8329 / MC0861: A Phase I/II Trial of ABT-888, an Inhibitor of Poly(ADP-ribose) Polymerase (PARP), and Topotecan (TPT) in Patients with Solid Tumors (Phase I) and Relapsed Ovarian Cancer or Primary Peritoneal Cancer (Phase II) After Prior Platinum Containing First-Line Chemotherapy

Summary of Changes

From Review of Amendment 19 dated September 29, 2016:

I. Comments Requiring a Response – Major Issues:

#	Section	Comments
1.	ICD	In response to CTEPs previous disapproval of the proposed amendment for this trial it was written: ***PI Response:*** *Please note that the Mayo Clinic IRB is the IRB of record for this study. As Mayo Clinic IRB has* ***disapproved*** *the replacement of the existing risk list with the condensed risk list format in previous CTEP-held IND studies, we respectfully decline to incorporate this at this time. We have ensured that all risks listed in the condensed risk list format are already included in this consent form.* Please provide a letter from the Mayo IRB detailing their justification for not accepting the Condensed Risk List for CTEP-held IND studies. Additionally, please provide the list of previous studies in which the Mayo clinic IRB has disapproved the use of the CTEP ICD Condensed Risk List. **PI Response:** Mayo IRB previously reviewed and disapproved the replacement of the very lengthy list of medication risks with the CTEP ICD Condensed Risk List in the Mayo consent form for protocol 8821 / MC093C; Mayo IRB did not wish to remove any risks from the consent form. We note that this disapproval came from the same Mayo IRB committee that reviews this protocol 8329 / MC0861. As responsibility for IRB oversight must now be transferred from Mayo IRB to the NCI CIRB, this is no longer a concern. The Condensed Risk Lists for both ABT-888 and topotecan are included in the CIRB consent form.

II. Company Comments - Requiring a Response:

#	Section	Comments
1.	8	In Section 8.0 Dose Modification Based on Adverse Events- phase 2 reductions, 3 levels of reductions are outlined for 'Neutrophil count decreased < 500 and/or Platelet count decreased < 25, 000,' but only one reduction is specified for 'Neutrophil count decreased 500 – 1000 and/or Platelet count decreased 25,000 – 50,000.' Footnotes suggest that 3 modifications are allowed. The investigators may want to clarify the other modifications for this second group. **PI Response**: Additional dose modifications have been added to the second group specified above.

III. CTSU Revisions:

#	Section	Comments
1.	Title page	Changed Lead Org and Participating Organizations as this will be conducted under ETCTN
2.	6	ETCTN language inserted in this section.
3.	18	ETCTN language inserted in this section.

IV. PI initiated Revisions:

#	Section	Comments
1.	Throughout Protocol	A notation added that the phase 1 portion of the study is complete and the phase 2 portion of the study is open.
2.	Throughout Protocol	Information applicable only to Mayo Clinic removed.
3.	Title Page	Daniel Satele added as a statistician.
4.	1.54	Updated to current study results.
5.	3.15	PTT value corrected to 48 from 42 seconds (1.5 x ULN)
6.	3.2.2	Prior therapy with topotecan is added as an exclusion
7.	3.2.14	Prior immunotherapy clarified to **not** be an exclusion.
8.	14.1	Clarified that pharmacogenetics tests are mandatory and BRCA tests are optional.
9.	14.2	Clarified that pharmacogenetics and BRCA tests can be performed from the same blood sample.

MC0861: A Phase I/II Trial of ABT-888, an Inhibitor of Poly(ADP-ribose) Polymerase (PARP), and Topotecan (TPT) in Patients with Solid Tumors (Phase I) and Relapsed Ovarian Cancer or Primary Peritoneal Cancer (Phase II) After Prior Platinum Containing First-Line Chemotherapy

Corresponding Organization: LAO-MN026 / Mayo Clinic Cancer Center LAO

Principal Investigator: [redacted] M.D.
Mayo Clinic
200 First Street SW
Rochester, MN 55905
Telephone: [redacted]
Telefax: [redacted]
Email: [redacted]

Co-Investigators: [redacted], M.D., Ph.D. √
[redacted], M.D.
[redacted], M.D.
[redacted], Ph.D. √
[redacted], Ph.D. √

√ Study contributor(s) not responsible for patient care.

Participating Organizations:

LAO-11030 / University Health Network Princess Margaret Cancer Center LAO
LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-NC010 / Duke University - Duke Cancer Institute LAO
LAO-NJ066 / Rutgers University - Cancer Institute of New Jersey LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / University of Pittsburgh Cancer Institute LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
LAO-NCI / National Cancer Institute LAO
EDDOP / Early Drug Development Opportunity Program

Statisticians
[redacted], MS
Mayo Clinic
Telephone: [redacted]
Email: [redacted]

[redacted]
Mayo Clinic
Telephone: [redacted]
Email: [redacted]

Project Manager
[redacted] MS
Mayo Clinic
Telephone: [redacted]
Email: [redacted]

Drug Availability:
DCTD Supplied Investigational Agents: ABT-888 (NSC 737664)
Commercially Supplied Agents: Topotecan

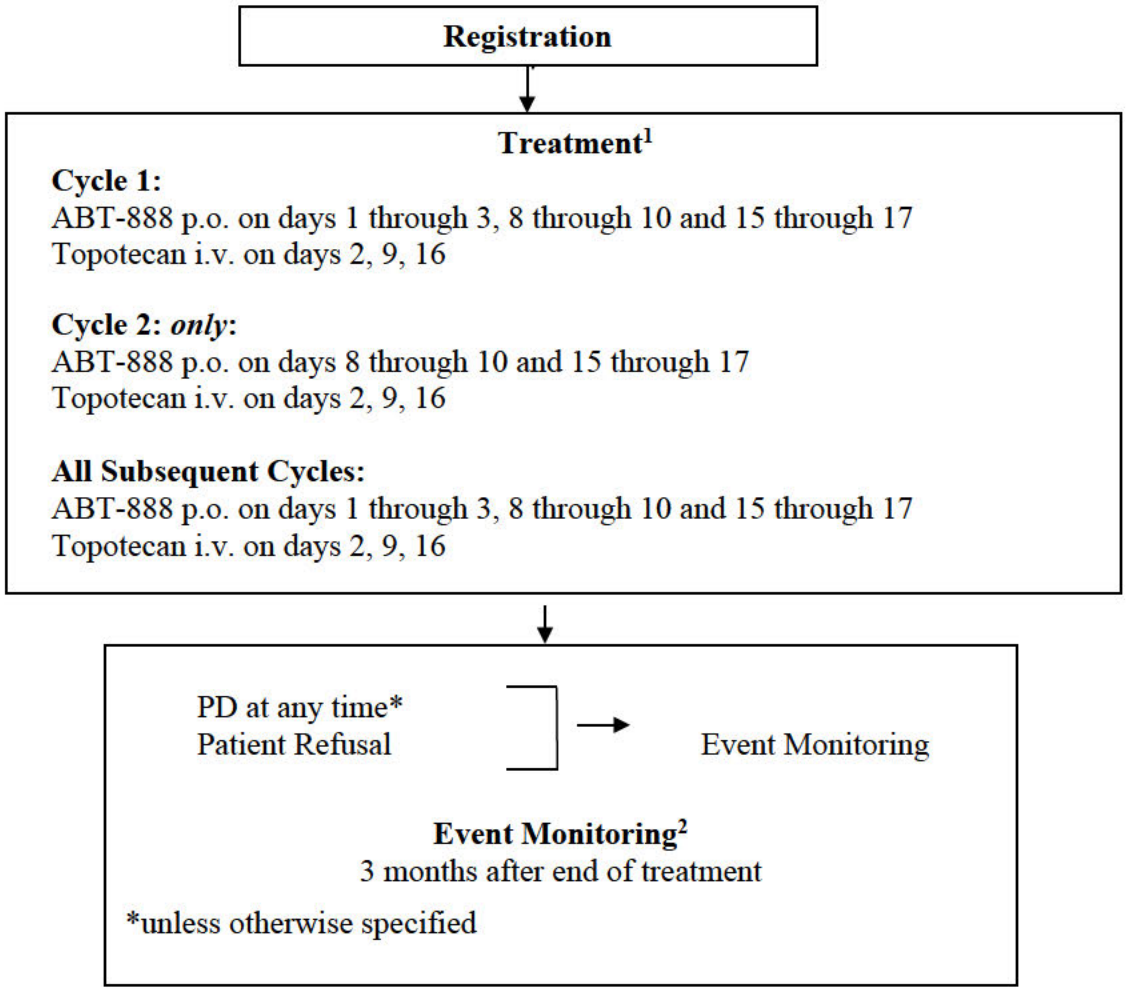
IND #: [redacted]
IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date:
Original ETCTN Protocol / Version 1 / January 13, 2017

Table of Contents

Schema: Phase 1 Dose Escalation

Note: The Phase 1 Dose Escalation part of the study is completed; the phase 2 MTD part of the study is open.

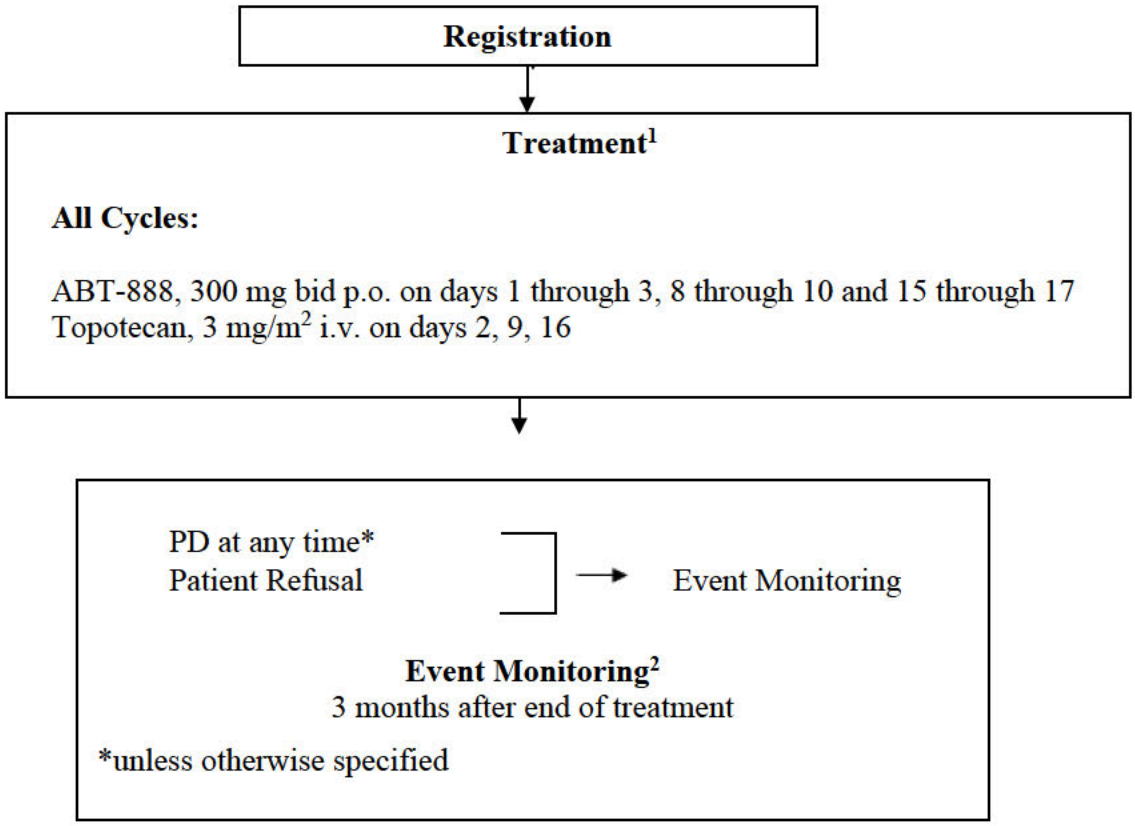


[1] Cycle length = 28 days

[2] Event monitoring will take place by means of a patient phone call or chart review to assess vital status and progression status only.

Generic name: Veliparib Brand name(s): N/A Mayo Abbreviation: ABT888 Availability: AbbVie	Generic name: Topotecan Brand name(s): Hycamptin® Mayo Abbreviation: TOPA Availability: Commercial

Schema: Phase 2 MTD



[1] Cycle length = 28 days

[2] Event monitoring will take place by means of a patient phone call or chart review to assess vital status and progression status only.

Generic name: Veliparib Brand name(s): N/A Mayo Abbreviation: ABT888 Availability: AbbVie	Generic name: Topotecan Brand name(s): Hycamptin® Mayo Abbreviation: TOPA Availability: Commercial

1.0 Background

1.1 Poly (ADP-ribose) Polymerase (PARP) Activity

1.1.1 Rationale for PARP as a Target of Anti-Cancer Therapeutics

Poly (ADP-ribose) polymerases (PARPs) are a highly conserved family of enzymes whose predominant function is to preserve genomic integrity following DNA damage (Burkle *et al*., 2001; Jagtap *et al.*, 2005; Gagne *et al.*, 2006; Hassa *et al.*, 2008). Although 18 members of this enzyme family have been identified in mammalian cells, only 6 have been shown to actually synthesize ADP-ribose polymers (Hassa *et al.*, 2008). Of these, PARP1 (referred to as PARP throughout the remainder of this protocol), the founding member and most abundant of these enzymes, has been shown to play critical roles in DNA repair, regulation of genomic stability, modulation of cellular energy pools, and the regulation of transcription (Burkle *et al.*, 2001; Jagtap *et al*., 2005; Gagne *et al.*, 2006; Hassa *et al*, 2008).

Adequate levels of PARP and normal activity are essential for normal function of the base excision repair (BER) pathway (*op cit.*). In addition, PARP appears to play a critical role in homologous recombination (Helleday *et al.*, 2005). Further, emerging evidence suggests that PARP is activated by and plays a role in repair of DNA double strand breaks that occur when replication forks stall and then collapse (Yang *et al.*, 2004; Haince *et al.*, 2005). Consistent with this possibility, data from several sources indicate that poly (ADP-ribose) (PAR) synthesis is stimulated by camptothecin-induced stalled replication forks when proliferating cells are exposed to camptothecin for prolonged periods of time (Sugimura *et al*., 2008; [redacted] and [redacted], unpublished observations). Moreover, this polymer synthesis can be inhibited by simultaneous treatment with a variety of PARP inhibitors, including NO125 (Sugimura *et al.*, 2008), PJ-34 ([redacted], unpublished observations) or ABT-888 (S. Kaufmann, unpublished observations). As described below, this combined treatment with a topoisomerase I (topo I) poison and PARP inhibitor is accompanied by increased activation of the intra-S checkpoint and increased killing by the topo I poison.

Based on the roles of PARP in DNA repair, there has been substantial interest in assessing whether PARP inhibitors increase the cytotoxicity of DNA damaging agents (Jagtap *et al.*, 2005; Haince *et al.*, 2005; Curtin *et al.*, 2005; Tentori *et al.*, 2005; Plummer *et al.*, 2006; Ratnam *et al.*, 2007; Drew and Calvert, 2008). A variety of preclinical studies have demonstrated that PARP inhibitors enhance the cytotoxicity of monofunctional alkylating agents such as temozolomide, which induce lesions that are reversed, in part, by BER (Delaney *et al.*, 2000; Calabrese *et al.,* 2004; Thomas *et al.*, 2007; Liu *et al.*, 2008b).

1.1.2 The Emerging Role of PARP Inhibitors in Ovarian Cancer

The tumor suppressors BRCA1 and BRCA2 are important components of a network of DNA repair pathways that contribute to the maintenance of genomic stability in the face of various lesions (Venkitaraman *et al.*, 2004). Current evidence suggests that BRCA1 and BRCA2 are particularly important in DNA double-strand break repair.

These observations led to the hypothesis that BRCA1- and BRCA2-deficient cells would, because of their defective double-strand break repair, be more dependent on other DNA repair mechanisms for their survival. In support of this hypothesis, two groups reported that BRCA1/2-deficient cell lines are selectively killed by PARP inhibitors (Bryant *et al.*, 2005; Farmer *et al.*, 2005). Subsequent studies have demonstrated that defects on other components of the DNA response network, including ATM, ATR, Chk1, Chk2, Rad51 and components of the Fanconi anemia pathway, also sensitize to PARP inhibitors (McCabe *et al.*, 2006). In contrast, PARP inhibitors by themselves have little or no toxicity in normal tissues (Ratnam *et al.*, 2007).

BRCA1 and BRCA2 are mutated in 10-15% of all ovarian cancers (Risch *et al.*, 2001). Acting on the assumption that BRCA1/2 mutant tumors, like the cell lines, would be hypersensitive to PARP inhibitors, Yap *et al*. completed a phase 1 trial of the PARP inhibitor AZD2281 in ovarian cancer patients with BRCA1/2 mutations and demonstrated an ~40% response rate (Ashworth *et al.*, 2008; Drew and Calvert, 2008).

While the preceding study was limited to patients with documented BRCA1/2 mutations, it is important to emphasize that the same pathway(s) can be inactivated by methylation or other chromatin alterations involving either the BRCA loci or some of the other loci listed above. Accordingly, it has been suggested that a substantial fraction of sporadic ovarian cancers might have dysfunction of this pathway (Turner *et al.*, 2004), providing the impetus for studying these inhibitors in patients with sporadic ovarian cancer as well (Ashworth *et al.*, 2008).

1.2 Veliparib (ABT-888)

1.2.1 Preclinical Anti-Cancer Activity

Veliparib (ABT-888) is an orally administered, potent and specific, small molecule inhibitor of PARP1 and PARP2 (Donawho *et al.*, 2007; Penning *et al.*, 2009). ABT-888 potentiates the cytotoxic actions of a number of DNA damaging agents, including temozolomide, cisplatin, cyclophosphamide and ionizing radiation in multiple *in vitro* and xenograft models (Donawho *et al.*, 2007; ABT-888 IB, 2008; Albert *et al.*, 2007; Liu *et al.*, 2008b; Penning *et al.*, 2009).

Therapeutic doses of ABT-888 have not been found to increase toxicity, although supratherapeutic doses have been associated with some increases in toxicity.

1.2.2 Preclinical Pharmacokinetics

In rats and dogs, ABT-888 is primarily cleared in the urine as intact parent drug, with minor contributions from metabolism. The renal clearance and minimal metabolism observed in rats and dogs and the minimal metabolism observed in vitro in all species evaluated are consistent with the low molecular weight (246.31 g/mol) and good solubility of ABT-888. These data support the prediction that in the human, ABT-888 will be primarily cleared as intact parent drug in urine. ABT-888 is not a potent inhibitor of the major human cytochrome P450s (CYPs), suggesting a minimal potential for drug-drug interactions at the anticipated therapeutic concentrations.

1.2.3 ABT-888 Toxicology

In a 4-week repeat dose dog toxicity studies, the No-Observed-Adverse-Effect-Level (NOAEL) was [redacted] mg/kg/day (C_{max} of [redacted] µg/mL and AUC0-24 of [redacted] µg•hr/mL). The dose-limiting toxicity in this study was seizure observed at [redacted] mg/kg/day. Seizures were also noted in a 2-week study, at dosages varying from [redacted] to [redacted] mg/kg/day. A dedicated EEG study in the conscious dog also determined that seizures were observed at a dose of [redacted] mg/kg BID, with no evidence of abnormal cortical activity or seizures occurring at a lower dose of [redacted] mg/kg BID. Plasma exposure at the [redacted] mg/kg BID dose corresponded to a mean plasma exposure approximately [redacted] the predicted clinical AUC_{0-24} of [redacted] µg•hr/mL. Therefore, preclinical dog studies determined an approximate [redacted] safety margin for seizure, when exposures were compared to anticipated therapeutic AUC of 0-24 (ABT-888 IB, 2008).

In repeat-dose oral rat toxicity studies, the NOAEL was [redacted] mg/kg/day with key findings at higher exposures includin [redacted] ABT-888 did not induce seizures at doses as high as [redacted] mg/kg/day. Additionally, ABT-888 did not induce seizures in a model of orthotopically implanted rat glioblastoma with a dose of up to [redacted] mg/kg. In safety pharmacology studies, ABT-888 did not affect the electronically induced seizure threshold, except for a small [redacted] at [redacted] mg/kg. The secondary and safety pharmacology studies conducted with ABT-888 demonstrated minimal effects on the cardiovascular, pulmonary, and GI systems. In the anesthetized dog model, there was a trend [redacted] at plasma concentrations [redacted] than the predicted clinical C_{max}. In humans, QT_c prolongation is predicted to be less than 3 ms at a dose of [redacted] mg BID. ABT-888 produced no effect on heart rate or cardiac output at a concentration of [redacted] µg/mL in the dog [redacted] predicted clinical exposure level) and no effect on pulmonary function at a plasma concentration of [redacted] µg/mL in the rat [redacted] predicted clinical exposure level). ABT-888

was determined to unlikely be emetic or to elicit adverse GI effects at efficacious plasma concentrations.

A detailed discussion of the pre-clinical toxicology, metabolism, and pharmacology can be found in the Information for Investigator's Brochure.

1.2.4 Clinical Trials

ABT-888 has been administered as a single dose, ranging from 10 to 50 mg, to 9 subjects enrolled in an exploratory investigational new drug (IND) study conducted by the Cancer Therapy Evaluation Program (CTEP). Preliminary pharmacokinetic data indicate ABT-888 peak plasma levels generally occurred between 0.5 and 1.5 hours post dosing. At a dose of 25 mg, plasma concentrations of ABT-888, averaging 0.151 μg/mL, were above the efficacious threshold of 0.070 μg/mL for an average of 4.1 hours. These results are consistent with the projected human pharmacokinetic profile based on preclinical data.

Preliminary data from this same Phase 0 trial have demonstrated inhibition of poly(ADP-ribose) polymer synthesis in human samples using an enzyme-linked immunosorbent assay for polymer (Liu *et al.*, 2008a; Kinders *et al.*, 2008). A 25 mg dose administered to 3 subjects resulted in greater than 85% decrease in polymer levels in peripheral blood mononuclear cells (PBMCs) in 2 of the 3 subjects; and significant inhibition of polymer levels (92% to 100%) was also observed in tumor tissue from all 3 subjects. A 50 mg dose resulted in complete inhibition of PBMCs in 3 subjects. For this dose group, PARP activity inhibition in tumor biopsies averaged 75% 3 to 6 hours after dosing (n = 3) and averaged 74% 24 hours after dosing (n = 3). No significant adverse events have occurred in subjects receiving a single dose of ABT-888.

Preliminary pharmacokinetic results are also available from a Phase 1 study of ABT-888 in combination with temozolomide (M06-862). Doses of 20 and 40 mg BID produce areas under the concentration-versus-time curve over 24 hours ($AUC0_{0–24}$) mean values of 2.0 μg•hr/mL and 3.7 μg•hr/mL, respectively, and maximum concentrations (C_{max}) in plasma mean values of 0.17 μg/mL and 0.35 μg/mL, respectively. These values span the optimal human exposure of an AUC of 3.0 μg•hr/mL and the optimal human C_{max} of 0.21 μg/mL predicted from preclinical studies. Preliminary safety results are available from 2 Phase 1 studies of ABT-888 in combination with a DNA-damaging agent. In Study M06-862, doses ranged from 10 mg ABT-888/150 mg temozolomide to 40 mg ABT-888/200 mg temozolomide. The most common adverse events were nausea, vomiting, fatigue, anorexia, and thrombocytopenia.

In CTEP Study 7981, doses ranged from 10 mg ABT-888 with 1.2 mg/m^2/day topotecan (x 5 days) to 50 mg ABT-888 with 1.5 mg/m^2/day topotecan (x 5 days). In this study, more than half of the subjects experienced decreases in neutrophils or leukocytes. Other potential hematologic toxicities were decreased platelets and

decreased hemoglobin. The causality assessment of these events to ABT-888 is complicated by the high rate of grade 4 platelet and neutrophil counts occurring with topotecan monotherapy on this 5-day schedule. Importantly, no new dose-limiting toxicity has been reported with doses of ABT-888 as high as 40 mg BID.

1.3 Topotecan in Ovarian Cancer

1.3.1 FDA-Approved Daily x 5 Schedule

Topotecan (9-[(dimethyl amino) methyl]-10-hydroxycamptothecin) is water soluble camptothecin with excellent antitumor activity in vitro. Tumour xenograft models showed activity in many tumor types, including adenocarcinomas of the ovary and colon, tumors of the central nervous system, and sarcomas. Initial phase I clinical trials showed that the dose-limiting toxic effect was myelosuppression. Although phase 1 studies seemed to suggest a higher response rate with extended infusions or frequent dosing, phase 2 studies in unresectable and metastatic non-small-cell lung cancer and in advanced breast cancer did not confirm this apparent advantage. Indications of activity in ovarian and small-cell lung cancer in phase 1 trials led to further investigation of topotecan in these diseases.

The pivotal study in the 1996 FDA approval of topotecan for relapsed ovarian cancer was a randomized phase 3 trial by ten Bokkel Huinink and colleagues (ten Bokkel Huinink *et al.*, 1997). In this study, patients with ovarian cancer that failed to respond to or recurred after a platinum-containing regimen were randomized to topotecan versus paclitaxel. Topotecan was administered at 1.5 mg/m^2 daily for 5 days, repeated every 21 days. Topotecan demonstrated significant benefit over paclitaxel in time to progression (23 vs 14 weeks, $p = 0.002$).

1.3.2 Weekly Topotecan Schedule More Widely Used for Ovarian Cancer

Due to concerns about the high rate of myelosuppression seen with the daily x 5 topotecan schedule in previously treated ovarian cancer patients, which might reflect decreased clearance as a consequence of cisplatin-induced renal dysfunction (Armstrong, 2004; Markman, 2005), alternative regimens have been investigated to improve or maintain efficacy while decreasing toxicity (Morris, 2002; Rowinsky, 2002). With this in mind, at least 10 phase 1 and phase 2 studies have examined the safety and efficacy of weekly topotecan in patients with pretreated ovarian cancer (Hoskins *et al.*, 1998; Homesley *et al.*, 2001; O'Malley *et al.*, 2005; Spannuth *et al.*, 2007; Vandenput *et al.*, 2007; Safra *et al.*, 2007; Morris *et al.*, 2008; Abushahin *et al.*, 2008; Le *et al.*, 2008; Muntz *et al.*, 2008). A phase 1 study in previously treated ovarian cancer patients demonstrated an MTD of 4 mg/m^2/dose when topotecan was administered intravenously as a bolus infusion on days 1, 8 and 15 every 21 days (Homesley *et al.*, 2001). Grade 2 anemia, fatigue and gastrointestinal toxicity limited further

dose escalation. A phase 2 study investigating weekly topotecan (median starting dose approximately 2.5 mg/m^2) on days 1, 8, and 15 of a 28-day cycle had a response rate of 18% in platinum refractory/resistant patients (O'Malley *et al.*, 2005). With this alternative schedule, the myelosuppression was again mild, with no grade 4 toxicities observed. The experience in subsequent trials has been similar, with grade 4 neutropenia occurring in 15% or fewer of the patients (Spannuth *et al.*, 2007; Vandenput *et al.*, 2007; Safra *et al.*, 2007; Morris *et al.*, 2008; Abushahin *et al.*, 2008; Le *et al.*, 2008). Response rates (PR + CR) have ranged from 9% (Vandenput *et al.*, 2007; Le *et al.*, 2008) to 24% (Safra *et al.*, 2007; Morris *et al.*, 2008) depending on eligibility criteria; and another 25-40% of patients had prolonged disease stabilization. This less myelosuppressive weekly regimen of topotecan provides the starting point for the present clinical trial.

1.4 Rationale for the Combination of ABT-888 and Topotecan

Studies described above suggest that topotecan and PARP inhibitors are active in ovarian cancer. Beyond the simple rationale of combining two active agents, a number of further observations support the development of topotecan/PARP inhibitor combinations. Preclinical studies with a number of different PARP inhibitors have demonstrated that PARP inhibition sensitizes tumor cells to camptothecin and/or topotecan *in vitro* and *in vivo* (White *et al.*, 2000; Delaney *et al.*, 2000; Canon Koch *et al.*, 2004; Calabrese *et al.*, 2003; Calabrese *et al.*, 2004; Tikhe *et al.*, 2004; Smith *et al.*, 2005; Thomas *et al.*, 2007; Smyth *et al.*, 2001; Smith *et al.*, 2005). While a number of mechanisms have been proposed to explain this observation, including i) a requirement for PARP to facilitate the resealing of DNA by topoisomerase I (Malanga *et al.*, 2004; Park *et al.*, 2005); ii) a requirement for PARP to help resolve stalled replication forks (Haince *et al.*, 2005; Yang *et al*, 2004), which are the types of lesions that are initially produced upon treatment with topoisomerase I poisons (Flatten *et al.*, 2005); and iii) the apparent involvement of the BER pathway in helping remove some of the topoisomerase I molecules that become covalently bound to DNA in the presence of camptothecin or topotecan (Smith *et al.*, 2005; He *et al.*, 2007), the mechanism of the synergy between topo I poisons and PARP inhibitors remains incompletely understood.

In addition to these studies with other PARP inhibitors, preclinical studies in the laboratory of Scott Kaufmann at Mayo have demonstrated that ABT-888 enhances the antiproliferative effects of topotecan in a variety of human ovarian cancer cell lines, including Ovcar3, Ovcar5, Ovcar8, SKOV3 and A2780. These effects are seen at a readily achievable concentration of 0.1 μM *in vitro* (Patel *et al.*, 2012). In view of the activity of PARP inhibitors in ovarian cancer and their ability as a class to synergize with topoisomerase poisons (see above), the present trial will assess the effect of combining ABT-888 with the less myelosuppressive weekly schedule of topotecan.

1.5 Results from the Phase 1 Dose Escalation Portion of MC0861

The goal of the phase 1 dose escalation portion of this clinical trial was to determine the MTD of the combination of ABT-888 and weekly topotecan in adult patients with

advanced solid tumors as well as to identify any pharmacokinetic interactions between ABT-888 and topotecan. 58 patients were enrolled between November 3, 2009 and February 9, 2015.

1.5.1 MTD

Dose-limiting toxicity, consisting of grade 4 neutropenia lasting > 5 days, was observed in 2 of 3 patients at dose level 13 and 1 of 6 patients at dose level 12. Accordingly, the MTD was dose level 12, i.e., ABT-888 at 300 mg twice daily by mouth on days 1-3, 8-10 and 15-17 along with topotecan 3 mg/m^2 intravenously on days 2, 9 and 16. Six patients were replaced due to adverse events or refusal but toxicity information was entered. One patient enrolled but was replaced before receiving any treatment. Therefore, there were 57 evaluable patients.

1.5.2 Toxicities

For cycle 1, the only grade 4 toxicities at least possibly related to treatment in the study were cytopenias (neutropenia in 11 patients, thrombocytopenia in 3 patients and leukopenia in 2 patients) and one febrile neutropenia. For all cycles, the most common grade 3-4 toxicities at least possibly related to treatment were again hematologic and included neutropenia (23), thrombocytopenia (12) and leukopenia (19) as well as grade 3 fatigue (1), grade 3 nausea (1) and 1 patient with electrolyte derangements.

1.5.3 Time On Study

The numbers of cycles ranged from 1 to 26. One woman with uterine cancer remained on study for 26 cycles with PR as her best response. There were 10 women with ovarian cancer who remained on study for 6 or more cycles (up to 18 cycles). The mean number of cycles for all patients on study was 4.5 cycles.

1.5.4 Responses

22 patients had stable disease as best response with 9 patients having stable disease for 6 or more cycles and 3 with 9 or more cycles. One patient had a complete response and remained on study for 14 cycles before disease progression. Four patients had partial response as their best response. The objective response rate for the trial was 10%; and the clinical benefit rate is 42%with the inclusion of stable disease for at least 4 cycles (and up to 26 cycles).

1.6 Correlative Studies Overview and Rationale

1.6.1 Assessment of TPT and ABT-888 Pharmacokinetics

In order for ABT-888 to modulate the activity of topotecan, sufficient levels need to be achieved. Because topotecan and ABT-888 are both cleared in the kidney, there is the potential for pharmacological interaction between these agents. To provide essential information for determining whether ABT-888 levels are sufficient to modulate PARP activity (Palma *et al*., 2008) and rule out a pharmacological interaction, plasma pharmacokinetics of topotecan and ABT-888 will be measured.

1.6.2 Poly(ADP-ribose) polymer measurements

Analysis of poly (ADP-ribose) polymer in peripheral blood mononuclear cells (PBMCs) in the dose escalation portion of the phase 1 will be performed to permit confirmation that PARP1 has been inhibited by ABT-888 at the levels achieved. The hypotheses being tested are i) that plasma drug levels are lower in patients where polymer synthesis is not inhibited and ii) failure to inhibit polymer synthesis correlates with a poor response to the topotecan/ABT-888 therapy.

1.6.3 Assessment of BRCA1/2 Mutational Status in the Phase 2 Portion of this Trial.

Cells lacking BRCA1, BRCA2 and other homologous recombination (HR) repair proteins are hypersensitive to ABT-888 (Ashworth, 2008). Additional data indicate that cells lacking BRCA2 are also hypersensitive to topo I poisons (Marple *et al*, 2006; A. Patel *et al*, 2012) and are sensitized even further by ABT-888 (A. Patel *et al*, 2012). On the one hand, these results suggest that the combination might be particularly efficacious against HR-deficient tumors. On the other hand, these observations also raise the possibility that BRCA1 or BRCA2 haploinsufficiency might enhance the toxicities of TPT and ABT-888 in normal tissues of carriers. In view of reports that i) a fraction of BRCA1 mutations in ovarian cancer (as opposed to breast cancer) are somatic (Merajver, *et al.*, 1995), ii) many other HR genes are also disrupted at low frequency in familial or sporadic ovarian cancers (e.g., Walsh *et al.*, 2011) and iii) chemotherapy can induce BRCA2 secondary mutations that could affect subsequent therapeutic response (Edwards *et al.*, 2008; Sakai *et al.*, 2008), we propose to determine mutation status using tumor DNA from pretreatment biopsies, when available, and then sequence germline DNA of patients whose tumors are HR repair gene-mutant, if available. The hypotheses being tested are that i) patients bearing tumors with mutant BRCA1, BRCA2 or other HR repair genes have a higher response rate to the topotecan/ABT-888 therapy and/or ii) patients with germline BRCA1/BRCA2/HR gene mutations experience more toxicity with this regimen.

1.6.4 Expression of polypeptides Affecting Efficacy of the TPT/ABT-888 Combination in the Phase 2 Portion of the trial.

The polypeptides include topo I, PARP1, XRCC1, TDP1, BRCA1, BRCA2, BCRP and P-glycoprotein.

Because variations in levels of each of these polypeptides have been implicated in sensitivity to TPT or ABT-888, relative levels of these polypeptides in cancer cells will be evaluated by IHC using formalin-fixed pretreatment tumor biopsies, if available. In particular, if all other factors were equal, we know that response might be affected by levels of:

- Topo I—cells expressing more topo I are more sensitive to topo I poisons (Madden and Champoux 1992; Hann *et al.*, 1998); and higher topo I levels predicted a more favorable outcome in our recent TPT/carboplatin/cyclophosphamide phase I trial (Litzow *et al*., 2008).

- PARP1-on the one hand, it has been reported that high PARP1 levels are associated with a poor outcome in serous ovarian cancers (Brustmann, 2007). On the other hand, preliminary data from the Kaufmann lab (Patel *et al*, 2012) suggest that cells expressing more PARP1 are more likely to be sensitized to TPT by ABT-888.

- BRCA1 and BRCA2— previous results not only indicate that cells lacking functional BRCA1 or BRCA2 are inhibited by PARP inhibitors (Bryant, et al, 2005; Farmer *et al*., 2005), but also suggest that lack of functional BRCA1 or BRCA2 confers hypersensitivity to topo I poisons such as topotecan (Marple *et al*., 2006; S. Kaufmann, unpublished observations). In addition, it has been suggested that a substantial fraction of ovarian cancers have functional inactivation of the BRCA1/BRCA2 pathway despite the lack of mutations (Turner *et al*., 2004). To complement the sequence analysis described above, we will also stain biopsies for BRCA1 and BRCA2 to assess expression at the protein level. This assay will detect tumors with diminished BRCA1 or BRCA2 as a consequence of gene methylation or other epigenetic changes.

- XRCC1 and TDP1—Previous reports (Smith *et al*., 2005; A Patel, unpublished observations) indicate that XRCC1-deficient cells are hypersensitive to TPT; and the same hypersensitivity to topo I poisons is expected in TDP1 deficient cells (Pouliot *et al.*, 1999).

- BCRP and P-glycoprotein—previous data from the Kaufmann laboratory (Hendricks *et al.*, 1992; Erlichman *et al.*, 2001) and others (Chen *et al.*, 1991; Rasheed and Rubin, 2003) have demonstrated that P-glycoprotein and BCRP modestly affect TPT accumulation and cytotoxicity.

Thus, the hypotheses being tested with the immunohistochemical assays are that response to therapy during the phase II portion of this trial will correlate with high

topo I content, high PARP content, low BRCA1 or BRCA2 expression, low XRCC1, low TDP1, low BCRP or low P-glycoprotein.

1.6.5 Transcriptional Profiling of Pretreatment Biopsies from Phase 2 Portion of this Trial

To complement the examination of candidate proteins that might correlate with response, we will also extract RNA from snap frozen aliquots of pretreatment biopsies, if available, and determine whether there is a transcriptional signature that correlates with outcome on this trial. The hypothesis to be tested (if the regimen appears promising) is that response to therapy correlates with a particular mRNA profile.

Collectively these assays are designed to not only confirm that ABT-888 is able to decrease TPT-induced poly (ADP-ribose) polymer synthesis in PBMCs (phase 1 portion) but also examine features of the tumor cells that might predict response to this combination.

2.0 Goals

2.1 Phase 1

2.1.1 To determine the maximum tolerated dose of the combination of ABT-888 and weekly topotecan in adult patients with advanced solid tumors.

2.1.2 To identify any anti-tumor activity of this treatment combination, as assessed by objective response in patients with advanced solid tumors.

2.2 Phase 1 Correlative Goals

2.2.1 To identify any pharmacokinetic interactions between ABT-888 and topotecan.

2.2.2 To determine whether topotecan stimulates ADP-ribose polymer formation in circulating peripheral blood mononuclear cells.

2.2.3 To determine whether ABT-888 inhibits basal or topotecan-stimulated ADP-ribose polymer formation.

2.3 Phase 2

2.3.1 Primary endpoint: To assess the confirmed response rate for patients with epithelial ovarian cancer, fallopian tube cancer or primary peritoneal carcinoma treated with the combination of ABT-888 and weekly topotecan.

2.3.2 Secondary endpoint: To assess the progression free response (PFS) for patients with epithelial ovarian cancer, fallopian tube cancer or primary peritoneal carcinoma treated with the combination of ABT-888 and weekly topotecan.

2.4 Phase 2 Correlative Goals

2.4.1 To assess differences in the toxicity and/or efficacy of this regimen based on BRCA1/2 mutational status

2.4.2 To determine whether pretreatment tumor cell levels of topoisomerase I, PARP, BRCA1, BRCA2, XRCC1, TDP1, P-glycoprotein or BCRP predict response to this regimen.

2.4.3 To identify, in an exploratory manner, any transcriptional profiles that may predict response to this regimen.

3.0 Patient Eligibility

Phase 1 Only: Prior to checking eligibility, contact the Mayo Clinic Registration Office at (507) 284-2753 for study status and dose level.

3.1 Inclusion Criteria

3.1.1 Age ≥ 18 years.

3.1.2 Phase 1: Adult patients with histologically confirmed solid tumor malignancy that is metastatic or unresectable and for which standard curative measures or other therapy definitely capable of extending life expectancy does not exist.

Phase 2: All patients enrolled in the Phase 2 portion of this trial must have a history of biopsy-proven ovarian, fallopian tube or primary peritoneal cancer.

3.1.3 Patients must have received < 3 lines of prior therapy and have relapsed less than a year from their last platinum regimen. Regimens that are used twice (for example carboplatin and paclitaxel) can be counted as one. If a regimen is changed during the course of treatment due to side effect profile or allergy, the course of therapy is counted as one regimen. (For example, if docetaxel is substituted for paclitaxel due to a reaction during the initial course of adjuvant therapy, this is considered one regimen).

3.1.4 Patients must have measurable disease as defined in Section 11.0 with at least one lesion whose longest diameter can be accurately measured as ≥ 2.0 cm with conventional techniques or as ≥ 1.0 cm with spiral CT. If spiral CT is used, it must be used for both pre- and post- treatment tumor assessments.

3.1.5 The following laboratory values obtained ≤ 7 days prior to registration:

- Absolute neutrophil count ≥ 1500/mcL
- Hemoglobin ≥ 9.0 g/dL
- Platelets ≥ 100,000/mcL
- Total bilirubin ≤ 1.5 x the upper limit of normal (ULN)
- SGPT (ALT) or SGOT (AST) ≤ 2.5 x ULN in the absence of hepatic metastasis. SGPT (ALT) ≤ 3 x ULN or SGOT (AST) ≤ 5 x ULN in the presences of hepatic metastasis
- Creatinine ≤ 1.5 x ULN
- INR ≤ 1.4 unless receiving therapeutic doses of coumadin
- PTT ≤ 48 seconds (1.25 x ULN)

3.1.6 ECOG Performance Status (PS) 0, 1, or 2. (See Appendix I).

3.1.7 Ability to provide informed consent.

3.1.8 Willingness to return to enrolling institution for follow-up.

3.1.9 Life expectancy ≥ 12 weeks.

3.1.10 Correlative Research

Willingness to provide the biologic specimens is required by the protocol. This is part of the mandatory correlative research component. (See Sections 6.9a and 14.0). These specimens include:

- Phase 1: Peripheral blood for plasma pharmacokinetic analysis and PBMC polymer assessment from 0-24 h after drug administration on days 1 and 2 of cycle 1 as well as day 2 of cycle 2; urine for assessment of ABT-888 renal clearance for 24 h after administration of drugs on days 1 and 2 of cycle 1 as well as day 2 of cycle 2; and a pretreatment peripheral blood sample for <u>possible</u> sequencing of the BRCA1, BRCA2 loci as well as possible pharmacogenomic analysis (see Section 14 for further information).

3.1.11 Negative urine or serum pregnancy test done ≤ 7 days prior to registration for females of child bearing potential only.

3.1.12 Able to swallow and absorb the medication

3.2 Exclusion Criteria

3.2.1 Known standard therapy for the patient's disease that is potentially curative or definitely capable of extending life expectancy.

3.2.2 Prior treatment with a PARP inhibitor or topotecan

3.2.3 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.4 Any of the following prior therapies:

- Chemotherapy ≤ 4 weeks prior to registration
- Mitomycin C/nitrosoureas ≤ 6 weeks prior to registration
- Immunotherapy ≤ 4 weeks prior to registration
- Biologic therapy ≤ 4 weeks prior to registration
- Radiation therapy ≤ 4 weeks prior to registration
- Radiation to > 25% of bone marrow
- Investigational therapy or any ancillary therapy considered investigational (utilized for a non-FDA-approved indication and in the context of a research investigation) ≤ 4 weeks prior to registration. Subjects with prostate cancer will be permitted to continue hormone therapy

3.2.5 Failure to fully recover from acute, reversible effects of prior chemotherapy regardless of interval since last treatment.

3.2.6 New York Heart Association classification III or IV (See Appendix II).

3.2.7 Known CNS metastases or seizure disorder. Patients with known brain metastases that have been successfully treated and stable for ≥ 6 months without requirement for corticosteroids and without seizure activity will be eligible.

3.2.8 Any of the following, because this study involves both ABT-888, an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown, and topotecan, an agent that has known genotoxic, mutagenic and teratogenic effects:

- Pregnant women

- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.2.9 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.2.10 Immunocompromised patients (other than that related to the use of corticosteroids) including patients known to be HIV positive.

3.2.11 Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

3.2.12 Other active malignancy, except non-melanotic skin cancer or carcinoma-in-situ of the cervix. **Note:** If there is a history of prior malignancy, they must not be receiving other specific treatment (other than hormonal therapy) for their cancer.

3.2.13 History of myocardial infarction ≤ 6 months, or congestive heart failure requiring use of ongoing maintenance therapy for life-threatening ventricular arrhythmias.

3.2.14 More than 2 prior chemotherapy regimens for the current malignancy. Full dose chemotherapy used in conjunction with concurrent radiation therapy will be included as prior therapy. **Note:** Prior hormonal therapy (e.g. leuprolide, aromatase inhibitors, and tamoxifen) and immunotherapy will be allowed and not included as a prior chemotherapy. If the chemotherapy regimen is altered during the course due to issues with tolerability or safety, the regimen will be counted as one. Using the same regimen at recurrence is counted as one regimen. The addition of bevacizumab to a prior regimen is considered one regimen.

4.0 Test Schedule

	Active Monitoring Phase				
Tests and procedures	≤ 21 days prior to registration	≤ 7 days prior to registration	During treatment	During interval between treatment	Prior to subsequent cycles
History and Physical Exam including weight and Performance Status (PS)		X			X
Height		X			
Adverse Event Assessment		X			X
Hematology[1]		X		Weekly	X
Chemistry[2]		X			X
Urine or serum pregnancy test[3]		X			
INR and PTT		X			
Chest X-ray[4]	X				
Phase 2 only: CA-125	X				X[5]
Tumor Measurement (CT, MRI imaging)	X				X[5]
Phase 1 only: Mandatory research blood specimens[R] (see Section 14.0)			X		
Phase 2 only: Optional research blood specimens[R] (see Section 14.0)	X				
Pharmacogenetics[R]	X				
Phase 1 only: Pharmacokinetics[R]			X		
Phase 2 only: Optional tissue specimen[R] (see Section 17.0)	X				

Footnotes for Section 4.0 Test Schedule appear on the following page

Footnotes for Section 4.0:

1. Hematology group includes total WBC (leukocytes), absolute neutrophil count (ANC), hemoglobin and platelets.

2. Chemistry group includes electrolytes, total bilirubin, creatinine, alkaline phosphatase, SGOT (AST) and SGPT (ALT).

3. For females who are of child bearing potential only.

4. A chest X-ray is not required if a chest CT was performed.

5. CT or MRI imaging and CA-125 to be performed after the completion of even cycles of therapy. Please use the same imaging modality throughout the study.

R. Research funded.

5.0 Grouping Factor

Grouping Factor: Phase 1 (Dose Escalation) vs. Phase 2.

6. Registration Procedures

6.1 Investigator and Research Associate Registration with CTEP

6.1.1 CTEP 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 about Investigator Registration, please contact the ***CTEP Investigator Registration Help Desk*** by email at pmbregpend@ctep.nci.nih.gov.

6.1.2 CTEP Associate Registration Procedures / CTEP-IAM Account

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 is required to access all CTEP applications and, if applicable (*e.g.*, all Network trials), all Cancer Trials Support Unit (CTSU) applications and websites.

Additional information can be found on the CTEP website at http://ctep.cancer.gov/branches/pmb/associate_registration.htm.

For questions about Associate Registration or CTEP-IAM Account Creation, please contact the ***CTEP Associate Registration Help Desk*** by email at ctepreghelp@ctep.nci.nih.gov.

6.2 Site Registration

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

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. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to: an active Federal Wide Assurance (FWA) number, an active roster affiliation with the Lead Network or a participating organization, a valid IRB approval, and compliance with all protocol specific requirements.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then

communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

6.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the *8329* protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP-IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select *LAO-MN026*, and protocol *#8329.*
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

6.2.2 Requirements For 8329 Site Registration

- CTSU Transmittal Sheet (optional)
- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

6.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

ONLINE: www.ctsu.org (members' section) → Regulatory Submission Portal
(Note: The use of the Regulatory Submission Portal will become **mandatory** in early 2017.)
EMAIL: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)
FAX: 215-569-0206
MAIL: CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

6.2.4 Checking **Site** Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- 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

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

6.3 Patient Registration

6.3.1 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

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

6.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar.
- To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- Have regulatory approval for the conduct of the study at their site.

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

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

6.3.3 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

6.4 General Guidelines

Following registration, patients should begin protocol treatment within 7 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

7.0 Protocol Treatment

7.1 Treatment Schedule
Use actual weight or estimated dry weight if fluid retention for Topotecan. Treatment will be administered on an outpatient basis.

Note: The Phase 1 Dose Escalation part of the study is completed; the phase 2 MTD part of the study is open.

Phase 1:

Agent	Dose	Route	Day	Retreatment
ABT-888*	As assigned by the registration office	Oral	Days 1, 2, 3, 8, 9, 10, 15, 16, 17	Every 28 days
Topotecan**		Intravenous	Days 2, 9, 16	

** Topotecan administered over 30 minutes

Phase 1 Cycle 2 only*

Agent	Dose	Route	Day
ABT-888	MTD Determined by Phase 1 Dose Escalation	Oral	Days 8, 9, 10, 15, 16, 17
Topotecan**		Intravenous	Days 2, 9, 16

** Topotecan administered over 30 minutes

Phase 2 (Phase 2 studies at MTD): **MTD has been established at Dose Level 12.**

Agent	Dose	Route	Day	Retreatment
ABT-888	300 mg PO twice daily	Oral	Days, 1, 2, 3, 8, 9, 10, 15, 16, 17	Every 28 days
Topotecan**	3 mg/m^2	Intravenous	Days 2, 9, 16	

** Topotecan administered over 30 minutes

7.2 Pretreatment Medication

Premedications will not be used routinely for this protocol. Anti-emetics will be provided on an as needed basis. For patients who do experience nausea and/or emesis, prophylactic use of a 5-HT_3 antagonist (e.g., ondansetron) and/or other agents with anti-emetic properties (phenothiazines, steroids, benzodiazepines) will be permitted.

7.1.2 Treatment Administration

ABT-888 is to be taken by mouth twice a day with or without meals. The patient will be given a patient diary and to return the diary at each clinic visit. (Appendix III). Patients will also be given a patient drug information handout and wallet card for the potential drug interactions (Appendix V). Topotecan will be given via intravenously over 30 minutes on days 2, 9 and 16 of every 28-day cycle.

Note: The Phase 1 Dose Escalation part of the study is completed; the phase 2 MTD part of the study is open

7.3 Dose Escalation (Phase 1)

Dose Level	ABT-888** (mg twice daily)	Topotecan (mg/m$^{2)}$
-2	10	1.0
-1	10	1.5
-1a	20	1.5
1*	10	2
2	20	2
2a	10	2.5
3	10	3
4	20	3
5	20	4
6	30	4
7	30	3
8	50	3
9	100	3
10	150	3
11	200	3

12 (**MTD)**	300	3
13	400	3

*Starting Dose
**See Section 7.26 for Dose de-escalation instructions.

7.3.1 Evaluation at Enrolling Institution
For this protocol, the patient must return to the enrolling institution for evaluation at least every 4 weeks.

7.3.2 Dose Levels
Three patients will be treated at each dose level and observed for a minimum of 4 weeks (i.e. one full cycle) before new patients are treated. Doses will not be escalated in any individual patient.

7.3.3 Definition of DLT
For this protocol, dose-limiting toxicity (DLT) will be defined as a cycle 1 adverse event attributed (definitely, probably, or possibly) to the study treatment and meeting the following criteria:

Toxicity	DLT Definition
Blood and lymphatic system disorders	Grade 4 anemia: Life-threatening consequences; urgent intervention indicated
Investigations	Grade 4 neutrophil count decrease: ANC < 500 (≥ 5 days)
	Grade 4 platelet count decrease: < 25,000
	Creatinine increased: Serum creatinine ≥ 2 times baseline or ≥ 2 times the upper limit of normal if baseline is < the upper limit of normal
Other non-hematologic	≥ Grade 3 as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0**

* ≥ Grade 3 nausea, vomiting, or diarrhea with maximal supportive treatment(s) will be considered dose-limiting. Grade 3 fatigue or anorexia will not be considered dose limiting.

7.3.4 MTD Determination

7.3.4.1 MTD is defined as the dose level below the lowest dose that induces dose-limiting toxicity in at least one-third of patients (at least 2 of a

maximum of 6 new patients). A total of 6 patients treated at the MTD will be sufficient to identify common toxicities at the MTD. For instance, those toxicities with an incidence of at least 25% will be observed with a probability of at least 82 % (1-(1-0.25).

7.3.4.2 Three patients will be treated at a given dose level combination and observed for at least 4 weeks to assess toxicity.

7.3.4.3 If dose-limiting toxicity (DLT) is not seen in any of the 3 patients, 3 new patients will be accrued and treated at the next higher dose level. If DLT is seen in 2 or 3 of 3 patients treated at a given dose level, then the next 3 patients will be treated at the next lower dose level, if only 3 patients were enrolled and treated at this lower dose level.

7.3.4.4 If DLT is seen in 1 of 3 patients treated at a given dose level, up to 3 additional patients will be enrolled and treated at the same dose level. If DLT is seen in at least one of these additional three patients ($\geq$ 2 of 6), the MTD will have been exceeded, and further accrual will cease to this cohort (see 7.55 for further details). If potentially dose-limiting toxicity (DLT) is not seen in any of the three additional patients, 3 new patients will be accrued and treated at the next higher dose level.

7.3.4.5 After enrolling 6 patients on a specific dose level, if DLT is observed in at least 2 of 6 patients, then the MTD will have been exceeded and defined as the previous dose unless only 3 patients were treated at the lower dose level. In that case, 3 additional patients will be treated at this lower dose level.

7.3.5 Dose De-Escalation

If dose-limiting toxicity is seen at dose level 1, patients will be entered at a dose level of -1. If no dose-limiting toxicity is seen at this dose, further patients will be accrued at the dose level of 1.

If dose de-escalation is required at dose level 2, the dose will be reduced to level -1a instead of dose level -1 (see section 7.2).

7.3.6 Unable to Complete Initial therapy

If a patient fails to complete the initial course of therapy (defined as drug administration and 4 weeks observation) for reasons other than toxicity, the patient will be regarded as uninformative with respect to the goals of the study treatment and an additional patient

will be treated at the current dose level; however, all toxicity information will be utilized in the analysis.

7.3.7 Missed Does of Topotecan

If a patient misses 2 doses of topotecan for grade 3 neutropenia or thrombocytopenia, the patient will be regarded as treatment intolerant and an additional patient will be treated at the current dose level. However, all toxicity information will be utilized in the analysis.

In the dose expansion cohort and phase 2 portion of this trial, ABT-888 and topotecan will be administered at the same dose and schedule as the MTD determined during the phase I portion of the study. This dose has been established at Dose Level 12 (300 mg twice a day of ABT-888 and 3 mg/m^2 topotecan per schedule as described in Section 7.1)

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table until individual treatment tolerance can be ascertained. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Dose modifications apply to the treatment given in the preceding cycle and are based on adverse events observed since the prior dose. Omitted doses will not be made up.

ALERT: *ADR reporting may be required for some adverse events. See Section 10.*

Note: The Phase 1 Dose Escalation part of the study is completed; the phase 2 MTD part of the study is open

Phase 1

BASED ON INTERVAL ADVERSE EVENTS			
CTCAE CATEGORY	**ADVERSE EVENT**	**AGENTS**	**DOSE MODIFICATIONS***
Investigations	Neutrophil count decreased < 500 and/or Platelet count decreased < 25, 000	ABT-888 and Topotecan	Omit therapy until neutrophil ≥ 1500 and/or platelets ≥ 100,000, and decrease topotecan dose only by 2 dose levels (if dose level 1, decrease by 1 dose level); treatment will be discontinued if toxicity persists beyond 14 days.

	Neutrophil count decreased 500 - 1000 and/or Platelet count decreased 25,000 – 50,000		Omit therapy until neutrophils ≥ 1500 and/or platelets ≥ 100,000, and decrease topotecan dose only by 1 dose level; treatment will be discontinued if toxicity persists beyond 14 days.
Other	Non-hematologic Grade 3 or 4	ABT-888 and Topotecan	Omit therapy until severity decreases to grade 0-1 and decrease topotecan dose only by one level; treatment will be discontinued if toxicity persists beyond 14 days.

AT SCHEDULED RETREATMENT (Day 1)			
Investigations	Neutrophil count decreased < 500 and/or Platelet count decreased < 25, 000	ABT-888 and Topotecan	Hold therapy (up to 14 days) until neutrophils ≥ 1500 and/or platelets ≥ 100,000, and decrease topotecan dose only by 2 dose levels (if dose level 1, decrease, by one dose level; treatment will be discontinued if toxicity persists beyond 14 days.
	Neutrophil count decreased 500 - 1000 and/or Platelet count decreased 25,000 – 50,000		Hold therapy (up to 14 days) until neutrophils ≥1500 and/or platelets ≥ 100,000, and decrease topotecan dose by 1 dose level; treatment will be discontinued if toxicity persists beyond 14 days.
Other	Non-hematologic Grade 3 or 4	ABT-888 and Topotecan	Hold therapy (up to 14 days) until severity decreases to grade 0-1 and decrease topotecan dose only by one level; treatment will be discontinued if toxicity persists beyond 14 days

*** Topotecan should be reduced to the next lower dosage.**

Phase 2

BASED ON INTERVAL ADVERSE EVENTS			
CTCAE CATEGORY	**ADVERSE EVENT**	**AGENTS**	**DOSE MODIFICATIONS***
Investigations	Neutrophil count decreased < 500 and/or Platelet count decreased < 25, 000	ABT-888 and Topotecan	Omit therapy until neutrophils ≥ 1500 and/or platelets ≥ 100,000, and decrease topotecan dose to 2 mg/m^2 . Decrease the ABT-888 to 200 mg twice daily at second occurrence and to 150 mg twice daily at third occurrence. Treatment will be discontinued if toxicity persists beyond 14 days.
	Neutrophil count decreased 500 - 1000 and/or Platelet count decreased 25,000 – 50,000		Omit therapy until neutrophils ≥ 1500 and/or platelets ≥ 100,000, and decrease topotecan dose only to 2.5 mg/m^2 Decrease the topotecan to 2 mg/m^2 at second occurrence and decrease ABT-888 to 200 mg twice daily at third occurrence. Treatment will be discontinued if toxicity persists beyond 14 days.
Other	Non-hematologic Grade 3 or 4	ABT-888 and Topotecan	Omit therapy until severity decreases to grade 0-1 and decrease topotecan dose only to 2.5 mg/m^2 ; treatment will be discontinued if toxicity persists beyond 14 days. Dose modification of ABT-888 is left to physician discretion (consider the dose reductions as per hematologic toxicities).

If dose limiting toxicities persist beyond three dose reductions, consider discontinuation of the study unless evidence of stable disease or disease response.

Phase 2

AT SCHEDULED RETREATMENT (day 1)			
CTCAE CATEGORY	**ADVERSE EVENT**	**AGENTS**	**DOSE MODIFICATIONS***
Investigations	Neutrophil count decreased < 500 and/or Platelet count decreased < 25, 000	ABT-888 and Topotecan	Hold therapy (up to 14 days) until neutrophils ≥ 1500 and/or platelets ≥ 100,000, and decrease topotecan dose only to 2 mg/m^2; treatment will be discontinued if toxicity persists beyond 14 days. Decrease the ABT-888 to 200 mg twice daily at second occurrence and to 150 mg twice daily at third occurrence.
	Neutrophil count decreased 500 – 1000 and/or Platelet count decreased 25, 000 - 50,000		Hold therapy (up to 14 days) until neutrophils ≥ 1500 and/or platelets ≥ 100,000, and decrease topotecan dose only to 2.5 mg/m^2 Decrease the topotecan to 2 mg/m^2 at second occurrence and decrease ABT-888 to 200 mg twice daily at third occurrence. Treatment will be discontinued if toxicity persists beyond 14 days.
Other	Non-hematologic Grade 3 or 4		Hold therapy (up to 14 days) until severity decreases to grade 0-1 and decrease topotecan dose only to 2.5 mg/m^2 ; treatment will be discontinued if toxicity persists beyond 14 days. Dose modification of ABT-888 is left to physician discretion (consider the dose reductions as per hematologic toxicities).

If dose limiting hematologic toxicities persist beyond three dose reductions, consider discontinuation of the study unless evidence of stable disease or disease response.

9.0 Ancillary Treatment/Supportive Care

9.1 Colony Stimulating Factors

Routine use of colony-stimulating factors (G-CSF or GM-CSF) is not recommended. Prophylactic use of colony-stimulating factors during the study is not allowed during cycle one of therapy; prophylactic use may be employed, at physician discretion, if a patient has developed grade 3 or 4 neutropenia during a previous cycle. Therapeutic use in patients with serious neutropenic complications such as tissue infection, sepsis syndrome, fungal infection, etc., may be considered at physician discretion. Recombinant erythropoietin to maintain adequate hemoglobin levels and packed red blood cell transfusions are allowed.

9.2 Full Supportive Care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and anti-emetics received from the first administration of study drugs until 30 days after the final dose are to be recorded in the medical record.

9.3 Concurrent Enrollment on Any Other Therapeutic Study

Patients participating in this clinical trial are not to be considered for concurrent enrollment in any other study involving a pharmacologic agent (drugs, biologics, immunotherapy approaches, gene therapy) whether for symptom control or therapeutic intent.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Common Terminology Criteria

This study will utilize the Common Terminology Criteria for Adverse Events (v4.0) for adverse event (AE) monitoring and reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. The CTCAE version 4.0 can be accessed from the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.).

10.1.1 Adverse Event Monitoring

Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE. Next, determine whether the event is expected or unexpected (as reflected with the CTEP Agent Specific Adverse Event List [ASAEL], see Sections 10.12 and 15.0) and if the adverse event is related to the medical treatment or procedure (see Section 10.13). With this information, determine whether an adverse event should be reported as an expedited report (see Section 10.2) in addition to the routinely reported clinical data (see Sections 10.3 and 18.0).

Expedited adverse event reporting under a CTEP Investigational New Drug Application (IND) requires submission of a CTEP Adverse Event Reporting System (CTEP-AERS) report(s). Other expedited reporting requirements and systems may also apply. Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.2 and 10.3.

10.1.2 Expected vs. Unexpected Events

Agents provided under a CTEP IND:

- Expected AEs for expedited reporting purposes are listed on the ASAEL. The ASAEL is a component of the Comprehensive Adverse Events and Potential Risks List (CAEPR). Refer to Section 15.0 of this protocol to locate the CAEPR for the CTEP IND agent(s).

- Unexpected AEs are those not listed in the ASAEL.

Non-CTEP IND agents:

- The determination of whether an AE is expected for commercial agents is based on agent-specific adverse event information provided in Section 15.0 of the protocol.

- Unexpected AEs for commercial agents are those not listed in the agent-specific adverse event information provided in Section 15.0 of the protocol.

10.2 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the investigational agent(s).
Probable - The adverse event is likely related to the investigational agent(s).
Possible - The adverse event may be related to the investigational agent(s).
Unlikely - The adverse event is doubtfully related to the investigational agent(s).
Unrelated - The adverse event is clearly NOT related to the investigational agent(s).

Additional instructions for trials that include both investigational agent(s) (those under an IND) and a commercial agent(s):

When an investigational agent (an agent under an IND) is used in combination with a commercial agent(s) <u>on the same treatment arm</u>, the combination is considered investigational. Expedited reporting will follow the requirements for investigational agents. However, if the event occurs prior to the participant having received any

investigational agent, expedited reporting may follow the requirements for commercial agents.

10.3 Expedited Adverse Event Reporting Requirements

10.3.1 CTEP Expedited AE Investigational Agent Reporting Requirements

Phase 1 Trials Utilizing an Agent under a CTEP IND: CTEP-AERS Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	7 Calendar Days	Not Required	7 Calendar Days	Not Required	24-Hour; 3 Calendar Days
Possible Probable Definite	Not Required	7 Calendar Days	Not Required	24-Hour; 3 Calendar Days	24-Hour; 3 Calendar Days	7 Calendar Days	Not Required	24-Hour; 5 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**
CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:
- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 4 unexpected events
- Grade 5 expected events and unexpected events

[2] Although a CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

December 15, 2004

Note: All deaths on study must be reported using expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

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

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates

hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

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

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

- **SECONDARY MALIGNANCIES** (defined as "cancer caused by treatment for a previous malignancy", e.g., treatment with radiation or chemotherapy) are to be reported through CTEP-AERS, as noted in Section 10.22. Secondary malignancies are not considered metastasis of the initial neoplasm. Secondary malignancy is unrelated to the first cancer that was treated, and may occur months or even years after initial treatment.

  Note: Second Primary malignancy (malignancy **not** due to prior treatment) should not be reported through CTEP-AERS.

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements

In the rare event when Internet connectivity is disrupted, a 24 hour notification must be made to NCI by telephone. An electronic report must be submitted immediately upon establishment of internet re-connection. Refer to section 10.24 for NCI Contact Information or Technical Help regarding CTEP-AERS reporting.

Mayo Clinic Cancer Center (MCCC) Institutions: Fax copies of the UPIRTSO and cover sheet to the MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist at (507) 538-7164. The RAU will determine and complete IRB reporting and send to the MCCC SAE Coordinator.

10.3.2 Other Required Reporting

Event	REPORTING PROCEDURE
Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Reportable	Complete a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form electronically via the MCCC Remote Data Entry System within 5 working days of the date the clinical research associate (CRA) is aware of the event(s) necessitating the form. If CTEP-AERS or other expedited report has been submitted, this form does not need to be submitted.

10.3.3 Contact Information for NCI Safety Reports

Website for submitting expedited reports	https://webapps.ctep.nci.nih.gov/openapps/plsql/gctep-aersmain$.startup
CTEP-AERS MD Help Phone (for CTEP)*	301-897-7497 Monday through Friday, 7:00 AM to 7:00 PM (US Eastern Time)
CIP Help Phone for SAE reporting*	301-897-1704 Monday through Friday, 7:00 AM to 7:00 PM (US Eastern Time)
Fax for expedited report supporting Medical Documentation for CTEP trials	301-230-0159 (back-up FAX: 301-897-7404)
Fax for expedited report supporting Medical Documentation for CIP trials	301-897-7402
CTEP-AERS MD Help Email:	CTEP-AERSmd@tech-res.com
CIP SAE Reporting Email	CIPSAEReporting@tech-res.com
Technical (e.g., IT or computer issues ONLY) Help Phone*	1-888-283-7457 or 301-840-8202
CTEP-AERS Technical Help Email	ncictephelp@ctep.nci.nih.gov.
CTCAE v4 Help/Questions Email	ncictcaehelp@mail.nih.gov
CTEP-AERS FAQs link	https://webapps.ctep.nci.nih.gov/ctep-html/adr_faq.htm
CTEP-AERS Computer Based Training link	http://ctep.cancer.gov/reporting/ CTEP-AERS _CBT_v3/start.html

*Office phone and fax are accessible 24 hrs per day 7 days a week (The CTEP-AERS MD phone line is staffed from Monday through Friday, 7:00 AM to 7:00 PM ET. Any phone call after these hours will go to voicemail. Please leave contact information and the phone call will be returned the following business day.

10.4 Adverse Events to be Graded

Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 grading unless otherwise stated:

System Organ Class (SOC)	Adverse Event	Baseline	Each evaluation
Skin and subcutaneous tissue disorders	Alopecia	X	X
	Pruritus	X	X
	Rash maculo-papular	X	X
Blood and lymphatic system disorders	Anemia	X	X
Investigations	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
	White blood cell decreased	X	X
	Weight loss	X	X
	Creatinine increased	X	X
Gastrointestinal disorders	Nausea	X	X
	Vomiting	X	X
	Number of Stools per day	X	
	Diarrhea		X
	Constipation	X	X
Metabolism and nutrition disorders	Anorexia	X	X
	Dehydration	X	X
General disorders and administration site conditions	Gait disturbance	X	X
	Fatigue	X	X
Nervous system disorders	Tremor	X	X
	Seizure	X	X

10.4.1 Phase II only: Submit the following AEs experienced by a patient and not specified in Section 10.3:

10.4.1.1 Grade 1 and 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.4.1.2 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure

10.4.1.3 Grade 5 AEs (Deaths)

10.4.1.3.1 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure

10.4.1.3.2 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

11.0 Treatment Evaluation

For the purposes of this study, patients should be re-evaluated every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 8 weeks following initial documentation of objective response. Modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria will be used.

11.1 Definitions

11.1.1 Measurable disease: the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

11.1.2 Measurable lesions: lesions that can be accurately measured in at least one dimension with longest diameter > 20 mm. With spiral CT scan, lesion must be > 10 mm in at least one dimension.

11.1.3 Non-measurable lesions: all other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT) and other non-measurable lesions. These include: bone lesions; leptomeningeal disease; ascites; pleural /pericardial effusion; inflammatory breast disease; lymphangitis cutis/pulmonis; abdominal masses that are not confirmed and followed by imaging techniques; and cystic lesions.

11.2 Response Criteria

11.2.1 Evaluation of Target Lesions

A maximum of 3 measurable lesions should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable

dimension of the disease.

Complete Response (CR): Disappearance of all target lesions

Partial Response (PR): At least 30% decrease in the sum of the longest diameter (LD) of target lesion taking as reference the baseline sum LD.

Progression (PD): As least a 20% increase in the sum of LD of target lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD.

11.2.2 Evaluation of Non-Target Lesions

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as "present" or "absent."

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor maker level.

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

Progression (PD): Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions. Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair).

Note:

- If tumor markers are measured and are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

- Cytology and histology.
  If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

  These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

  The cytological confirmation of the neoplastic origin or any effusion

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

11.2.3 Evaluation of Best Overall Response

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	**CR**
CR	Non-CR/ Non-PD	No	**PR**
PR	Non-PD	No	**PR**
SD	Non-PD	No	**SD**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	Any	Yes	**PD**

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

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

11.3 Guidelines for Evaluation of Measurable Disease

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

Note: Tumor lesions in a previously irradiated area are not optimally considered measurable disease.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

- **Clinical lesions** will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

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

- Conventional **CT and MRI** should be performed with cuts of 10mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen, and pelvis. Head and neck and extremities usually require specific protocols.

11.4 Duration of Response

11.4.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks.

11.4.2 Duration of Overall Response

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

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

11.4.3 Duration of Stable Disease

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

12.0 Descriptive Factors

12.1 Number of Prior Chemotherapy Regimens

12.2 Dose Level
(Phase 1 only): To be assigned by Registration Office): -2 vs. -1 vs. 1 vs. 2 vs. 3 vs. 4 vs. 5 vs. 6 vs. 7 vs. 8 vs. 9 vs. 10 vs. 11 vs. 12 vs. 13

12.3 BRCA Status
Mutated vs. normal

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 No Progressive Disease (PD)
Patients who have not had PD at time of their reassessment and have not experienced intolerable toxicity will be allowed to continue protocol treatment at the same dose level until PD.

13.2 No PD, Unacceptable Toxicity
Those patients who have not had PD but have experienced unacceptable toxicity may be eligible for retreatment at a lower dose (see Section 8.0).

13.3 Progressive Disease / Refuse Further Treatment
Those patients with PD or who refuse further treatment will go off treatment and will be followed for the purpose of this study as described in Section 18.0.

13.4 Off Protocol Treatment
Patients who go off protocol treatment for reasons other than PD will be followed for the purpose of this study as described in section 18.0.

13.5 Cohort 1 Dose Escalation
If a patient enrolled to Cohort 1 dose escalation part of the study fails to complete the initial course of therapy (defined as drug administration and 4 weeks observation) for reasons other than dose-limiting toxicity defined adverse events, the patient will be regarded as uninformative in regard to the primary study goal and an additional patient will be treated at the current dose level; however, all toxicity information will be utilized in the analysis.

13.6 Major Violation
A patient is deemed a major violation, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study (Phase

2) or 3 months of follow-up (Phase 1). The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered.

13.7 Ineligible

A patient is deemed ineligible if after registration, it is determined that the patient did not satisfy each and every eligibility criteria for study entry.

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Follow-up will be required per Section 18.0 of the protocol (Phase 1 dose escalation and MTD, and Phase 2 patients).
- If the patient never received treatment,
    - Phase 1 MTD and Phase 2 patients only: on-study material must be submitted. No further data submission is necessary.
    - Phase 1 dose escalation patients: refer to section 13.5 for patient replacement if possible. On-study material must be submitted. No further data submission is necessary

13.8 Cancel

A patient is deemed a cancel if he/she is removed from the study for any reason before any study treatment is given. Phase 1 patients will be replaced at that dose level and no further data submission is necessary. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted for all patients. No further data submission is necessary.

14.0 Body Fluid Biospecimens

NOTE: Patients must have consented to submission of the biospecimen(s) listed in the following table. Label all specimens with protocol number, patient initials, patient study number, date of birth, collection date, visit and timepoint.

14.1 Summary Table of Mandatory Biospecimens for This Protocol

Note: The Phase 1 Dose Escalation part of the study is completed; the phase 2 MTD part of the study is open.

Phase 1 Dose Escalation only

Correlative Study	Optional or Mandatory	Type of Sample Collected	Volume of Sample Collected	Timepoints to collect	Shipping and Storage Conditions
Pharmacogenetics (Section 14.21)	Mandatory	Whole Blood, EDTA purple top tube	One 10 mL tube	Baseline	Refrigerate/ Cold Pack (Section 14.31)
Possible BRCA1 and BRCA2 sequencing (Section 14.21)	Mandatory	Whole Blood, EDTA purple top tube	One 10 mL tube	Baseline	Refrigerate/ Cold Pack (Section 14.31)
PBMCs (Section 14.22)	Mandatory	Whole Blood, CPT tube	One 10 mL tube	Multiple timepoints (See Section 14.42)[1]	Ambient; (Section 14.32)

1 Timepoints to collect are at 0, 2, 4 and 8 h after ABT-888 administration on C1D1 and C1D2; and at 0, 2, 4 and 8 h after start of topotecan infusion on C2D2.

Phase 2

Correlative Study	Optional or Mandatory	Type of Sample Collected	Volume of Sample Collected	Timepoints to collect	Shipping and Storage Conditions
Pharmacogenetics (Section 14.21)	Mandatory	Whole Blood, EDTA purple top tube	One 10 mL tube	Baseline	Refrigerate/ Cold Pack (Section 14.31)
Possible BRCA1 and BRCA2 sequencing[1] (Section 14.21)	Optional	Whole Blood, EDTA purple top tube	One 10 mL tube	Baseline	Refrigerate/ Cold Pack (Section 14.31)

1 If patient has had germline BRCA testing done by Myriad Laboratories, and the results are available for review, repeat germline BRCA testing will not be repeated. If germline BRCA testing was done by other organizations, a genetic consultation report from a qualified medical profession confirming that the laboratory results should be recognized germ line deleterious BRCA1 or BRCA2 mutation or BRCA rearrangement is required to confirm the result.

14.2 Specimen Collection and Processing

Collect blood specimens as indicated in the following sections of 14.2.

Ship specimens Monday – Thursday ONLY. Do not send samples on weekends or holidays.

The listed laboratories will process samples per Section 14.3.

14.21 Pharmacogenetic and BRCA Sequencing Specimens

One 10 mL EDTA whole blood specimen will be collected prior to treatment. Only one 10 ml tube in total is needed per patient.

Whole bloodc specimens should be kept refrigerated and shipped with cold pack (do not freeze) the same day to:

Mayo Clinic
BAP Freezer
Attn: BAP Supervisor
150 Third Street SW
Stabile SL-39

Rochester, MN 55902

14.22 Peripheral Blood Mononuclear Cells (PBMCs) ***Phase 1 only***

One 10 mL CPT whole blood specimen will be collected at the following time points:

- **Cycle 1 Day 1:** Draw blood at 0, 2, 4 and 8 hours after ABT-888.
- **Cycle 1 Day 2:** Draw blood at 0, 2, 4 and 8 hours after ABT-888.
- **Cycle 2 Day 2:** Draw blood at 0, 2, 4 and 8 hours after start of topotecan infusion.

Thus, 12 samples will be collected for a total of 120 ml.

Blood should be cooled to room temperature and delivered to the Kaufmann laboratory (Gonda 19-205B, Mayo Clinic Rochester), where peripheral blood mononuclear cells will be handled as specified by CTEP.

Peripheral Blood Mononuclear Cell Specimens should shipped ambient on the same day as collected to:

Mayo Clinic
Attn: [redacted]
221 4th Ave SW
Gonda 19-205B
Rochester, MN 55905

14.23 Pharmacokinetic Specimens (Blood; ***Phase 1 Only***)

10 mL aliquots of heparinized whole blood will be collected at the following time points:

For ABT-888: On C1D1 and C1D2, prior to ABT-888 administration and at 15 minutes, 30 minutes and 1, 2, 4, 6, 9 hours following administration.

For Topotecan: On C1D1 and C1D2, prior to topotecan infusion; 15 and 30 minutes after start of infusion and 15 minutes, 30 minutes, 1, 1.5, 3.5, 5.5 and 8.5 hours after the end of the infusion.

Blood samples will be collected in heparinized tubes and immediately cooled in an ice water bath. Within 20 min of collection, blood will be delivered to the central laboratory to isolate plasma.

Blood will be subjected to centrifugation (2,000 rpm for 10 minutes) in a refrigerated centrifuge kept at 4°C. Following centrifugation, the plasma will be aliquoted into at least two samples (one for topotecan and one for ABT-888), transferred to polypropylene tubes, capped and immediately frozen at -70°C. Tube labels must contain the following data: patient identification code, date, and time elapsed after the oral dose (ABT-888) or after beginning of the 30–minute infusion (topotecan). These same data should be recorded in nurses' notes, on the flow sheet, and on the pharmacology reporting form that is to be sent with the samples.

Pharmacokinetic Specimens for each patient should be stored at -20°C. When all samples have been collected for each patient (ship each patient's samples together), frozen plasma samples should be shipped on dry ice to:

Mayo Clinic
Pharmacology Shared Resource
Attn: [redacted]
221 4th Avenue SW
Gonda 19-151
Rochester, MN 55905

14.3 Background/Methodology Information

Patient Considerations

All patients participating in the phase 1 study will be asked to provide blood samples during Cycle 1 and Cycle 2 of treatment. Patients participating in the phase 2 portion of the trial will be asked to provide blood samples during Cycle 1 of treatment. A heparin lock will be placed in the arm opposite the infusion device to facilitate this pharmacokinetic sampling.

14.3.1 Pharmacogenetics and Repair Gene Sequencing of Peripheral Blood Mononuclear Cell (PBMC) DNA

DNA extraction and storage of DNA for future assays, including possible sequencing of the BRCA1, BRCA2 and other repair gene loci (Section 1.6) as well as pharmacogenetic assays (e.g., for genetic polymorphisms such as breast cancer resistance protein ABCG2 that may correlate with efficacy and tolerability) will be performed at the conclusion of the trial. Dr. Elizabeth Swisher's laboratory at the University of Washington will initially apply Next Generation sequencing to sequence the loci encoding BRCA1, BRCA2 and other repair genes known or suspected to be mutated in ovarian cancer (Walsh *et al*., 2011) from biopsy samples (see below) and, if abnormal, will sequence the germline DNA as well. Genomic DNA, if analyzed, will be screened for mutations of the repair gene(s) found to mutated in the cancer. Remaining DNA

will be stored frozen by BAP, according to patient consent information (see Section 6.9) until specific analyses are identified. As protocols are developed, they will be presented for IRB review and approval.

14.3.2 Peripheral Blood Mononuclear Cells ***(Phase 1 Only)***

[redacted] laboratory will be evaluating the feasibility of monitoring poly(ADP-ribose) polymer in circulating peripheral blood mononuclear cells (phase I dose escalation portion of this study) to determine/follow the ability of ABT-888 to inhibit basal and topotecan-induced polymer formation.

In brief, PBMCs will be isolated using CPT tubes, washed with Plasma-LyteA 7.4, and quantitated on a hemocytometer. During the course of the phase I trial, replicate aliquots of cells will be

- snap frozen on liquid nitrogen for shipment to NCI for polymer measurement using a validated enzyme-linked immunoassay (Kinders *et al*., 2008);
- ii) snap frozen on liquid nitrogen for shipment to the [redacted] lab, where polymer measurement will be performed using the Standard Operating Procedure provided to phase 2 investigators by CTEP; and
- iii) immediately lysed in SDS sample buffer under reducing conditions

for shipment to the [redacted] lab, where polymer measurements will be performed using their standard protocol (Haince *et al*, 2004). Results obtained in the [redacted] lab and CTEP reference lab will be compared. Because CTEP has tentatively decided not to assay polymer in conjunction with phase 2 trials of ABT-888, only samples ii) and iii) will be prepared in conjunction with the phase 2 portion of the trial. If the two assays yield comparable conclusions about the extent of ABT-888-induced polymer decrease in the phase 1 portion of this study, the less labor-intensive assay will be performed in conjunction with the phase 2 portion. If the two assays yield divergent results, the two assays will be compared to physical chemical assays for polymer as described previously by the [redacted] lab (Shah *et al*, 1996); and the more reliable assay performed.

Samples should be shipped to:

[redacted], PhD
Université Laval Research Center
Health and Environment Unit and Department of Medical Biology
2705 Blvd Laurier, Rm 9700
Québec, QC, G1V 4G2, Canada

14.3.3 Pharmacokinetics (Blood) ***(Phase 1 Only)***

The Mayo Clinic Cancer Center Pharmacology Shared Resource will assess the plasma pharmacokinetics of topotecan and ABT-888 as indicated in Table 14.1.

These samples will be analyzed for ABT-888 or topotecan as indicated using a validated high performance liquid chromatography assays for topotecan (Kaufmann *et al*., 2005) and ABT-888 (Kinders *et al*., 2008).

14.4 Results of Genetic Testing

Because the results generated by the peripheral blood genetic testing for the BRCA1 and BRCA2 mutation have clinical relevance, all patients enrolled in the phase 2 portion who have not yet been tested for the BRCA1/BRCA2 mutations will be offered a Medical Genetics appointment to discuss testing within a CLIA-certified laboratory as well as discussion of results if results are requested.

15.0 Drug Information

15.1 ABT-888 (NSC 737664, IND #[redacted]

15.1.1 Background

Poly (ADP-ribose) polymerase (PARP) is a nuclear enzyme that recognizes DNA damage and facilitates 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. PARP activity is essential for the repair of single-stranded DNA breaks through the base-excision repair (BER) pathways and is an important modulator of the nonhomologous end-joining and homologous recombination double-stranded break repair pathways. Consequently, inhibition of PARP should enhance the effects of DNA-damaging agents, including alkylators, platinums, topoisomerase poisons, and radiation therapies.

15.1.2 Formulation

ABT-888 capsules are available from the National Cancer Institute (NCI) as 10 mg, 20 mg, 40 mg, 50 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. The capsules are packaged in HDPE bottles, and each HDPE bottle contains 16 capsules or 64 capsules.

15.1.3 Preparation and Storage

ABT-888 capsules may be repackaged from the supplied HDPE bottles into amber (or other low-actinic) child resistant pharmacy dispensing bottles. Expiration will be 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).
Storage: Store the original bottle at 15^0 to 25^0 C (59^0 to 77^0 F).
Stability: Shelf-life stability studies for ABT-888 capsules are on-going.

15.1.4 Administration

Administer ABT-888 orally without regards to meals.

15.1.5 Pharmacokinetic Information

Pharmacokinetic results are available in a limited number of human subjects, who received either the oral solution or immediate release capsules given once or twice daily.

a) **Absorption** – The absorption of ABT-888 after oral dosing was relatively rapid, with average time to maximum observed plasma concentration (T_{max}) ranging from 1 to 2 hours across dose levels. The maximum observed plasma concentration (C_{max}) and the area under the plasma concentration curve from time zero to infinity (AUC∞) of ABT-888 were approximately dose-proportional across the dose range studied, with minimal accumulation following BID dosing. Food does not have a significant effect on ABT-888 bioavailability. The administration of a high-fat meal had no significant effect on AUC and only caused a slight decrease in veliparib Cmax (17%) and a delay of approximately 1 hour in Tmax.

b) **Distribution** – The apparent volume of distribution (V/F) of ABT-888 was large, and oral clearance was rapid.

c) **Metabolism** – Results from in vitro analysis reveal that this agent is metabolized by multiple isoenzymes – CYP1A1, 2D6, 2C19 and 3A4. ABT-888 has one major metabolite in plasma, M8, a lactam derivative of the parent drug. The cellular PARP-inhibitory activity of M8 is 18-fold lower than ABT-888.

d) **Excretion** – The terminal half-life (t½) of ABT-888 is about 6 hours with minimal accumulation following multiple BID dosing. Recovery of the dose as parent drug in the urine over 24 hours after dosing averaged 78% (n = 6). Following multiple oral doses given twice daily, total recovery of the dose in the urine (as both parent drug and M8 metabolite) over 12 hours averaged 86% (n = 34). ABT-888 is primarily cleared in the urine as intact parent drug along with metabolites, suggesting that renal function plays an important role in the clearance of ABT-888 and its metabolites. Renal excretion is a major pathway in ABT-888 elimination. Coadministration of ABT-888 with oxaliplatin, carboplatin, cisplatin, and topotecan should be used with caution in patients

with pre-existing renal impairment since the primary elimination route of all of these drugs is renal.

15.1.6 Potential Drug Interactions

Nonclinical studies suggest ABT-888 is a substrate of P-gp, OCT2, and MATE1/MATE2K transporters. Co-administration of ABT-888 with strong inhibitors of P-gp, OCT2, and MATE1/MATE2K drugs may result in a decrease of ABT-888 renal clearance and an increase in ABT-888 plasma concentration. Therefore, use caution when administering ABT-888 with strong inhibitors of P-gp, OCT2, and MATE1/MATE2K drugs. At high dose (e.g., 400 mg BID), ABT-888 may inhibit OCT1 in the liver and MATE1/MATE2K in the kidney.

Additional clinical studies also demonstrate that ABT-888 is a weak inhibitor/inducer of the major CYP450 enzymes such as CYP1A2, 2C8/9, 2C19, 2D6, or 3A4/5; thus, potential drug-interactions with these CYP enzymes are not significant.

In humans, ABT-888 clears primarily in the urine as intact parent drug along with metabolites suggesting that renal function plays an important role in the drug clearance and its metabolites. Drug-associated with kidney toxicities or kidney diseases could change ABT-888 pharmacokinetics. Use caution when concomitantly administering oxaliplatin, carboplatin, cisplatin, and topotecan in patients with pre-existing renal impairment.

15.1.7 Known Potential Toxicities

Comprehensive Adverse Events and Potential Risks list (CAEPR)
For Veliparib (ABT-888, NSC 737664)

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

Adverse Events with Possible Relationship to ABT-888 (Veliparib) (CTCAE 4.0 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)***
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 - Blood and lymphatic system disorders - Other (bone marrow failure); Blood and lymphatic system disorders - Other (pancytopenia)

CARDIAC DISORDERS - Cardiac disorders - Other (Takotsubo cardiomyopathy); Heart failure; Left ventricular systolic dysfunction; Palpitations; Sinus bradycardia; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Vertigo
EYE DISORDERS - Blurred vision
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Colitis; Colonic obstruction; Dental caries; Dry mouth; Duodenal ulcer; Dyspepsia; Dysphagia; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Lower gastrointestinal hemorrhage; Mucositis oral; Obstruction gastric; Rectal hemorrhage; Rectal pain; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Fever; Flu like symptoms; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (cirrhosis)
INFECTIONS AND INFESTATIONS - Appendicitis; Catheter related infection; Infections and infestations - Other (peritonsillar abscess); Infections and infestations - Other (shingles); Lung infection; Lymph gland infection; Mucosal infection; Sepsis; Skin infection; Upper respiratory infection; Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Dermatitis radiation; Injury, poisoning and procedural complications - Other (radiation proctitis)
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; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Myalgia; Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Myelodysplastic syndrome; Treatment related secondary malignancy; 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 - Hematuria; Proteinuria; Renal and urinary disorders - Other (dysuria)
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; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (nail bed changes)
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.

15.1.8 Drug Procurement

ABT-888 is supplied by Abbott Laboratories and distributed by the Division of Cancer Treatment and Diagnosis (DCTD). **Please specify the container size (i.e., 16 capsules/bottle and/or 64 capsules/bottle) in your Clinical Drug Request Form (CDR) when submitting it to PMB.**

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 agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

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 Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time Refer to the PMB's website for specific policies and guidelines related to agent management.

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

The following are useful Links and Contacts:

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://eapps-ctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help:

ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

15.2 Topotecan (Hycamtin®)

15.2.1 Background

Topotecan binds to topoisomerase I and stabilizes the cleavable complex so that relegation of the cleaved DNA strand cannot occur. This results in the accumulation of cleavable complexes and single-strand DNA breaks. Topotecan acts in S phase of the cell cycle.

15.2.2 Formulation

Commercially available Injection, powder for reconstitution, as hydrochloride: 4 mg [base]

15.2.3 Preparation, Storage and Stability

Store intact vials at room temperature and protect from light. Reconstitute with 4 mL Sterile Water for Injection. This solution is stable for up to 28 days at room temperature. Topotecan should be further diluted in 50-100 mL of D5W or 0.9% Sodium Chloride. Refer to the treatment section for final dilution volume. This solution is stable for 24 hours at room temperature or up to 7 days under refrigeration.

15.2.4 Administration

Administer IV piggyback over 30 minutes or by 24-hour continuous infusion. See specific administration instructions in the treatment section of the protocol.

15.2.5 Pharmacokinetic Information

Distribution: V_{dss} of the lactone is high (mean: 87.3 L/mm^2; range: 25.6-186 L/mm^2), suggesting wide distribution and/or tissue sequestering
Protein binding: ~35%
Metabolism: Undergoes a rapid, pH-dependent hydrolysis of the lactone ring to yield a relatively inactive hydroxyl acid in plasma; metabolized in the liver to N-demethylated metabolite
Half-life elimination: I.V.: 2-3 hours; renal impairment: 5 hours;
Excretion: I.V.: Urine (51%; 3% as N-desmethyl topotecan); feces (18%; 2% as N-desmethyl topotecan)

15.2.6 Potential Drug Interactions

Increased Effect/Toxicity: Filgrastim may cause prolonged and sever neutropenia and thrombocytopenia if administered concurrently with

topotecan; initiate filgrastim at least 24 hours after topotecan. Platinum derivatives (carboplatin, cisplatin, oxaliplatin) may enhance the adverse/toxic effects of topotecan; monitor for hematologic toxicity, especially if the platinum derivative is administered prior to topotecan.

15.2.7 Known Potential Adverse Events
Consult the package insert for the most current and complete information including U.S. Boxed Warnings pertaining to severe diarrhea and severe myelosuppression.

Common known potential toxicities, > 10%:
Central nervous system: Fatigue, fever, pain, headache
Dermatologic: Alopecia, rash
Gastrointestinal: Nausea, vomiting, diarrhea, constipation, abdominal pain, anorexia, stomatitis
Hematologic: Neutropenia, leukopenia, anemia, thrombocytopenia, neutropenic fever/sepsis
Neuromuscular & skeletal: Weakness
Respiratory: Dyspnea, cough

Less common known potential toxicities, 1% - 10%:
Hepatic: Transient increase in liver enzymes
Neuromuscular & skeletal: Paresthesia
Miscellaneous: Sepsis

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Abdominal pain, allergic reactions, anaphylactoid reactions, angioedema, bleeding (severe, associated with thrombocytopenia), dermatitis (severe), injection site reactions (mild erythema, bruising), neutropenic colitis, pancytopenia, pruritus (severe)

15.2.8 Drug Procurement
Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

16.0 Statistical Considerations and Methodology

16.1 Overview
This is a phase 1/phase 2 study of the topotecan/ABT-888 combination. The phase 1 portion of this study is designed to determine the maximum tolerated dose (MTD) of this combination in patients with solid tumors. The phase 2 portion will use a 2-stage Simon design with interim analysis to assess the efficacy of ABT-888 and weekly topotecan in

ovarian cancer and primary peritoneal cancer patients with platinum resistant disease. The MTD determined in the phase 1 portion of the trial will be used as the starting dose for the phase 2 portion.

16.1.1 Primary Endpoint

The primary endpoint of the phase 1 portion of this trial is to find the MTD of topotecan+ABT-888. For the phase 2 portion of the trial, the primary endpoint is confirmed response. Throughout section 16.0, confirmed response will be considered synonymous with "success" for the phase 2 portion of this study, unless speficied otherwise.

16.1.2 Sample Size

The phase 1 portion of this study is expected to require a minimum of 9 patients and a maximum of 102 patients The phase 2 portion of this study is expected to require a minumum of 26 and a maximum of 44 platinum resistant patients. We anticipate accruing an additional 4 patients during the phase 2 portion of the trial to account for ineligibility, cancellation, major treatment violoation, or other reasons. Therefore, the phase 2 portion is expected to accrue a maximum of 44 patients and overall sample size will be a maximum of 48 patients.

16.1.2.1 At the time of Amendment 11 (i.e. after the MTD was determined), there were 58 patients accrued to the study. Since the phase 2 portion requires between 26 and 44 evaluable patients, and 48 total patients to account for ineligibility, cancellation, major treatment violation, or other reasons, the maximum study accrual will be 106 (58+48).

16.1.3 Accrual Rate and Study Duration

The anticipated accrual rate for cohort 1 is 3 patients per month. At this rate, it will likely take about 2 months to enroll, treat, and evaluate each set of 3 patients in the phase 1 portion of this study. The phase 1 portion is expected to take between 7 and 14 months. The anticipated accrual rate for cohort 2 is approximately 1-2 patients per month for platinum resistant disease. Therefore, the accrual period is expected to be between 13 and 32 months, depending upon whether patients are accrued beyond the first stage. The total study duration is expected to be approximately 38 months until the last patient accrued has been observed for at least 6 months.

16.1.3.1 At the time of amendment 10, this study had accrued 36 patients to 11 cohorts at 9 different dose levels. This suggests it requires approximately 3.3 months to accrue and assess each phase 1 cohort. It is expected that at most 5 more cohorts (DL10, 11, 12, 13 with a confirmatory cohort at level 12 or 13) will be required to determine the MTD. This means it will take approximately 17 more months to complete the phase 1 accrual portion of this trial. At 2 patients per month for the MTD cohort and phase 2 portion, the

estimated maximum accrual time for these portions is 34 months (assuming the conservative rate of 1/month for the 20+44+4=68 required patients). The phase 2 portion for the trial also has a planned stop to assess the primary endpoint for the stage 1 patients. This stop will require at least 7 months (6 months for data maturation and 1 month for data entry). In total, the estimated accrual duration, from ammendment 10 on is 58 months (17 for the phase 1 portion, 34 for accruing the MTD cohort and phase 2 patients, and 7 months to assess the stage I patients). Additionally, we will require another 7 months for data maturation and entry at the end of the phase 2 portion. These estimates indicate that a final analysis can begin on the phase 2 primary endpoint approximately 65 months from the date of amendment 10.

16.1.3.2 At the time of Amendment 11 (i.e. after the MTD was determined) update: At 2 patients per month, the phase II portion will require 24 months to fully accrue. Allowing for patient follow up (~6 months) and data entry (~1 month), the means that the final analysis can begin on the phase 2 primary endpoint approximately 31 months from the date of amendment 11.

16.2 Phase 1 Portion (Cohort 1)

The phase I portion of this trial is a single arm phase I study utilizing cohort-of-3 design to determine the MTD of the combination of ABT-888 and weekly topotecan in the treatment of solid tumors.

16.2.1 MTD Determination

MTD is defined as the dose level below the lowest dose that induces dose-limiting toxicity in at least one-third of patients (at least 2 of a maximum of 6 new patients). See section 7.25 for the MTD determination and section 7.24 for DLT definitions.

16.2.2 Analysis Plans

All the relevant results pertaining to toxicity, MTD, laboratory correlates will be examined in an exploratory and hypothesis-generating fashion.

16.2.2.1 Adverse Events Profile

The number and severity of all adverse events (overall, by dose-level, and by tumor group) will be tabulated and summarized in this patient population. The grade 3+ adverse events will also be described and summarized in a similar fashion. This will provide an indication of the level of tolerance for this treatment combination in this patient group

16.2.2.2 Toxicity Profile

The term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. Non-hematologic toxicities will be evaluated via the ordinal CTC standard toxicity grading. Hematologic toxicity measures of thrombocytopenia, neutropenia, and leukopenia will be assessed using continuous variables as the outcome measures (primarily nadir) as well as categorization via CTC standard toxicity grading. Overall toxicity incidence as well as toxicity profiles by dose level, patient and tumor site will be explored and summarized.

Toxicity incidence by BRCA mutation will also be evaluated for the 12-20 patients enrolled in the expanded phase I MTD cohort. Frequency distributions, graphical techniques and other descriptive measures will form the basis of these analyses.

16.2.2.3 Response

Objective responses, as defined per RECIST, will be summarized by simple descriptive summary statistics delineating complete and partial responses as well as stable and progressive disease.

We will exam response profile by BRCA mutation status in the MTD expansion cohort. Data will be summarized descriptively.

16.3 Phase 2 Portion (Cohort 2)

The phase 2 portion of this trial is a single arm two-stage phase 2 study to assess the response rate and toxicity of the combination of ABT-888 and weekly topotecan in the treatment of platinum resistant epithelial ovarian or primary peritoneal cancer.

16.3.1 Primary Endpoint

The primary endpoint is the proportion of tumor responses. Tumor response will be considered synonymous with success, unless specified otherwise. A confirmed tumor response is defined to be a CR, or PR noted as the objective status on two consecutive evaluations at least 4-6 weeks apart. Tumor response will be evaluated using all cycles of treatment. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response.

16.3.2 Decision Rule

The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 15%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 30%. The following two-stage 2-outcome design uses a minimum of 26 and a maximum of 44 patients to test the null hypothesis that the true success proportion in a given patient population is at most 15%:

16.3.2.1 STAGE 1

Enter 26 patients into study. If 4 or fewer successes are observed, we will consider this regimen ineffective in this patient population and terminate the study. Otherwise, if at least 5 successes are observed, we will proceed to Stage 2 and continue accrual.

16.3.2.2 STAGE 2
The regimen will be considered ineffective in platinum resistant patients if either enrollment is discontinued after stage 1 or if 9 or fewer successes are observed in the first 44 evaluable patients. This regimen will be considered promising in platinum resistant patients if 10 or more successes are observed in the first 44 evaluable patients.

16.3.2.3 Over Accrual
If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section 16.45.

16.3.2.4 Suspension of Accrual
We will not suspend accrual between stages to allow the first 20 patients to become evaluable, unless undue toxicity is observed. Given the limited overall sample size and the inclusion of an adverse event stopping rule, we feel it is ethical to not halt accrual after the first stage. However, if accrual is extremely rapid, we may temporarily suspend accrual in order to obtain safety data on these patients before re-opening accrual to further patients.

16.3.3 Power and Significance Level
Assuming that the number of successes is binomially distributed, the significance level is 0.09, the probability of declaring that this regimen warrants further studies (i.e. statistical power) under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

If the true response rate is…	15%	20%	25%	30%
…then the probability of declaring the regimen warrants further studies is…	0.10	0.35	0.65	0.86
…and the probability of stopping after stage 1 is…	0.65	0.38	0.18	0.07

16.3.4 Other considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or

changes in standard care will be taken into account in any decision to terminate the study.

16.4 Phase 2 Portion Analysis Plan

16.4.1 Primary Endpoint Analysis

16.4.1.1 Definition

The primary endpoint is the proportion of tumor responses. Tumor response will be considered synonymous with success, unless specified otherwise. A confirmed tumor response is defined to be a CR, or PR noted as the objective status on two consecutive evaluations at least 4-6 weeks apart. Tumor response will be evaluated using up to 12 cycles of treatment. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response.

16.4.1.2 Estimation

The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Confidence intervals for the trues success proportion will be calculated according to the approach of Duffy and Santner (1987).

16.4.2 Secondary Endpoint Analyses

16.4.2.1 Overall Survival

Survival time is defined as the time from registration to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier (1958).

16.4.2.2 Progression-Free Survival

Progression-free survival is defined as the time from registration to the earliest date documentation of disease progression or death due to any cause. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier (1958)

16.4.2.3 Duration of Response

Duration of response is defined for all evaluable patients who have achieved an objective response as the date at which the patient's earliest best objective status is first noted to be either a CR or PR to the earliest date progression is documented.

16.4.2.4 Time to Treatment Failure

Time to treatment failure is defined to be the time from the date of registration to the date at which the patient is removed from treatment due to progression, adverse events, or refusal. If the patient

is considered to be a major treatment violation or is taken off study as a non-protocol failure, the patient will be censored on the date he or she is removed from treatment.

16.4.2.5 Adverse Events
Adverse events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.4.3 Analysis of Correlative Studies

16.4.3.1 To determine any differences in the toxicity and/or efficacy of this regimen based on BRCA1/2 mutational status: The primary endpoint is BRCA1 and BRCA2 mutation status. The primary null hypothesis is that there is no association between mutation status and response rate or toxicity, as measured by dose limiting neutropenia. Fisher's exact test will be used to assess significance of relationships between mutation status and both response and toxicity. In addition, associations between mutation status and progression free survival will be illustrated graphically using Kaplan-Meier curves and log-rank tests in an exploratory fashion.

16.4.3.2 To assess whether pretreatment tumor cell levels of topo I, PARP, BRCA1, BRCA2, XRCC1, TDP1, P-glycoprotein or BCRP predict response to this regimen: The primary endpoint is biomarker expression measured via IHC staining. The primary null hypothesis is that there is no association between expression of a particular biomarker and response rate. The best response to therapy will be categorized as CR, PR and SD for > 2 cycles or PD. To assess the relationship between each potential marker and response, we will graph the values obtained for intensity (0, 1+, 2+ or 3+) and estimated percentage of positive cells (extent) vs. best response to therapy. In addition, staining intensity will be dichotomized two ways, high (2+ and 3+) vs. low (0 and 1+) or negative (0) vs. positive (1+, 2+ and 3+); extent will be dichotomized into low (e.g., ≤ 25%) vs. high (> 25%); response will be dichotomized into (CR, PR) vs. (SD, PD) or benefit (CR, PR, SD) vs. no benefit (PD).

Appropriateness of dichotomization cut-points will be examined based on the distribution of the outcomes. Prevalence of biomarker expression will be estimated along with 95% confidence intervals overall and within responders vs. non-responders. Fisher's exact test

will be used to assess significance of relationships between these dichotomous variables and treatment response. In addition, associations between molecular markers and progression free survival will be illustrated graphically using Kaplan-Meier curves and log-rank tests in an exploratory fashion.

16.4.3.3 To explore the possibility that a particular transcriptional profile predicts response to this regimen: Gene expression results will be used to test the hypothesis of differential expression between responders and non-responders. Biological interpretation will be aided by pathway analysis. In addition, log rank tests will be used to assess the association of gene expression with time to progression in an exploratory manner.

16.4.4 Over Accrual

If more than the target number of patients is accrued, the additional patients will not be used to evaluate the stopping rule; however, they will be included in final endpoint estimates and confidence intervals.

16.4.5 Data and Safety Monitoring

16.4.5.1 This study will be monitored by the Phase 1 DOG. The accrual report is available on the web site at http://hsrwww.mayo.edu/ccstumor/teams/phase1/phase1team.html. The accrual report is updated daily. Toxicity, efficacy and administrative information for this trial will be reviewed by the study team routinely.

16.4.5.2 Phase 2 Adverse Event Stopping Rules

The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study reopening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as “possible”, “probable”, or “definite”) that satisfy either of the following:

Overall, if 3 out of the first 10 or if at any time 4 or more patients experience grade 4 non-hematologic toxicity, accrual to the study

will be suspended to allow for investigation. After consideration by the study team (study chair, statistician) and consultation at the Phase 1 DOG, a decision will be made as to whether accrual can be resumed.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.5 Inclusion of Women and Minorities

16.5.1 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.5.2 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.5.3 The geographical region served by MCCC has a population which includes approximately 3% minorities. Based on prior MCCC studies involving similar disease sites, we expect about 3% of patients will be classified as minorities by race There was 1 male in the phase 1 portion (out of 58) and 100% of patients will be women for the Phase 2 portion. Expected sizes of racial by gender subsets for patients registered to this study (Phase 1 and 2) are shown in the following table

Ethnic Category	**Sex/Gender**			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	3	0	0	3
Not Hispanic or Latino	102	1	0	103
Ethnic Category: Total of all subjects*	105	1	0	106
Racial Category				
American Indian or Alaskan Native	1	0	0	0
Asian	1	0	0	1
Black or African American	1	0	0	1
Native Hawaiian or other Pacific Islander	0	0	0	0
White	102	1	0	103
Racial Category: Total of all subjects*	105	1	0	106

Ethnic Categories:	**Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino." **Not Hispanic or Latino**
Racial Categories:	**American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment. **Asian –** a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.) **Black or African American –** a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American." **Native Hawaiian or other Pacific Islander –** a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. **White –** a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Summary Table of Optional Biospecimens for This Protocol

Phase 2 only

Correlative Study	Optional or Mandatory	Type of Sample Collected	Volume of Sample Collected	Timepoints to collect	Shipping and Storage Conditions
Biomarkers (Section 17.21)	Optional	Tumor Biopsy	2[1]	Baseline	Snap Frozen; -80º C
Biomarkers (Section 17.22)	Optional	Tumor Biopsy	2[1]	Baseline	Fixed in 10% buffered neutral formalin; Ambient

1 Two tissue samples, half of each specimen from 2 needle passes

Pretreatment biopsies will be obtained after registration and before day 1 therapy unless a biopsy including paraffin-embedded material and, preferably, flash frozen material is available since the patient's most recent chemotherapy.

Biopsies should be obtained by interventional radiology using two passes of an 18 gauge biopsy needle under ultrasound or CT guidance

Half of each biopsy is to be fixed in 10% buffered neutral formalin. The other half is to be snap frozen in liquid nitrogen, transferred to a properly marked cryovial that has been pre-cooled to liquid nitrogen temperature, and stored at or below -80°C.

Frozen Tumor Biopsies should shipped on dry ice when collected, and Formalin Fixed Paraffin Embedded Tissue should be shipped ambient when available to Dr. Kaufmann's Laboratory:

Mayo Clinic
Attn: [redacted]
221 4th Avenue SW
Gonda 19-205B
Rochester, MN 55905

17.2 Background/Methodology

During the phase 2 portion of this trial, optional pretreatment tumor biopsies may be obtained to assess BRCA1/2 mutational status as well as expression of polypeptides and messages that might correlate with response of ovarian cancer to the topotecan/ABT-888 combination.

Prior biopsies will also be obtained from archival material whenever available.

17.2.1 Formalin-Fixed Tissue

Using a portion of the formalin-fixed biopsy material, the Tissue and Molecular Analysis Shared Resource of the Mayo Clinical Cancer Center will create a tissue microarray (TMA) that contains tumor material for pretreatment biopsies and, when available, at the time of diagnosis from all patients enrolled in the phase 2 portion of the trial. After review of the pertinent biopsies and identification of representative tumor areas by a pathologist specializing in gynecological oncology, the TMA will be created from patient blocks using a custom fabricated device that utilizes a 0.6 mm tissue corer and a mold for the 216 capacity recipient block. These arrays will incorporate 3-5 cores from each specimen. The design of the array will be laid out on a spreadsheet, indicating column and row placement of each core, along with relevant tumor information. These TMAs will then be stained with antibodies that recognize the antigens of interest (see below) using standard histochemical techniques that will include dissolution of paraffin in xylene; rehydration; incubation with 3% H_2O_2 in methanol to inactivate any endogenous peroxidases; microwave-induced antigen retrieval; and sequential incubation with primary antibodies, biotinylated secondary antibody and horseradish peroxidase-labeled streptavidin (Chien *et al*, 2006). Antibodies to be used in these studies will include the best commercially available antibody to the following antigens: topo I (e.g., clone 1A1, GeneTex), PARP1 (e.g., clone E102, Epitomics), BRCA1 (e.g., clone GLK-2, Dako), BRCA2 (e.g., clone 234403, R & D Systems), XRCC1 (e.g., clone 33-2-5 mouse monoclonal, Acris), TDP1 (e.g., polyclonal from ProteinTech), BCRP/ABCG2 (e.g., clone BXP-21, a gift from Jan Schellens to the Kaufmann laboratory), and ABCB1/P-glycoprotein (e.g., clones C219 and JSB-1, Novus).

Stained TMAs will be scanned in the Tissue and Cell Molecular Analysis Shared Resource of the Mayo Clinic Cancer Center using a Bliss "Virtual Microscopy" microscope and computer system from Bacus Laboratories. The virtual slide will then be accessed (by a pathologist specializing in gynecological oncology) via the Mayo intranet and examined at high magnification so that each core can be scored for intensity of staining (0, 1+, 2+, or 3+) and estimated percentage of cells that are positive.

17.2.2 Frozen Tissue

Using a portion of the snap frozen tumor, the Swisher laboratory at the University of Washington will apply Next Generation sequencing to sequence the splice junctions and exons of roughly 50 repair genes, including BRCA1, BRCA2, BARD1, BRIP1, CDL12, CHEK2, MRE11A, MSH6, NBN, PALB2, RAD50, RAD51C, and TP53, that have been implicated in pathogenesis of familial and sporadic ovarian cancer.

To complement the IHC experiments and provide an alternative approach to biomarker identification, correlations between pretreatment tumor transcript levels and clinical outcome will also be assessed. RNA will be isolated from aliquots of snap-frozen pretreatment biopsies obtained from all patients enrolled on the phase II portion of this trial as well as earlier biopsies (e.g., obtained at diagnosis) when available. In brief, 2 mm aliquots of snap-frozen tumor will be lysed in RNA isolation solution and purified using a Qiagen RNeasy kit. For paraffin-embedded samples, 1 mm punches will be taken from areas of interest; and RNA will be isolated from these cores using the Qiagen RNeasy FFPE kit. All further steps will be performed in the Microarray Core of the Mayo Advanced Genomics Technology Center. RNA will be analyzed using the Agilent BioAnalyzer 2100 to confirm that quality is sufficient for hybridization to arrays. Transcriptional profiling will then be completed by synthesis of cDNA and hybridization to Affymetrix U133 Plus 2.0 GeneChips, which assay expression on > 54,000 transcripts. Differences in Affymetrix profiles will be assessed in collaboration with a biostatistician who has an active interest in the analysis of transcriptional profiling experiments and a bioinformatics specialist from the Microarray Core using software provided by Affymetrix and Genespring, as well as more statistically efficient algorithms developed at Mayo.

18. Study Oversight and Data Reporting/Regulatory Requirements

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10.0 (Adverse Events: List and Reporting Requirements).

18.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

During the Phase 2 portion of the study, the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician through IWRS and Medidata Rave.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

18.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (https://eapps-ctep.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, or Site Investigator) on either the Corresponding Organization 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 site 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 or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

18.2.1 Method

The monitoring method will be determined by CTEP and communicated to you. Please use the appropriate text relating to your assigned monitoring method, and DELETE any text relating to the unused monitoring methods.

*For studies assigned for **CTMS Comprehensive** Monitoring:*
This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/CTMS. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at ctms@theradex.com for additional support with Rave and completion of CRFs.

*For studies assigned for **CTMS Routine** Monitoring:*
This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/CTMS. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at ctms@theradex.com for additional support with Rave and completion of CRFs.

*For studies assigned for **CDUS** monitoring (2 paragraphs):*
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 by FTP burst of data. 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, but expedited adverse events are still required to be submitted via CTEP-AERS.

18.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission

for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include the recommended phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

19.0 Budget

19.1 Costs Charged to Patient

- Routine clinical care
- Topotecan

19.2 Tests to be Research Funded

- Biopsy
- Research blood tests

19.3 Other Budget Concerns

Funding through the Ovarian SPORE will be provided for laboratory correlates during the Phase 2 portion of the study.

20.0 References

ABT-888 (A-861695) Investigator's Brochure (v 213Jun2008), pp. 1-178.

Abushahin, F., D. K. Singh, et al. (2008). "Weekly topotecan for recurrent platinum resistant ovarian cancer." Gynecol Oncol 108(1): 53-7.

Albert, J. M., C. Cao, et al. (2007). "Inhibition of poly(ADP-ribose) polymerase enhances cell death and improves tumor growth delay in irradiated lung cancer models." Clin Cancer Res 13(10): 3033-42.

Armstrong, D. K. (2004). "Topotecan dosing guidelines in ovarian cancer: reduction and management of hematologic toxicity." Oncologist 9(1): 33-42.

Ashworth, A. (2008). "A Synthetic Lethal Therapeutic Approach: Poly(ADP) Ribose Polymerase Inhibitors for the Treatment of Cancers Deficient in DNA Double-Strand Break Repair." J Clin Oncol 26(22): 3785-90.

Brustmann, H. (2007). "Poly(adenosine diphosphate-ribose) polymerase expression in serous ovarian carcinoma: correlation with p53, MIB-1, and outcome." Int J Gynecol Pathol 26 (2): 147-53.

Bryant, H. E., N. Schultz, et al. (2005). "Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase." Nature 434(7035): 913-7.

Burkle, A. (2001). "Physiology and pathophysiology of poly(ADP-ribosyl)ation." Bioessays 23(9): 795-806.

Calabrese, C. R., R. Almassy, et al. (2004). "Anticancer chemosensitization and radiosensitization by the novel poly(ADP-ribose) polymerase-1 inhibitor AG14361." Journal of the National Cancer Institute 96(1): 56-67.

Calabrese, C. R., M. A. Batey, et al. (2003). "Identification of potent nontoxic poly(ADP-Ribose) polymerase-1 inhibitors: chemopotentiation and pharmacological studies." Clin Cancer Res 9(7): 2711-8.

Canan Koch, S. S., L. H. Thoresen, et al. (2002). "Novel tricyclic poly(ADP-ribose) polymerase-1 inhibitors with potent anticancer chemopotentiating activity: design, synthesis, and X-ray cocrystal structure." J Med Chem 45(23): 4961-74.

Chen, A. Y., C. Yu, et al. (1991). "Camptothecin Overcomes mdrl-Mediated Resistance in Human KB Carcinoma Cells." Cancer Research 51: 6039-6044.

Chien, J., G. Aletti, et al. (2006). "Serine protease HtrA1 modulates chemotherapy-induced cytotoxicity." J Clin Invest 116(7): 1994-2004.

Curtin, N. J. (2005). "PARP inhibitors for cancer therapy." Expert Reviews Molecular Medicine 7(4): 1-20.

Delaney, C. A., L. Z. Wang, et al. (2000). "Potentiation of temozolomide and topotecan growth inhibition and cytotoxicity by novel poly(adenosine diphosphoribose) polymerase inhibitors in a panel of human tumor cell lines." Clin Cancer Res 6(7): 2860-7.

Donawho, C. K., Y. Luo, et al. (2007). "ABT-888, an orally active poly(ADP-ribose) polymerase inhibitor that potentiates DNA-damaging agents in preclinical tumor models." Clin Cancer Res 13(9): 2728-37.

Drew, Y. and H. Calvert (2008). "The potential of PARP inhibitors in genetic breast and ovarian cancers." Ann N Y Acad Sci 1138: 136-45.

Duffy, D., and T. Santner (1987). "Confidence intervals for a binomial parameter based on multistage tests." Biometrics, 43: 81-93.

Edwards, S. L., R. Brough, et al. (2008). "Resistance to therapy caused by intragenic deletion in BRCA2." Nature 451(7182): 1111-5.

Erlichman, C., S. A. Boerner, et al. (2001). "The HER Tyrosine Kinase Inhibitor CI1033 Enhances Cytotoxicity of 7-ethyl-10-hydroxycamptothecin and Topotecan by Inhibiting Breast Cancer Resistance Protein-Mediated Drug Efflux." Cancer Research 61(2): 739-748.

Farmer, H., N. McCabe, et al. (2005). "Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy." Nature 434(7035): 917-21.

Flatten, K., N. T. Dai, et al. (2005). "The Role of Checkpoint Kinase 1 in Sensitivity to Topoisomerase I Poisons." Journal of Biological Chemistry 280: 14349-14355.

Gagne, J. P., M. J. Hendzel, et al. (2006). "The expanding role of poly(ADP-ribose) metabolism: current challenges and new perspectives." Curr Opin Cell Biol 18(2): 145-51.

Haince, J. F., G. G. Poirier, et al. (2004). "Nonisotopic methods for determination of poly(ADP-ribose) levels and detection of poly(ADP-ribose) polymerase." Curr Protoc Cell Biol Chapter 18: Unit18 7.

Haince, J. F., M. Rouleau, et al. (2005). "Targeting poly(ADP-ribosyl)ation: a promising approach in cancer therapy." Trends Mol Med 11(10): 456-63.

Hann, C., D. L. Evans, et al. (1998). "Increased Camptothecin Toxicity Induced in Mammalian Cells Expressing *Saccharomyces Cerevisiae* DNA Topoisomerase I." Journal of Biological Chemistry 273 (14): 8425-8433.

Hassa, P. O. and M. O. Hottiger (2008). "The diverse biological roles of mammalian PARPS, a small but powerful family of poly-ADP-ribose polymerases." Front Biosci 13: 3046-82.

He, X., R. C. van Waardenburg, et al. (2007). "Mutation of a conserved active site residue converts tyrosyl-DNA phosphodiesterase I into a DNA topoisomerase I-dependent poison." J Mol Biol 372(4): 1070-81.

Helleday, T., H. E. Bryant, et al. (2005). "Poly(ADP-ribose) polymerase (PARP-1) in homologous recombination and as a target for cancer therapy." Cell Cycle 4(9): 1176-8

Hendricks, C. B., E. K. Rowinsky, et al. (1992). "Effect of P-Glycoprotein Expression on the Accumulation and Cytotoxicity of Topotecan (SK&F 104864), a New Camptothecin Analogue." Cancer Research 52: 2268-2278.

Homesley, H. D., D. J. Hall, et al. (2001). "A dose-escalating study of weekly bolus topotecan in previously treated ovarian cancer patients." Gynecologic Oncology 83(2): 394-9.

Hoskins, P., E. Eisenhauer, et al. (1998). "Randomized Phase II Study of Two Schedules of Topotecan in Previously Treated Patients with Ovarian Cancer: a National Cancer Institute of Canada Clinical Trials Group study." Journal of Clinical Oncology 16(6): 2233-2237.

Jagtap, P. and C. Szabo (2005). "Poly(ADP-ribose) polymerase and the therapeutic effects of its inhibitors." Nat Rev Drug Discov 4(5): 421-40.

Kaplan, E. and P. Meier (1958). "Nonparametric estimation from incomplete observations." Journal of the American Statistical Association 53: 457-448.

Kaufmann, S. H., J. E. Karp, et al. (2005). "Phase I and Pharmacological Study of Infusional Topotecan and Carboplatin in Relapsed and Refractory Leukemia." Clinical Cancer Research 11: 6641-6649.

Kinders, R.J., M. Hollingshead, et al. (2008). "Preclinical Modeling of a Phase 0 Clinical Trial: Qualification of a Pharmacodynamic Assay of Poly(ADP-ribose) Polymerase in Tumor Biopsies of Mouse Xenografts. " Clinical Cancer Research 14:6877-6885.

Le, T., L. Hopkins, et al. (2008). "Prospective evaluation of weekly topotecan in recurrent platinum-resistant epithelial ovarian cancer." Int J Gynecol Cancer 18(3): 428-31.

Litzow, M. R., P. P. Peethambaram, et al. (2008). "Phase I Trial of Autologous Hematopoietic Stem Cell Transplantation with Escalating Doses of Topotecan Combined with Cyclophosphamide and Carboplatin in Patients with Relapsed or Persistent Ovarian or Primary Peritoneal Carcinoma." Submitted.

Liu, X., J. Palma, et al. (2008a). "An enzyme-linked immunosorbent poly(ADP-ribose) polymerase biomarker assay for clinical trials of PARP inhibitors." Anal Biochem 381(2): 240-7.

Liu, X., Y. Shi, et al. (2008b). "Potentiation of temozolomide cytotoxicity by poly(ADP)ribose polymerase inhibitor ABT-888 requires a conversion of single-stranded DNA damages to double-stranded DNA breaks." Mol Cancer Res 6(10): 1621-9.

Malanga, M. and F. R. Althaus (2004). "Poly(ADP-ribose) Reactivates Stalled DNA Topoisomerase I and Induces DNA Strand Break Resealing." Journal of Biological Chemistry 279: 5244-5248.

Madden, K. R. and J. J. Champoux (1992). "Overexpression of Human Topoisomerase I in Baby Hamster Kidney Cells: Hypersensitivity of Clonal Isolates to Camptothecin." Cancer Research 52: 525-532.

Markman, M. (2005). "Topotecan as second-line therapy for ovarian cancer: dosage versus toxicity." Oncologist 10(9): 695-7.

Marple, T., T. M. Kim, et al. (2006). "Embryonic stem cells deficient for Brca2 or Blm exhibit divergent genotoxic profiles that support opposing activities during homologous recombination." Mutat Res 602(1-2): 110-20.

McCabe, N., N. C. Turner, et al. (2006). "Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose) polymerase inhibition." Cancer Res 66(16): 8109-15.

Merajver, S. D., T. M. Pham, et al. (1995). "Somatic mutations in the BRCA1 gene in sporadic ovarian tumours." Nat Genet 9(4): 439-43

Morris, R., R. D. Alvarez, et al. (2008). "Topotecan weekly bolus chemotherapy for relapsed platinum-sensitive ovarian and peritoneal cancers." Gynecol Oncol 109(3): 346-52.

Morris, R. and A. Munkarah (2002). "Alternate dosing schedules for topotecan in the treatment of recurrent ovarian cancer." Oncologist 7 Suppl 5: 29-35.

Muntz, H. G., T. W. Malpass, et al. (2008). "Phase 2 study of intraperitoneal topotecan as consolidation chemotherapy in ovarian and primary peritoneal carcinoma." Cancer 113(3): 490-6.

O'Malley, D. M., M. Azodi, et al. (2005). "Weekly topotecan in heavily pretreated patients with recurrent epithelial ovarian carcinoma." Gynecol Oncol 98(2): 242-8.

Palma, J. P., L. E. Rodriguez, et al. (2008). "The PARP inhibitor, ABT-888 potentiates temozolomide: correlation with drug levels and reduction in PARP activity in vivo." Anticancer Res **28**(5A): 2625-35.

Park, S.-Y. and Y.-C. Cheng (2005). "Poly(ADP-Ribose) Polymerase-1 Could Facilitate the Relegation of Topoisomerase I-linked DNA Inhibited by Camptothecin." Cancer Research 65: 3894-3902.

Patel, A. G., K. S. Flatten et al. (2012) "Enhanced killing of cancer cells by poly(ADP-ribose) polymerase inhibitors and topoisomerase I inhibitors reflects poisoning of both enzymes." J Biol Chem 287:4198-4210.

Penning, T. D., G. D. Zhu, et al. (2009). "Discovery of the Poly(ADP-ribose) polymerase (PARP) inhibitor 2-[(R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide (ABT-888) for the treatment of cancer." J Med Chem 52(2): 514-23.

Plummer, E. R. (2006). "Inhibition of poly(ADP-ribose) polymerase in cancer." Curr Opin Pharmacol 6(4): 364-8.

Pouliot, J. J., K. C. Yao, et al. (1999). "Yeast Gene for a Tyr-DNA Phosphodiesterase that Repairs Topoisomerase I Complexes." Science 286: 552-555.

Rasheed, Z. A. and E. H. Rubin (2003). "Mechanisms of resistance to topoisomerase I-targeting drugs." Oncogene 22(47): 7296-304.

Ratnam, K. and J. A. Low (2007). "Current development of clinical inhibitors of poly(ADP-ribose) polymerase in oncology." Clin Cancer Res 13(5): 1383-8.

Risch, H., J. McLaughlin, et al. (2001). "Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer." American Journal of Human Genetics 68: 700-710.

Rowinsky, E. K. (2002). "Weekly topotecan: an alternative to topotecan's standard daily x 5 schedule?" Oncologist 7(4): 324-30.

Safra, T., I. Ron , et al. (2006). "Heavily pretreated ovarian cancer patients treated by single-agent gemcitabine. A retrospective outcome comparison between platinum-sensitive and platinum-resistant patients." Acta Oncol 45:463-468.

Safra, T., J. Menczer, et al. (2007). "Efficacy and toxicity of weekly topotecan in recurrent epithelial ovarian and primary peritoneal cancer." Gynecol Oncol 105(1): 205-10.

Sakai, W., E. M. Swisher, et al. (2008). "Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers." Nature 451(7182): 1116-20.

Shah, G. M., D. Poirier, et al. (1996). "Complete Inhibition of Poly(ADP-ribose) Polymerase Activity Prevents the Recovery of C3H10T1/2 Cells From Oxidative Stress." Biochimica Et Biophysica Acta 1312(1): 1-7.

Smith, L. M., E. Willmore, et al. (2005). "The Novel Poly(ADP-Ribose) Polymerase Inhibitor, AG14361, Sensitizes Cells to Topoisomerase I Poisons by Increasing the Persistence of DNA Strand Breaks." Clinical Cancer Research 11(23): 8449-57.

Spannuth, W. A., C. A. Leath, 3rd, et al. (2007). "A phase II trial of weekly topotecan for patients with secondary platinum-resistant recurrent epithelial ovarian carcinoma following the failure of second-line therapy." Gynecol Oncol 104(3): 591-5.

Sugimura, K., Takebayashi, S-i., et al. (2008) "PARP-1 ensures regulation of replication fork progression by homologous recombination on damaged DNA." Journal of Cell Biology 183:1203-1212.

ten Bokkel Huinink, W., M. Gore, et al. (1997). "Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer." Journal of Clinical Oncology 15: 2183-2193.

Tentori, L. and G. Graziani (2005). "Chemopotentiation by PARP inhibitors in cancer therapy." Pharmaceutical Research 52(1): 25-33.

Thomas, H. D., C. R. Calabrese, et al. (2007). "Preclinical selection of a novel poly(ADP-ribose) polymerase inhibitor for clinical trial." Mol Cancer Ther 6(3): 945-56.

Tikhe, J. G., S. E. Webber, et al. (2004). "Design, synthesis, and evaluation of 3,4-dihydro-2H-[1,4]diazepino[6,7,1-hi]indol-1-ones as inhibitors of poly(ADP-ribose) polymerase." J Med Chem 47(22): 5467-81.

Turner, N., A. Tutt, et al. (2004). "Hallmarks of "BRCAness" in sporadic cancers." Nature Reviews Cancer 4: 814-819.

Vandenput, I., F. Amant, et al. (2007). "Effectiveness of weekly topotecan in patients with recurrent epithelial ovarian cancer." Int J Gynecol Cancer 17(1): 83-7.

Venkitaraman, A. (2004). "Tracing the network connecting BRCA and Fanconi anemia proteins." Nature Reviews Cancer 2004: 266-276.

Walsh T, Casadei S, Lee MK, Pennil CC, Nord AS, Thornton AM, et all. Mutations in 12 genes for inherited ovarian, fallopian tube and peritoneal carcinoma identified by massively parallel sequencing. Proc Natl Acad Sci USA. 2011; 108: 18032-7.

White, A. W., R. Almassy, et al. (2000). "Resistance-modifying agents. 9. Synthesis and biological properties of benzimidazole inhibitors of the DNA repair enzyme poly(ADP-ribose) polymerase." J Med Chem 43(22): 4084-97.

Yang, Y. G., U. Cortes, et al. (2004). "Ablation of PARP-1 does not interfere with the repair of DNA double-strand breaks, but compromises the reactivation of stalled replication forks." Oncogene 23(21): 3872-82.

Appendix I: ECOG Performance Status

Grade	
0	Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100).
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 (Karnofsky 70-80).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50 percent of waking hours (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair 50 percent or more of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).
5	Dead

Appendix II: New York Heart Association Classifications

Clinical Evaluation of Functional Capacity of Patients
with Heart Disease in Relation to Ordinary Physical Activity

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

Reference: Bruce, R. A.: Mod. Concepts Cardiovasc. Dis. 25:321, 1956. (Modified from New York Heart Association, 1953).

Appendix III: Study Medication Diary

Please record the times that you take your study medications. Return this diary and the medication bottles (even if unopened or empty) along with any unused pills at your next visit.

Day	Date/time **ABT-888** taken (mm/dd/yy)	mg per day
1		
2	(Also a Topotecan Infusion)	
3		
4	**No ABT-888 Taken**	
5		
6		
7		
8		
9	(Also a Topotecan Infusion)	
10		
11	**No ABT-888 Taken**	
12		
13		
14		
15		
16	(Also a Topotecan Infusion)	
17		
18	**No ABT-888 Taken**	
19		
20		
21		
22		
23		
24		
25		
26		
27		
28		

_____ _____
Participant Signature Date

_____ _____
Medical Personnel Signature Date

Cycle 2 Pill Diary (Phase I Dose Escalation only)

Please record the times that you take your study medications. Return this diary and the medication bottles (even if unopened or empty) along with any unused pills at your next visit.

Day	Date/time **ABT-888** taken (mm/dd/yy)	mg per day
1	**No ABT-888 Taken**	
2	Have a Topotecan Infusion **No ABT-888 Taken**	
3	**No ABT-888 Taken**	
4		
5		
6		
7		
8		
9	(Also have a Topotecan Infusion)	
10		
11		
12		
13	**No ABT-888 Taken**	
14		
15		
16	(Also have a Topotecan Infusion)	
17		
18	**No ABT-888 Taken**	
19		
20		
21		
22		
23		
24		
25		
26		
27		
28		

_

_____ _____
Participant Signature Date

_____ _____
Medical Personnel Signature Date

Appendix IV: Cooperative Research and Development Agreement (CRADA)

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/default.htm#guidelines_for_collaborations.) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational 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 prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own 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 investigational 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.. Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection

of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

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

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

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

    Regulatory Affairs Branch, CTEP, DCTD, NCI
    Executive Plaza North, Suite 7111
    Bethesda, Maryland 20892
    FAX 301-402-1584
    Email: anshers@mail.nih.gov

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

Appendix V: 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 specific enzymes in the liver.

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

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

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

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

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

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

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

_____ and he or she can be contacted at

_____. May 2015

STUDY DRUG INFORMATION WALLET CARD

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

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

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

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

  and can be contacted at _____.