomization for all patients.

Laboratory conducting the 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

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