TITLE: Pilot Trial of Talazoparib (BMN 673), an Oral PARP Inhibitor, in Patients With Advanced Solid Tumors and Deleterious BRCA Mutations

Abbreviated Title: Pilot Talazoparib (BMN 673)

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NCI Supplied Agent: Talazoparib (BMN 673) (NSC 771561)

IND Number: 119558

Version Date: August 24, 2020

NCT Number: NCT01989546

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PRÉCIS

Background:

- The poly (ADP-ribose) polymerase (PARP) family of enzymes is critical for maintaining genomic stability by regulating a variety of DNA damage repair mechanisms.
- Talazoparib (BMN 673) is a PARP inhibitor with greater in vitro activity than any other PARP inhibitor currently in development. Talazoparib (BMN 673) has been shown to cause single-agent synthetic lethality in BRCA1/2- and PTEN-deficient cell lines, and has potent antitumor activity in animal models of tumors harboring mutations in DNA repair pathways.
- Talazoparib (BMN 673) is showing promising single-agent activity in patients with advanced ovarian and breast cancer harboring deleterious BRCA mutations.
- This pilot study will evaluate the pharmacodynamic effects of Talazoparib (BMN 673) on DNA damage and apoptosis markers in tumor biopsy tissue.

Primary Objective:

- Determine the pharmacodynamic effect of talazoparib (BMN 673) in tumor biopsies from patients with advanced ovarian, breast, or other solid tumor and deleterious BRCA mutations.

Secondary Objectives:

- Determine the response rate (CR + PR) of treatment with talazoparib (BMN 673) in patients with deleterious BRCA mutations.

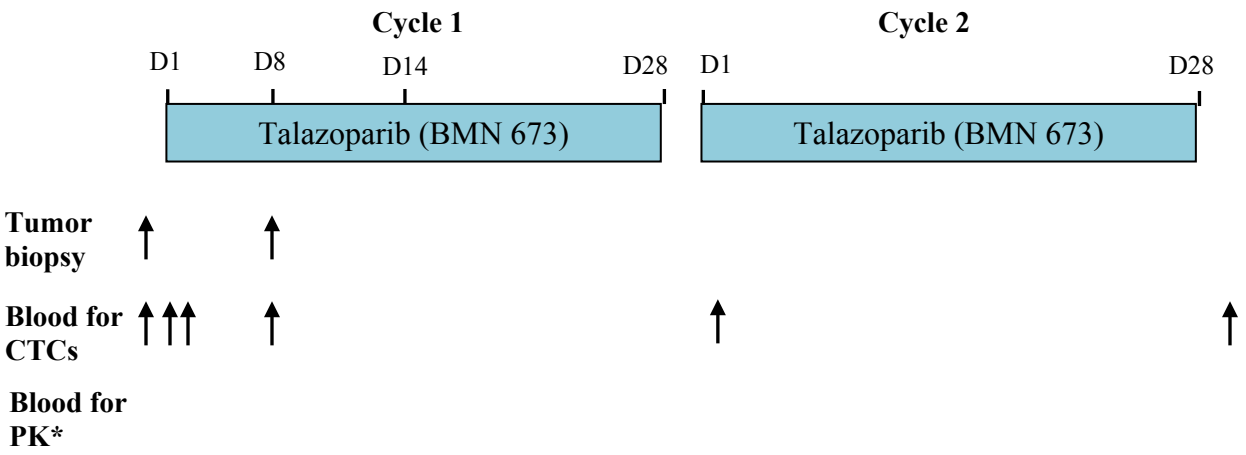
Eligibility:

- Adult patients with documented deleterious BRCA 1 or 2 mutations with histologically confirmed ovarian, primary peritoneal, breast, prostate, pancreas, gastric or other solid tumor whose disease has progressed following at least one standard therapy or who have no acceptable standard treatment options.
- No major surgery, radiation, or chemotherapy within 4 weeks prior to study enrollment, and recovered from toxicities of prior therapies to at least eligibility levels.
- Age ≥18 years of age; ECOG performance status ≤ 2
- Adequate organ function.
- Willingness to undergo tumor biopsies.

Study Design:

- Talazoparib (BMN 673) will be administered orally each day in 28-day cycles.
- Dosing will be at the established recommended Phase II dose of 1000 μg/day each day for 28 days.
- To meet the primary, pharmacodynamic endpoint of the trial, we plan to accrue a total of 12 patients with matched, evaluable baseline and day 8 biopsies. To allow for some patients whose biopsies will not be evaluable (i.e., will contain <5% tumor content), the accrual ceiling is 24 patients. The number of patients evaluable for objective response, while relevant to the secondary objective of the trial, will not be considered in determining completion of accrual.
- Tumor biopsies will be mandatory at baseline (pre-dose), and then approximately 3-6 hours post talazoparib (BMN 673) on day 8. One optional tumor biopsy may also be collected either on day 1 (± 2 days) of the cycle following any restaging at which a 10-19% increase in tumor volume is observed (according to RECIST criteria) if the patient has been on study for at least 4 cycles, or at time of disease progression.

SCHEMA



Talazoparib (BMN 673) is administered orally each day in 28-day cycles

Tumor biopsies will be performed at baseline (pre-treatment) and 3-6 hrs post dose on cycle 1 day 8. One optional tumor biopsy may also be collected either on day 1 (± 2 days) of the cycle following any restaging at which a 10-19% increase in tumor volume is observed (according to RECIST criteria) if the patient has been on study for at least 4 cycles, or at time of disease progression. Tumor biopsies will be evaluated for PAR levels, DNA damage response markers such as γH2AX, cleaved caspase 3, ERCC1, pNbs1, XPF, RAD51, and pT1989ATR, and, as indicators of ATR/ATM activation, chk1 and chk2

Blood samples for CTC analyses will be collected at baseline (pre-treatment), on cycle 1 day 1 (3-6 hours post dose and approximately 24 hours post dose/before day 2 dose), on cycle 1 day 8 (3-6 hours post dose), on cycle 2 day 1 (3-6 hours post dose, ± 3 days for scheduling conflicts), on day 1 of every subsequent cycle before drug administration (day 1 of every 3 cycles for patients on study for more than 12 months), at the time of the optional restaging follow-up biopsy (if applicable), and at time of disease progression.

***Please note:** *As of Amendment H (2/5/2018) blood for PK analysis will no longer be collected.* Blood samples for PK analysis will be collected on cycle 1 day 1 pre-dose and 0.5, 1, 2, 3, 4, 6, 8, and 24 hours post-dose, on cycle 1 day 8 (3-6 hours post dose), and on cycle 2 day 1 pre-dose and 3-6 hours post dose (± 2 days for scheduling conflicts).

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1 OBJECTIVES

Primary Objective:

- Determine the pharmacodynamic effect of talazoparib (BMN 673) in tumor biopsies from patients with advanced ovarian, breast, or other solid tumor and deleterious BRCA mutations.

Secondary Objective:

- Determine the response rate (CR + PR) of treatment with talazoparib (BMN 673) in patients with deleterious BRCA mutations.

2 BACKGROUND

2.1 Poly-ADP-ribosylation

Poly-ADP-ribosylation occurs after single- or double-stranded DNA damage and represents the posttranslational modification of histones and other nuclear proteins by poly (ADP-ribose) polymerase (PARP) [1]. PARP has been implicated in many cellular processes, including replication, transcription, differentiation, gene regulation, protein degradation, and mitotic spindle maintenance. Enhanced PARP-1 expression and/or activity in tumor cells, as compared to normal cells, has been demonstrated in malignant lymphomas [2], hepatocellular carcinoma [3], cervical carcinoma [4], colorectal carcinoma [5], non-Hodgkin's lymphoma [6], leukemic lymphocytes [7], and colon adenomatous polyps [8]. In knockout mouse models, deletion of PARP-1 is sufficient to impair DNA repair [9-11]. The residual PARP-dependent repair activity (~ 10%) is due to PARP-2. This suggests that only PARP-1 and PARP-2 need to be inhibited to impair DNA repair [12-14].

Poly-ADP-ribosylation of proteins is a dynamic process with a short half-life (t1/2) of <1 min. The enzymes responsible for degrading these polymers are poly (ADP-ribose) glycohydrolase (PARG), which cleaves ribose-ribose bonds, and ADP-ribosyl protein lyase, which removes the protein proximal to the ADP-ribose monomer.

Increased PARP activity is one of the mechanisms by which tumor cells avoid apoptosis caused by DNA damaging agents. PARP activity is essential for the repair of single-stranded DNA breaks through the base excision repair (BER) pathways [14, 15]. Therefore, inhibition of PARP sensitizes tumor cells to cytotoxic agents (e.g., alkylators (temozolomide, cyclophosphamide, BCNU) and topoisomerase I inhibitors (e.g., irinotecan, camptothecin, topotecan) that induce DNA damage that would normally be repaired through the BER system. Double-stranded breaks are strong activators of PARP-1, resulting in PARP-1–mediated activation of DNA-PK and Ku80, important components of the non-homologous end-joining double-stranded break repair pathway [16, 17]. Small molecule inhibitors of PARP directly inhibit repair of double-stranded breaks [9, 18].

Deleterious *BRCA* Mutations and the Concept of Synthetic Lethality

There are also data suggesting that PARP inhibitors have activity against some BRCA-deficient cells in the absence of any DNA damaging agent [19-21]. It is possible that, in BRCA-deficient cells, PARP inhibition stops the BER pathway, and thus, single-stranded breaks are carried through DNA synthesis, resulting in double-stranded breaks. The increase in double-stranded breaks cannot be repaired by homologous recombination, due to the lack of BRCA1 or 2, resulting in increased cell death.

BRCA1$^{-/-}$ and *2* $^{-/-}$ embryonic stem cells were observed to be extremely sensitive to PARP inhibition (Figure 1) [20]. This might be due to inhibition of the BER pathway by the PARP inhibitor in the background of defective homologous repair in BRCA-deficient cancer cells (Figure 2) [21, 22].

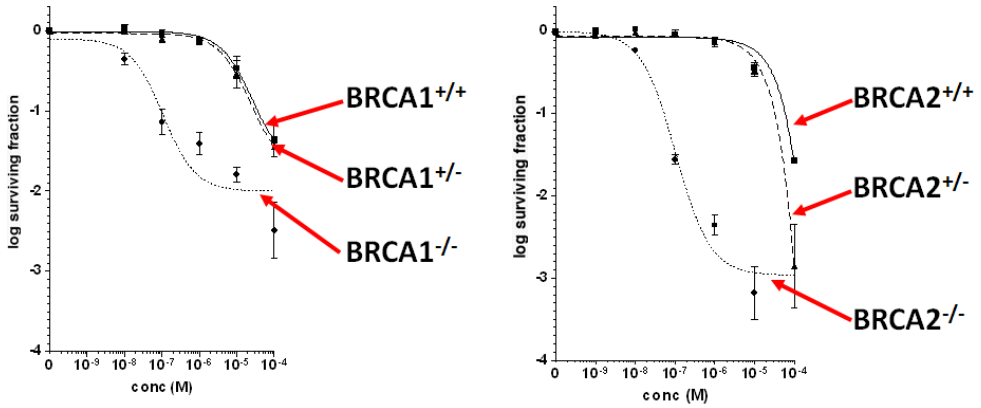

Figure 1: Inhibition of PARP activity inhibits the survival of cells lacking wild-type *BRCA1* or *BRCA2* after 10-12 days of continuous exposure to PARP inhibitor [20].

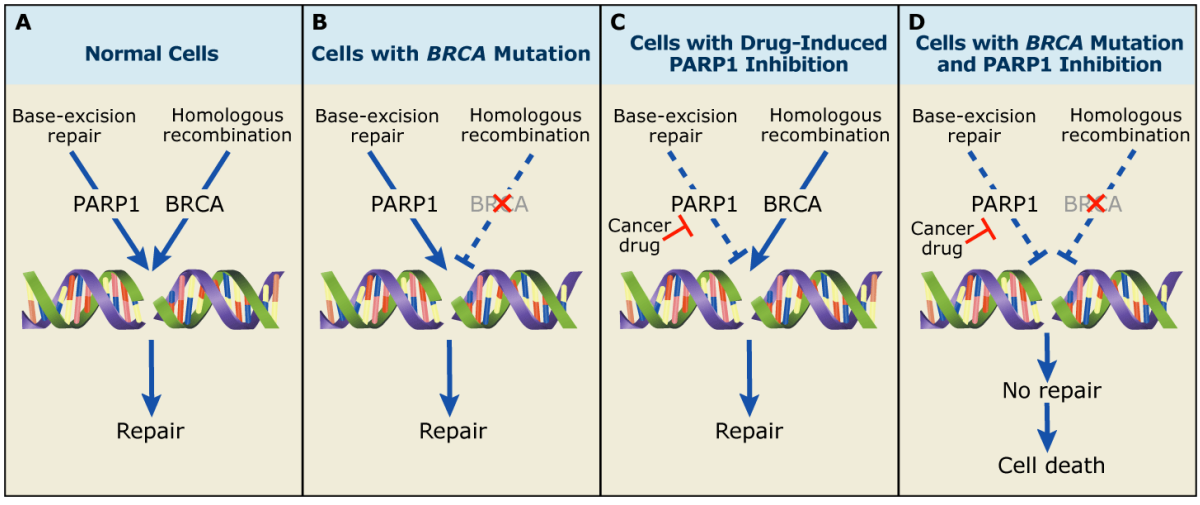

Figure 2: Inhibition of PARP in tumor cells with *BRCA* mutations leads to persistence of DNA lesions normally repaired by homologous recombination [21].

These observations led to the evaluation of single-agent PARP inhibitors in patients with deleterious *BRCA* mutations [23]. Results from recent Phase II studies of single-agent olaparib, an oral PARP inhibitor, in patients with recurrent ovarian cancer or refractory breast cancer and confirmed *BRCA1* or *2* mutations are encouraging. Confirmed overall response rates for patients with ovarian cancer treated with 400 or 100 mg two times a day (BID) of olaparib were 33% and 13%, respectively; a further 33% and 29% of patients experienced stable disease. It is also worth noting that median progression-free survival (PFS) in these two cohorts was 5.8 and 1.9 months, respectively [24]. For the companion trial of olaparib in patients with deleterious *BRCA* mutations and breast cancer, the objective response rate was 38% (9/24) on the 400 mg BID dose (41% [11/27] in the investigator's presentation to ASCO 2009) [25]. These data support the hypothesis that BRCA-deficient cancer cells are sensitive to PARP inhibition.

2.2 Talazoparib (BMN 673)

Mechanism of Action
Talazoparib (BMN 673) has been shown to be a highly selective and potent cytotoxic agent in human cancer cell lines and in animal models of tumors harboring mutations that compromise DNA repair pathways. Talazoparib (BMN 673) inhibits PARP *in vitro* at a lower concentration
(IC_{50}= 0.57 nM) than the PARP inhibitors ABT 888 (IC_{50}=4.73 nM), AG14447 (IC_{50}=1.98 nM), or olaparib (IC_{50}=1.94 nM) [26, 27].

Pharmacodynamic Studies
IC_{50} values for the inhibition of recombinant human PARP-1 enzymatic activity are approximately the same for the talazoparib tosylate salt (BMN 673ts) and freebase forms (BMN 673fb) (0.83 and 1.2 nM, respectively), indicating that the tosylate salt does not affect mechanism of action of BMN 673fb. In contrast, the enantiomeric isomer (LT-00674) is a poor inhibitor of PARP-1 enzymatic activity (IC_{50}>100 nM). BMN 673fb inhibited PARP-2 to a comparable extent as its inhibition of PARP-1.

Assessment of BMN 673fb and related compounds for their tumor cell cytotoxicity revealed selective and potent cytotoxicity in human cancer cell lines harboring mutations that compromise DNA repair pathways. Gene mutations that confer selective tumor cell cytotoxicity included BRCA1 (MX-1 mammary tumor cells), BRCA2 (Capan-1 pancreatic tumor cells), PTEN (MDA-MB-468 mammary, LNCap and PC-3 prostate tumor cells), and MLH-1 mutations (HCT-116 colorectal tumor cells) (Table 1). The IC_{50} values of BMN 673fb in these tumor cell lines were in the single-digit nanomolar or sub-nanomolar range. In contrast, the IC_{50} of talazoparib (BMN 673) against normal human primary cell MRC-5 and several tumor cell lines that do not have reported DNA repair-related mutations are significantly greater (250 nM to > 1000 nM).

	IC_{50} (μM)					IC_{50} Ratio (Selectivity)	
Cell Line	Capan-1 (BRCA2-/-)	MX-1 (BRCA1-/-)	SW620	MDA-MB-231	MRC-5 (Normal)	IC_{50} Ratio MRC5/ Capan1	IC_{50} Ratio MRC5/ MX-1
AG14447	0.609	0.0053	ND	5.53	8.53	14	1609
AZD2281	0.259	0.0232	ND	6.41	5.83	22	251
BMN 673	0.005	0.0003	0.13	1.85	0.31	62	1033

Table 1. The cytotoxicity of talazoparib (BMN 673) and reference PARP inhibitors was compared in normal human cells (MRC-5) or in tumor cells that either wild-type for BRCA-1/BRCA-2 (SW620, MB231), deficient in BRCA-1 (MX-1), or BRCA-2 (Capan-1). Cells were seeded in their recommended growth medium and allowed to grow overnight at 37°C, then incubated in media containing increasing concentrations of PARP inhibitors for 12-14 days.

In the BRCA1-deficient MX-1 xenograft tumor model, oral administration of 0.33 mg/kg BMN 673fb once daily for 28 days resulted in significant antitumor activity (tumor growth delay/tumor regression; Figure 3). Dose-related inhibition of tumor growth was observed at lower doses, while a higher dose (1.0 mg/kg/day) induced significant body weight loss with associated mortality. Consistent with the antitumor effect, profound reduction in poly (ADP-ribose) (PAR) level (a measure of PARP activity) was observed in MX-1 xenografts following oral administration. Complete suppression of BRCA1-deficient tumor growth was achieved in a 3-month study dosed at 0.165 mg/kg/BID [26]. Oral administration (0.33 mg/kg/day for 28 days) also resulted in antitumor activity in the PTEN-deficient LNCap, MDA-MB-468, and PC-3 xenograft models [26]. In addition, BID oral administration of BMN 673fb (0.33 mg/kg/day for 28 days) delayed the growth of the MLH-1–deficient HCT-116 xenograft tumor in nude mice.

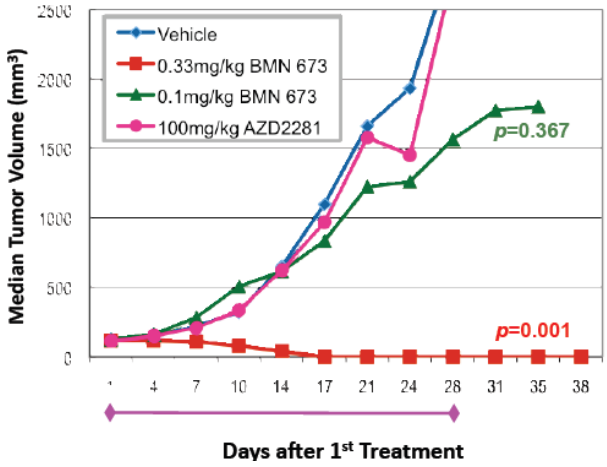

Figure 3. Single-agent antitumor efficacy in the BRCA1/2-deficient MX-1 model. PARP inhibitors AZD2281, talazoparib (BMN 673), or vehicle (10% DMAc, 6% Solutol HS15

and 84% PBS) was administered orally once daily for 28 consecutive days beginning Day 1 (n=6). Purple straight line indicates the daily dosing period. P-value compares each treatment group with the vehicle only group.

Assessment of various dosing schedules in the mouse xenograft models indicated that continuous daily administration of BMN 673fb resulted in greater antitumor activity than intermittent administration at the same or higher dose levels (Figure 4). BID dosing resulted in extended tumor growth delay or extended tumor regression compared to single daily (QD) dosing at an identical total daily dose level for 28-days. These results suggest that continuous suppression of PARP activity is required for optimal antitumor activity.

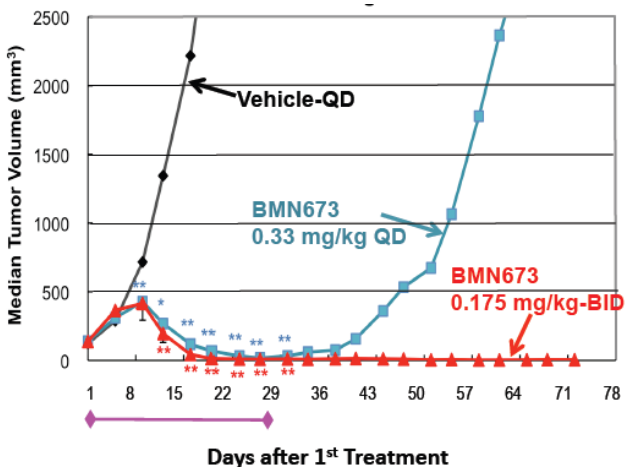

Figure 4. QD versus BID dosing in the MX-1 xenograft model. Talazoparib (BMN 673) administered orally at either 0.33 mg/kg once daily or 0.175 mg/kg BID for 28 consecutive days beginning Day 1 (n=6). Purple straight line indicates the daily dosing period.

Pharmacokinetic Studies

Pharmacokinetic studies were performed in rats and dogs. BMN 673ts (tosylate salt) was selected as the dosing form by comparing the bioavailability of the free base and salt forms in 3 dogs; thereafter, all GLP pharmacokinetic and toxicology/TK studies used the salt form for oral and IV administration. The oral formulation used in the GLP studies was a suspension in CMC (0.5% w/v). The clinical presentation and formulation developed for the Phase 1 studies is a HPMC capsule containing BMN 673ts in a dry powder blend (25, 50, 250 and 1000 µg free base equivalents/capsule. A GLP bridging study compared the PK and bioavailability of the suspension and capsule in male and female dogs using the 250-µg capsule. BMN 673ts' relative bioavailability following capsule administration compared to the suspension was 185% and 212% for males and females, respectively; for males and females combined, 197%.

Oral bioavailability, calculated from the ratio of area under the concentration-time curve (AUC) following oral administration relative to the AUC following intravenous (IV) administration (AUC_{oral}/AUC_{IV}), was > 42.7% in rats and > 50.5% in dogs based on single dose comparisons. The compound was metabolically stable. The terminal half-life (t½) of

talazoparib (BMN 673) at various doses in rats and dogs ranges from 28.5 to 32.0 hour and 69.7 to 91.2 hour, respectively, which allows for once daily dosing. Steady state concentrations were reached on Day 15 in rats and on Day 20 in dogs using daily administration of talazoparib (BMN 673). Comparing Day 15 and 28 with Day 1 for all dose levels in dogs, AUC and C_{max} increased from Day 1 to Day 15 to Day 28.

Preclinical Studies

Five-day repeat dose toxicity and toxicokinetic (TK) studies with 28-day recovery were conducted in rats and dogs. In dogs (the most sensitive species), talazoparib (BMN 673) was administered at dosage levels of 0.003, 0.01, 0.03, 0.1 mg/kg/day over 5 consecutive days. Severe pancytopenia was observed in dogs treated at the two highest dose groups (0.03 and 0.1 mg/kg/day). At these doses, the mean reticulocyte nadir occurred on day 6 and the platelet and WBC nadirs on day 11. These changes were reversed in the group treated at 0.03 mg/kg/day on days 17-18 (i.e., 12-13 days after the last dose of the drug). In contrast, some animals in the group treated at 0.1 mg/kg/day died due to bacterial septicemia associated with bone marrow hypocellularity and lymphoid organ depletion. Remaining animals in this dose group were euthanized due to hypoactivity, hyperthermia, hypersalivation, and/or fecal abnormalities on day 12-13. Coagulation parameters were unaffected. After repeat-dose administration of daily oral talazoparib (BMN 673) in dogs for 5-days, the highest non-severely toxic dose (HNSTD) was 0.03 mg/kg/day.

Twenty-eight day repeat dose toxicity and TK studies with 28-day recovery were also conducted in rats and dogs. In dogs (the most sensitive species), talazoparib (BMN 673) was administered at dosage levels of 0.0005, 0.0015, 0.005, 0.01 mg/kg/day over 28 consecutive days. Talazoparib related signs included hematology findings in males and females given 0.005 or 0.01 mg/kg/day such as mildly lower red cell mass, mildly to moderately lower platelet and absolute reticulocyte counts, and minimally to mildly lower white blood cell counts with a generalized decrease in all leukocytes. All of these signs reversed or were reversing by the end of the recovery phase. After repeat-dose administration of daily oral talazoparib (BMN 673) in dog for 28 days, the HNSTD was 0.01 mg/kg/day.

The main nonclinical dose-related findings were changes in reticulocytes, platelet, white and red blood cell counts in repeat dose studies in rat and dog that were indicative of bone marrow hypocellularity and lymphoid tissue depletion. Findings of increased cellular turnover in the gastrointestinal system and focal necrosis of the liver, testes, and ovary were dose related in severity and incidence. BMN 673ts related mortalities were dose related, categorized as secondary toxicity and were due to either 1) septicemia secondary to bone marrow and lymphoid organ depletion (rat and dog) or 2) at higher dose levels, enteropathy defined by villous atrophy (rat only). All primary toxicity findings were completely or partially reversible in the 28-day recovery time frame tested—decreased reticulocyte, platelet, RBC, and WBC counts were sensitive and early markers of target organ toxicity.

Non-Clinical Pharmacokinetics

Talazoparib (BMN 673) was assessed for activities on PARG, receptor/ion channel and enzyme activity, CYP450, effects on hERG cell current, respiratory and CNS systems and in mutagenic AMES tests, in vitro. No significant undesired effects or talazoparib-related genotoxicity were observed in these studies.

Clinical Experience

The following includes potentially proprietary information from the July 2017 talazoparib Investigator's Brochure:

Approximately 17 studies of talazoparib (single-agent and combination) are ongoing, and as of 30 Nov 2016, approximately 439 patients and 18 healthy volunteers have received talazoparib at doses up to 2 mg/day in company-sponsored clinical studies in hematologic malignancies and solid tumors. Two ongoing investigator-sponsored studies are evaluating the combination of talazoparib with DNA-damaging chemotherapy (temozolomide, irinotecan). The majority of available efficacy and safety data was obtained from studies in solid tumors. A Phase 1 study in patients with advanced or recurrent solid tumors defined the maximum tolerated dose (MTD) of talazoparib as 1 mg/day. Data from this study demonstrated objective responses and/or clinical benefit in patients with breast, ovarian/peritoneal, and pancreatic cancer; SCLC; and Ewing sarcoma. A Phase 2 study evaluating single-agent talazoparib in patients with locally advanced or metastatic breast cancer with deleterious germline BRCA mutations demonstrated single-agent activity with an objective response rate of 27.7%. In the cohort of patients who were previously treated with platinum-containing regimens (N = 48 who were tumor-evaluable), 2 patients had complete responses (CRs). An ongoing Phase 3 study is evaluating talazoparib and physician-choice therapies in patients with germline BRCA mutations who have received no more than 3 prior chemotherapy regimens for locally advanced or metastatic breast cancer. In a Phase 1 study of talazoparib in combination with temozolomide or irinotecan, confirmed partial responses (PRs) were observed in patients with platinum-resistant ovarian cancer, cervical adenocarcinoma, SCLC, and triple-negative breast cancer.

Treatment-emergent adverse events (TEAEs) of all causality reported in ≥20% of patients administered single-agent talazoparib 1 mg/day are related to myelosuppression (anemia, thrombocytopenia, neutropenia), GI toxicity (nausea, diarrhea, constipation), fatigue, alopecia, and headache. TEAEs of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade ≥3 severity in ≥5% of patients were related to myelosuppression. The adverse events (AEs) associated with talazoparib are detectable through routine laboratory and clinical monitoring and may be managed with supportive care or dose reductions or interruptions as described in each study protocol.

The pharmacokinetics (PK) of talazoparib as a single agent was evaluated in 142 adult patients with hematologic malignancies and solid tumors at doses of 0.025 to 2 mg/day administered orally, as a single dose or as multiple doses. The PK was similar in patients of each cancer type and no differences were apparent between males and females. Oral absorption of talazoparib was rapid and independent of dose after administration of single or multiple doses. Elimination appeared to follow biphasic kinetics; at 1 mg/day (the recommended dose), the mean terminal half-life (t1/2) was approximately 2 days. Renal excretion was a major elimination pathway for unchanged parent talazoparib. Following

repeated administration at 1 mg/day, talazoparib accumulated approximately 2.4-fold relative to a single dose. A food-effect study showed that food had no clinically meaningful effect on the extent of absorption; talazoparib is being administered without regard to food in ongoing safety and efficacy studies.

At test concentrations in excess of therapeutic exposures (approximately 200-fold Cmax), talazoparib does not markedly induce or inhibit CYP enzymes. Furthermore, concentrations in excess of therapeutic exposures (approximately 20-fold Cmax) did not inhibit membrane transporter function. Therefore, it is unlikely that talazoparib will demonstrate clinically significant DDIs when co-administered with corresponding CYP or transporter substrates. However, talazoparib is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and plasma talazoparib concentrations may increase or decrease when Co-administered with P-gp or BCRP inhibitors or inducers, respectively.

Additional ongoing Phase 1 company-sponsored clinical studies are evaluating the excretion and plasma PK of carbon 14 (14C)-labeled talazoparib; the PK of talazoparib in patients with renal impairment or hepatic impairment, DDIs, and the effects of talazoparib on cardiac repolarization. Clinical development of talazoparib is ongoing in solid tumors as monotherapy and in combination with other agents.

Potential Food and Drug Interactions
Based on in vitro data, talazoparib (BMN 673) is not likely to inhibit metabolism via human cytochrome P450 (CYP 450) enzymes. Effects of co-administration of repeat dosing of BMN 673 with other drugs are unknown.

Preliminary data from a study to evaluate the effect of food on the pharmacokinetics of talazoparib (BMN 673) in healthy male subjects suggest that food delayed absorption of talazoparib (BMN 673) as indicated by a prolonged T_{max} and reduced C_{max} in the fed compared to fasted state, but did not affect the overall extent of absorption as indicated by equivalent $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ values in the fed and fasted states. Based on these findings, talazoparib (BMN 673) will be taken without regard to food in this current study.

2.3 Rationale

Talazoparib (BMN 673), a highly selective and potent PARP inhibitor, has shown anticancer activity in preclinical models and early clinical trials in the setting of defects in the DNA repair pathway. This pilot study will evaluate the pharmacodynamic effects of talazoparib (BMN 673) on DNA damage and apoptosis markers in tumor biopsy tissue and assess for the antitumor effect of treatment with talazoparib (BMN 673) in patients with advanced ovarian, breast, or other solid tumors, and deleterious BRCA mutations.

2.4 Correlative Studies Background

Tumor biopsies will be mandatory and will be evaluated for pharmacodynamic (PD) studies for evidence of DNA damage repair and apoptosis (e.g., γH2AX, ERCC1, pNbs1, XPF, RAD51, pT1989ATR, activated cleaved caspase 3, and as indicators of ATR/ATM

activation, chk1 and chk2). Circulating tumor cells (CTCs will be collected pre-dose and following study drug administration, on day 1 of every subsequent cycle (every 3 cycles for patients on study for more than 12 months), at the time of the optional restaging follow-up biopsy (if applicable), and at time of disease progression to measure any changes in the number of circulating CTCs and the level of γH2AX, and to evaluate whether we can measure changes in the phenotype over time to explore any correlation with response to treatment or disease progression. Analysis will be performed in Dr. Bob Kinders' lab at the Frederick National Laboratory for Cancer Research.

Histone H2AX is one of the H2A histones present in nucleosomes in normal and cancer tissues and is one of the earliest markers of DNA double-strand breaks [28-30]. γH2AX is phosphorylated at its C-terminus (serine 139 in humans) within minutes following DNA double-strand breaks marking the chromatin domain around the broken chromosomal DNA ends, thus allowing the recruitment of repair factors [28, 30-33]. The levels of γH2AX are directly correlated to the amounts of double-strand breaks, and can be used as a dosimeter and biomarker for DNA double-strand breaks.

Because the product of the PARP enzyme is PAR molecules, a validated immunoassay will be used to determine the amount of cellular PAR in tumor biopsies as a clinical biomarker of PARP inhibition [34, 35].

Additionally, to further understand the potential for carcinomas to adapt to treatment by undergoing epithelial-mesenchymal transition (EMT) and the implications of initial epithelial-mesenchymal phenotype on the response of patients to talazoparib [36, 37], tumor biopsies will be evaluated for markers of epithelial/mesenchymal state, such as E-cadherin, vimentin, and β-catenin.

3 PATIENT SELECTION

3.1 Eligibility Criteria

Adult patients with documented deleterious BRCA 1 or 2 mutations with histologically confirmed ovarian, primary peritoneal, breast, prostate, pancreas, gastric or other solid tumor whose disease has progressed following at least one standard therapy or who have no acceptable standard treatment options.

Patients with ovarian cancer should have one prior platinum-based chemotherapeutic regimen for management of primary disease containing carboplatin, cisplatin, or another organoplatinum compound. This initial treatment may have included intraperitoneal therapy, consolidation, biologic/targeted (non-cytotoxic) agents or extended therapy administered after surgical or non-surgical assessment. Ovarian cancer patients with both platinum-sensitive and platinum-resistant disease are eligible. Patients with platinum-refractory disease are NOT eligible.

Definitions:

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

Patients with metastatic disease must have received at least one line of standard of care (SOC) treatment for metastatic disease prior to enrollment.

3.1.1 Age ≥18 years of age.

3.1.2 ECOG performance status ≤ 2 (see Appendix A).

3.1.3 Life expectancy of greater than 3 months.

3.1.4 Patients must have normal organ and marrow function as defined below:

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	≤1.5 X institutional upper limit of normal
– AST(SGOT)/ALT(SGPT)	≤3 X institutional upper limit of normal
– creatinine	≤1.5X institutional upper limit of normal
	OR
– creatinine clearance	≥60 mL/min for patients with creatinine levels above institutional normal.

3.1.5 The effects of talazoparib (BMN 673) on the developing human fetus are unknown. For this reason and because PARP inhibitors are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 30 days after completing study treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 3 months after completion of talazoparib (BMN 673) administration.

3.1.6 Patients must be able to swallow whole tablets or capsules. Nasogastric or G-tube administration is not allowed. Any gastrointestinal disease which would impair ability to swallow, retain, or absorb drug is not allowed.

3.1.7 Ability to understand and the willingness to sign a written informed consent document.

3.1.8 Patients with HER2-positive advanced breast cancer or ovarian cancer should have received at least two lines of systemic therapy in the advanced setting.

3.1.9 Patients with prostate cancer can continue to receive treatment with GnRH agonists while on study, as long as there is evidence of disease progression on therapy.

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier. Patients who have had prior treatment with any PARP inhibitors are ineligible.

3.2.2 Patients who are receiving any other investigational agents.

3.2.3 Patients with known active brain metastases or carcinomatous meningitis are excluded from this clinical trial. Patients whose brain metastatic disease status has remained stable for ≥ 4 weeks following treatment of brain metastases are eligible to participate at the discretion of the principal investigator.

3.2.4 Eligibility of subjects receiving any medications or substances with the potential to affect the activity or pharmacokinetics of talazoparib (BMN 673) will be determined following review by the principal investigator.

3.2.5 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.

3.2.6 Pregnant women are excluded from this study because the effects of the study drugs on the developing fetus are unknown.

3.2.7 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with talazoparib (BMN 673). In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.2.8 Patients who require use of coumarin-derivative anticoagulants such as warfarin are excluded. Low molecular weight heparin is permitted for prophylactic or therapeutic use. Low-dose warfarin (≤1 mg/day) is permitted.

3.2.9 Women who are currently lactating.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	3	+	1	=	4
Not Hispanic or Latino	17	+	3	=	20
Ethnic Category: Total of all subjects	20 (A1)	+	4 (B1)	=	24 (C1)
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	1	+	0	=	1
Black or African American	2	+	1	=	3
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	17	+	3	=	20
Racial Category: Total of all subjects	20 (A2)	+	4 (B2)	=	24 (C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

3.4 Screening Evaluation

3.4.1 Histologic confirmation of primary tumor tissue or of known recurrence will be required from each participant to confirm diagnosis. Documentation of presence of deleterious BRCA mutations should be available at the time of enrollment.

3.4.2 History and physical examination: Complete history and physical examination (including height, weight, vital signs, and performance score) will be conducted within 72 hours prior to enrollment.

3.4.3 Imaging Studies (Baseline): Every participant should have an evaluation of known sites of disease as part of the baseline evaluation. All patients will be required to undergo a CT scan of the chest/abdomen/pelvis to evaluate sites of disease within 28 days prior to enrollment. MRI evaluation of site of disease may be performed in lieu of CT evaluation at the discretion of the principal investigator if it is the opinion of the investigator that this modality would provide a more accurate assessment of disease than a CT would, for a given site.

3.4.4 Laboratory Evaluation: Baseline laboratory data are to be obtained within 72 hours prior to enrollment:

- Hematological Profile: CBC with differential.
- Biochemical Profile: albumin, total bilirubin, BUN, calcium, creatinine, phosphorus, SGOT [AST], SGPT [ALT], magnesium, potassium, and sodium.

- Coagulation Profile: PT, PTT, INR as clinically indicated prior to tumor biopsy.
- Serum pregnancy test for female participants of childbearing potential.

4 REGISTRATION PROCEDURES

4.1 Registration Process

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the Web site **(**http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail. Please note that it is very important for all registrars to acquire encrypted e-mail from NIH Help Desk, since the verification of registration includes patient's information. A recorder is available during non-working hours.

Off Protocol Therapy and Off-Study Procedure: Authorized staff must notify the Central Registration Office (CRO) when a patient is taken off protocol therapy and when a subject is taken off-study. A Participant Status Update Form from the Web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) ncicentralregistration-l@mail.nih.gov.

5 TREATMENT PLAN

This is an open-label pilot trial of single-agent talazoparib (BMN 673), an oral PARP inhibitor, in patients with histologically confirmed *BRCA*-positive ovarian or primary peritoneal carcinoma; BRCA-positive breast cancer; other solid tumors (other than breast or ovarian) whose disease has progressed following at least one line of standard therapy or who have no acceptable standard treatment options.

Reported adverse events and potential risks for talazoparib (BMN 673) are described in Section 7. Appropriate dose modifications for talazoparib (BMN 673) are described in Section 6.

History and physical examination can be done up to 3 days before the start of a new cycle. Patients will be examined at baseline and within 2 days of day 8 at the clinical center during the first cycle and then prior to every new cycle (up to 3 days before start of a new cycle).

Labs (CBC with differential; serum chemistries) will be performed at baseline, within 2 days of day 8, and during week 3 of cycle 1, and then at the start of each subsequent cycle (up to 3 days before start of a new cycle).

CT scans will be performed at baseline, and repeat-imaging scans will be performed every 2 cycles. MRI evaluation of site of disease may be performed in lieu of CT evaluation at the discretion of the principal investigator if it is the opinion of the investigator that this modality would provide a more accurate assessment of disease than a CT would for a given site.

5.1 Agent Administration

Talazoparib (BMN 673) will be administered orally at 1000 µg/day each day, which is the recommended Phase II dose. Each cycle is 28 days (± 1 day for scheduling). Patients will be asked to maintain a Study Medication Diary (Appendix B) and record each dose of study medication. Patients will be given instructions for completing the medication diary and will be asked to return it to the clinic staff at the end of each cycle. After cycle 2, patients may miss up to 10% of the planned doses for any cycle without causing a protocol violation.

Patients will be considered evaluable for the primary objective of the trial if their biopsy procedures yield matched, evaluable (i.e., ≥5% tumor content) baseline and day 8 tumor biopsies.

Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.2 General Concomitant Medication and Supportive Care Guidelines

The predominant toxicity observed in clinical and non-clinical toxicology studies was bone marrow suppression, with effects on reticulocytes, platelets, and red and white blood cell counts. Weekly blood counts will be obtained during the first cycle, and then at the start of each cycle. If any weekly evaluation demonstrates grade ≥ 2 neutropenia or thrombocytopenia, a repeat hematology assessment will be obtained 3-5 days later.

All patients will be provided with the best available supportive care. All concurrent medications should be documented prior to initiation of treatment, and be periodically reviewed with the patient.

Based on in vitro data, talazoparib (BMN 673) is not likely to inhibit metabolism via human cytochrome P450 (CYP 450) enzymes. Because there is a potential for interaction with other concomitantly administered drugs, the case report form will capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.

5.2.1 Nausea/Vomiting

Anti-emetics will not be administered routinely prior to talazoparib (BMN 673). However, if a patient develops nausea/vomiting, anti-emetics such as but not limited to prochlorperazine, metoclopramide, 5-HT3 antagonists may be given. In addition, if a patient develops nausea and/or vomiting that is Grade 2 or greater,

antiemetics may be instituted prophylactically at the discretion of the investigator. Nausea and vomiting will be considered refractory if it does not resolve to≤ Grade 1 with treatment with a combination of at least 2 of the antiemetics within 24 hours.

5.2.2 Diarrhea

If diarrhea develops and does not have an identifiable cause other than study drug administration, anti-diarrheals such as Lomotil (diphenoxylate HCl 2.5 mg + atropine sulfate 0.025 mg/tablet) dosed according to package insert or loperamide 4 mg po after the first unformed stool with 2 mg po with every 2 hours as long as unformed stools continue (4 mg every 4 hours while asleep). No more than 16 mg of loperamide should be taken during a 24-hour period). This regimen can be repeated for each diarrheal episode. Diarrhea will be considered refractory if it does not resolve within 24 hours ≤ to Grade 2 with the above regimen (16 mg, or less if there is resolution of the symptoms, of loperamide in a 24-hour period). If the patient develops blood or mucus in the stool, dehydration, or hemodynamic instability, or fever along with the diarrhea, anti-diarrheals will be discontinued and the patient will be treated with IV fluids and antibiotics as medically indicated.

5.2.3 Neutropenia

To reduce the risk of severe myelosuppression events, a complete blood count (CBC) should be performed weekly during cycle 1, and at the start of each subsequent cycle (up to 3 days before start of new cycle). Febrile neutropenia is a life-threatening complication requiring hospitalization and urgent broad-spectrum antibiotics, as well as an aggressive search for the source and microbial cause of the episode. Growth factors to prevent neutropenia will not be administered prophylactically. If necessary, they may be administered according to accepted American Society of Clinical Oncology (ASCO) guidelines to allow re-treatment.

5.2.4 Anemia

Symptomatic anemia should be treated with red blood cell transfusion and is recommended if the hemoglobin falls below 8 g/dL. The initiation of erythropoietic therapy for the management of chemotherapy-induced anemia follows the American Society of Hematology/ASCO clinical practice guidelines (http://www.asco.org).

5.2.5 Thrombocytopenia

Thrombocytopenia will be treated conservatively. In the absence of bleeding, or a necessary invasive procedure, platelet transfusions should be given for a platelet count ≤10,000/mm^3. If invasive procedure(s) is (are) planned, or the patient develops bleeding, platelet transfusions should be administered in accordance with the standard of practice, usually maintaining a platelet count above 50,000/mm^3.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Significant toxicity occurs despite 2 dose reductions as described in Section 6
- Pregnancy
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.4 Duration of Follow Up

Patients will be followed for 30 days after the last dose is administered or until one of the following occurs: patient enrolls on another protocol, patient receives standard of care, or death, whichever comes first. The follow-up will consist of a phone call between Days 27-30 after the last dose to evaluate adverse events that were ongoing and any new events that might be deemed related to the therapy. Toxicities felt to be possibly, probably, or definitely related to the study drugs that have not resolved or stabilized by Day 30 post-treatment will be followed until stabilization or resolution via phone calls as clinically indicated.

5.5 Criteria for Removal from Study

Patients will be removed from study for one of the following reasons: completed 30-day follow up period or toxicities are unresolved but stabilized, patient enrolls on another protocol, or patient receives standard of care. The reason for study removal and the date the patient was removed must be documented in the medical record and communicated by fax to Central Registration per Section 4.

6 DOSING DELAYS/DOSE MODIFICATIONS

Toxicities should have resolved to ≤ Grade 2 prior to starting the next cycle. Treatment may be delayed for a maximum of 2 weeks beyond the actual cycle length of 28 days for toxicities that develop and do not resolve as defined above. Beyond two weeks, the patient will not receive further therapy on this protocol and will be followed for resolution of toxicities. Treatments may be delayed up to 7 days past the end of the previous cycle of 28 days for scheduling conflicts at the discretion of the investigator.

Patients will be allowed up to 2 dose reductions per the table below. If more than 2 dose reductions are required, the patient will be removed from the study.

Dose Level	Dose (µg/day)
1	1000
-1	750
-2	500

6.1 Dose Modifications

Dose modifications are defined below:

6.1.1 Patients with creatinine clearance of 30-59 mL/min will be dose reduced to DL-1 (750 µg/day), per the approved talazoparib package insert, and may be re-escalated to DL1 with a creatinine clearance ≥60 mL/min.

6.1.2 Grade 2 Drug-related toxicity: No changes will be made to the dose of talazoparib (BMN 673) for Grade 2 toxicities. Therapy will not be interrupted for Grade 2 hematologic toxicities.

6.1.3 Grade 3-4 Drug-related non-hematologic toxicities: Doses of talazoparib (BMN 673) will be held until toxicities recover to ≤ Grade 2 or baseline prior to re-initiating treatment at the next lower dose level. Electrolyte abnormalities will not require dose reduction if resolution to Grade 2 or less is documented within 72 hours. Dose modifications for nausea, vomiting, and diarrhea will be made only if they are refractory to treatment (See Section 5.2).

6.1.4 Grade 3 Drug-related hematologic toxicities: Dose of talazoparib (BMN 673) will be held until hematologic toxicities, except anemia, lymphopenia, or leucopenia in the absence of Grade 3 or higher neutropenia, have resolved to ≤ Grade 2 prior to re-initiating treatment at the same dose level.

6.1.5 Grade 4 Drug-related Hematologic Toxicities: Dose of talazoparib (BMN 673) will be held until hematologic toxicities, except anemia, lymphopenia, or leucopenia in the absence of Grade 4 neutropenia, have resolved to ≤ Grade 2 prior to re-initiating treatment at the next lower dose level.

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Talazoparib (BMN 673, NSC 771561)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 553 patients.* Below is the CAEPR for Talazoparib (MDV3800, BMN 673).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, June 7, 2019(1)

Adverse Events with Possible Relationship to Talazoparib (MDV3800, BMN 673) (CTCAE 5.0 Term) [n= 553]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 2)***
		Febrile neutropenia	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dyspepsia		
	Mucositis oral		
Nausea			***Nausea (Gr 2)***
		Typhlitis	
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
	Pain		***Pain (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Infection (2)		***Infection[2] (Gr 2)***
INVESTIGATIONS			
	Lymphocyte count decreased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			

Adverse Events with Possible Relationship to Talazoparib (MDV3800, BMN 673) (CTCAE 5.0 Term) [n= 553]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
		Treatment related secondary malignancy	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
Headache			***Headache (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia			***Alopecia (Gr 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]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[3]Neuropathy peripheral may include both Peripheral sensory neuropathy and Peripheral motor neuropathy under the NERVOUS SYSTEM DISORDERS SOC.

Adverse events reported on talazoparib (MDV3800, BMN 673) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that talazoparib (MDV3800, BMN 673) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia)
CARDIAC DISORDERS - Atrial flutter; Sinus bradycardia
GASTROINTESTINAL DISORDERS - Abdominal distension; Flatulence; Intra-abdominal hemorrhage; Small intestinal obstruction; Toothache
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; General disorders and administration site conditions - Other (accidental overdose); Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure; Sinusoidal obstruction syndrome
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Hyperkalemia; Hypokalemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Generalized muscle weakness; Muscle cramp; Myalgia; Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (glioblastoma multiforme); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (metastatic breast cancer); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (metastases to meninges)
NERVOUS SYSTEM DISORDERS - Dysgeusia; Intracranial hemorrhage; Nervous system disorders - Other (neuropathy peripheral)(3); Nervous system disorders - Other (nonserious axonal sensorimotor polyneuropathy); Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Insomnia; Psychiatric disorders - Other (mental status changes)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Epistaxis; Oropharyngeal pain; Pleural effusion; Respiratory, thoracic and mediastinal disorders - Other (obstructive airways disorder)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Rash maculo-papular
VASCULAR DISORDERS - Thromboembolic event

Note: Talazoparib (BMN 673) 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.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP Web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Attribution of the AE:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Expedited Reporting System), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Section 7.3.2).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 Expedited Reporting Guidelines

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

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease Progression"** in the system organ class (SOC) "General disorders and

administration site conditions". Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

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

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

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

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

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

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

Expedited AE reporting timelines are defined as:

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

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

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

7.3.3 Protocol-specific expedited AE reporting exclusions

For this protocol only, certain AEs/grades are exceptions to the Expedited Reporting Guidelines and do not require expedited reporting (i.e., CTEP-AERS). These are any grade lymphopenia, any grade alopecia, Grade 2 electrolyte (sodium, potassium, phosphorous, magnesium) abnormalities, Grade 2 anemia, Grade 2 hypoalbuminemia, Grade 2 hyperglycemia, Grade 2 INR, Grade 2 PTT, Grade 2 hyperglycemia, and Grade 2 hyperuricemia will NOT be reported through CTEP-AERS but will be reported in the routine data submissions.

7.3.4 Pregnancy, Fetal Death, and Death Neonatal

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

7.3.4.1 Pregnancy

- Because patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic, DCTD/DCP is requesting that pregnancy should be reported in an expedited manner via CTEP-AERS as Grade 3 "***Pregnancy, puerperium and perinatal conditions – Other (pregnancy)***" under the ***Pregnancy, puerperium and perinatal conditions*** SOC.
- The pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

7.3.4.2 Pregnancy loss

- Pregnancy loss is defined in CTCAE as "Death in utero." Any pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC.
- A pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

7.3.4.3 Death Neonatal

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

- A neonatal death should be reported expeditiously as Grade 4 "Death neonatal" under the General disorders and administration SOC.
- Neonatal death should NOT be reported as Grade 5 "Death neonatal" under the General disorders and administration SOC. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.

7.3.5 NCI-IRB Expedited Reporting of Adverse Events, Unanticipated Problems, and Deaths

7.3.5.1 Definitions

Adverse event
An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted in Section 7.3.3.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last dose of study drug. AEs that are considered treatment related, expected, continuing, but not resolvable by 30 days after treatment completion (e.g., alopecia) will not be followed after the 30-day period.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

Suspected adverse reaction
Suspected adverse reaction means any adverse event for which there is a *reasonable possibility* that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal

relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse reaction
An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Serious
An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare, or rights of subjects or others.

Serious Adverse Advent
An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Disability
A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse drug experience
Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

Protocol Deviation (NIH Definition)
Any change, divergence, or departure from the IRB-approved research protocol.

Non-compliance (NIH Definition)
The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

Unanticipated Problem
Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to
  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and
  (b) the characteristics of the subject population being studied; A**ND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.3.5.2 NCI IRB and Clinical Director Reporting Requirements

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All protocol deviations
- All unanticipated problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

7.3.5.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must <u>also</u> be reported in routine study data submissions**.

7.4.1 NCI-IRB Requirements for PI Reporting of Adverse Events at Continuing Review

System Organ Class	CTCAE Term	Grade	# of events since last CR	Total # of events	Attribution to Research	Serious?	Unexpected?

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation, and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:

- All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
- All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
- All Grade 5 events regardless of attribution;
- All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

7.5 Secondary Malignancy

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

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

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

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

7.6 Second Malignancy

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

8 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational administered in this study can be found in Section 7.

8.1 Talazoparib (BMN 673; NSC 771561)

Other Names:	BMN 673ts
Chemical Name:	3*H*-Pyrido[4,3,2-de]phthalazin-3-one, 5-fluoro-8-(4-fluorophenyl)-2,7,8,9-tetrahydro-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-, (8***S***,9***R***)-, 4-methylbenzenesulfonate (1:1)
Classification:	PARP Inhibitor
(CAS):	(1207456-01-6)
Mode of Action:	Talazoparib (BMN 673) is a potent and specific inhibitor of PARP1 and PARP2, preventing PARP-mediated DNA repair of single strand DNA breaks via the base-excision repair pathway. It has demonstrated synthetic lethality in tumors with defects in DNA repair pathways such as BRCA mutations and PTEN dysfunction.
Mol. Formula (BMN 673ts)**:**	$C_{26}H_{22}F_2N_6O_4S$
Mol. Weight (BMN 673ts)**:**	552.5624
Description:	Talazoparib (BMN 673) free base is the active moiety of the BMN 673ts (tosylate salt) formulation.
Solubility:	Unknown
How Supplied:	Talazoparib (BMN 673) capsules are supplied by Pfizer, Inc., and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. BMN 673 is supplied as 250 mcg capsules (opaque white, size 4) packaged in 30-count HDPE bottles with an induction seal and child-resistant cap. The hypromellose capsules contain a blend of BMN 673 drug substance, silicified microcrystalline cellulose, titanium dioxide, red iron oxide, and yellow iron oxide. Talazoparib (BMN 673) capsules may be repackaged from the manufacturer-supplied HDPE bottle into a pharmacy-supplied HDPE bottle for dispensing purposes.
Storage:	Drug product is stored at room temperature (15-30°C/59-86° F) and protected from light. If a storage temperature excursion is identified, promptly return BMN 673 to between 15-30°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.
Stability:	Shelf-life surveillance studies of talazoparib (BMN 673) are

	ongoing.
Route of Administration:	Oral: talazoparib (BMN 673) can be taken without regard to food.
Potential Drug Interaction:	Based on in vitro data, talazoparib (BMN 673) is not likely to demonstrate clinically significant CYP450 inhibition- or induction-based drug-drug interactions. Talazoparib (BMN 673) is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) drug transporters. The PK parameters of talazoparib (BMN 673) could be altered if talazoparib (BMN 673) is coadministered with P-gp and BCRP inhibitors/inducers. Studies have shown that talazoparib (BMN 673) is not a substrate or an inhibitor of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, or BSEP transporters.
Availability	Talazoparib (BMN 673) is an investigational agent supplied to investigators by DCTD, NCI. Talazoparib (BMN 673) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and DCTD, NCI.

8.2 Agent 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.

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 anytime. Refer to the PMB’s website for specific policies and guidelines related to agent management.

8.3 Agent Accountability

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.

8.4 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.5 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://ctepcore.nci.nih.gov/iam/index.jsp
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.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)

9 CORRELATIVE/SPECIAL STUDIES

We plan to evaluate the in vivo molecular effects of talazoparib (BMN 673) using pre- and post-treatment tumor biopsy specimens and CTCs. Blood samples for CTCs will be collected during cycle 1 at baseline, 3-6 hours post-drug administration on day 1, approximately 24 hours post-drug administration on day 1 (before day 2 dose), 3-6 hours post-drug administration on day 8, and on cycle 2 day 1, 3-6 hours post dose (± 3 days for scheduling conflicts), on day 1 of every subsequent cycle (every 3 cycles for patients on study for more than 12 months), at the time of the optional restaging follow-up biopsy (if applicable), and at time of disease progression. Mandatory tumor biopsies will be collected for evaluation of levels of DNA-damage repair and apoptosis at baseline and 3-6 hours post-dose on day 8 during cycle 1. One optional tumor biopsy may also be collected either on day 1 (± 2 days) of

the cycle following any restaging at which a 10-19% increase in tumor volume is observed (according to RECIST criteria) if the patient has been on study for at least 4 cycles, or at time of disease progression.

9.1 Pharmacodynamic and Pharmacokinetic Assays

Evaluation of drug effect on DNA damage response will be performed using immunoassays to measure PAR levels and immunofluorescence assays to measure DNA damage-repair markers such as γH2AX, ERCC1, pNbs1, XPF, RAD51, pT1989ATR, activated cleaved caspase 3, and, as indicators of ATR/ATM activation, chk1 and chk2. Evaluation of drug effect on tumor epithelial-mesenchymal phenotype will be performed using immunoassays to measure phenotypic markers of epithelial and mesenchymal states (such as E-cadherin, vimentin, and β-catenin).

9.1.1 Laboratory Contact

At least 24 hours prior to tumor biopsy or blood sample collection, the research nurse will contact the NCI Phase I/II PK/PD Support Group in NIH Building 10: E-mail: NCIPK-PDsupportgroup@mail.nih.gov, Pager: 102-12798 Phone: 301-451-1169 Fax: 301-480-5871. For biopsies, tubes pre-labeled with the information specified in Section 9.3, biopsy date, and site of tissue biopsy will be provided. Initial processing and shipping of the samples will be completed as described below.

9.1.2 Blood Collection for CTC Studies

Whole blood will be collected aseptically by venipuncture or from a venous port into two 4 mL K3-EDTA tubes. The collected blood samples are stable for up to 72 hours at room temperature (15°C to 30°C) prior to processing. Blood samples for CTCs will be collected from all patients at the following (approximate) time points:

- Cycle 1 prior to treatment,
- Cycle 1, day 1: 3-6 hours after dose
- Cycle 1, day 1: approximately 24 hours after first dose (before second dose)
- Cycle 1, day 8: 3-6 hours after dose
- Cycle 2, day 1: 3-6 hours after dose (± 3 days for scheduling conflicts)
- Every subsequent cycle on day 1 prior to treatment (day 1 of every 3 cycles for patients on study more than 12 months)
- At the time of the optional restaging follow-up biopsy, if applicable
- At time of disease progression

9.1.3 Tumor Biopsies

9.1.3.1 Timing of tumor biopsies

Biopsies will be mandatory. Biopsies will be collected at the following time points:

- before drug administration on study (baseline)
- on cycle 1 day 8, 3-6 hours after treatment with talazoparib (BMN 673)
- ***Optional***: one additional biopsy either on day 1 (± 2 days) of the cycle following any restaging at which a 10-19% increase in tumor volume is observed (according to RECIST criteria) if the patient has been on study for at least 4 cycles, or at disease progression

9.1.3.2 Biopsy Procedure

Serial tumor biopsies will be obtained by the Interventional Radiology team by a percutaneous approach. It is preferred that up to 5 core biopsies 18-gauge in diameter and ≥1 cm in length will be obtained during each procedure if considered safe and feasible. It is estimated that there will be between 2 million–5 million cells from each biopsy. If a site is deemed appropriate for biopsy with minimal risk to the participant by agreement between the investigators and Interventional Radiology team, an attempt for biopsy will be made. If possible, the lesion from which each biopsy is taken will be documented, and an attempt will be made to collect biopsies at subsequent timepoints from the same lesion, at the discretion of the Interventional Radiology team.

The use of imaging to facilitate biopsies will be decided by members of the Interventional Radiology team and may include ultrasound, CT scan, or MRI. Should a CT scan be needed for biopsy, the number of scans for each procedure will be limited to the minimum number needed to safely obtain a biopsy. Tumor biopsies and local anesthesia will be administered only if they are considered to be of low risk to the participant, as determined by the investigators and Interventional Radiology.

If the participant chooses not to undergo tumor biopsy, he/she will still remain in the study and receive study medication, and all the other correlative studies will be performed.

Tumor biopsies are mandatory. Baseline biopsies will be performed following patient enrolling on study. If an initial attempt at percutaneous biopsy is unsuccessful, the patient will be given an option to proceed with a repeated attempt at percutaneous biopsy. A separate consent form must be signed for each biopsy procedure, so patients may choose not to undergo subsequent biopsies. If the baseline biopsy is unsuccessful or the patient refuses to undergo subsequent biopsies, no further biopsies will be performed but the patient will remain on study, receive study medication, and other correlative studies will be performed.

9.1.3.3 Solid Tumor Biopsy Processing

Up to five tissue cores will be collected. The cores will be transferred into a 1.5-mL pre-chilled cryovial and then flash frozen in liquid nitrogen per DCTD SOP340507 (http://dctd.cancer.gov/ResearchResources/biomarkers/

docs/par/SOP340507_Biopsy_Frozen.pdf). Samples will be submitted to Dr. Kinders' laboratory for evaluation of DNA damage markers, and H&E pathology evaluation. The frozen biopsy specimens are transferred to PADIS on dry ice, where the core biopsy samples are stored at -80°C and subsequently processed within 7-10 days for analysis. Biopsy samples will be analyzed for PAR levels and DNA damage response and apoptosis as described above; any additional cores will be flash-frozen and kept for future analysis.

9.1.4 Shipping of samples for pharmacodynamic analysis

Biopsies for PD analysis will be shipped on dry ice to:
Attention: Dan Danner
NCI-F/FNLCR
1073 Beasley Street, Building 1073
Fort Detrick
Frederick, MD 21701
Phone: 301-846-5748
NCI_PD_Support@mail.nih.gov

Blood for CTC analysis will be shipped at room temperature (15°C to 30°C) to:

Attention: Dan Danner
NCI-F/FNLCR
1073 Beasley Street, Building 1073
Fort Detrick
Frederick, MD 21701
Phone: 301-846-5748
NCI_PD_Support_CellSearch@mail.nih.gov

Shipment should be by CSP Courier and may be arranged by contacting Jenn Bangh, FNLCR, Tel.: 301-846-5893

9.1.5 Blood Collection for Pharmacokinetic Analysis

Please note: *As of Amendment H (2/5/2018) blood for PK analysis will no longer be collected.*
Whole blood will be collected aseptically by venipuncture or from a venous port into a 5 mL K3 EDTA vacutainer at room temperature for plasma separation per Appendix D.
Blood samples will be collected from all patients at the following time points:

- cycle 1 day 1 pre-dose and then 0.5, 1, 2, 3, 4, 6, 8, and 24 hours post-dose
- cycle 1 day 8 (3-6 hours post dose)
- cycle 2 day 1 pre-dose and 3-6 hours post dose (± 2 days for scheduling conflicts)

Plasma samples should be shipped as described in Appendix D.

9.2 Sample Collection and Processing

Biospecimens will be collected and processed using validated SOPs that will ensure both specimen quality and patient confidentiality pursuant to informed consent provisions. Information about each specimen (e.g., blood, tumor biopsy, circulating tumor cells, per specific protocol) will be recorded on a PK/PD collection worksheet included in Appendix C.

Using a computerized inventory system and a backup hardcopy process, all specimen collection and processing steps will be documented and the specific location of each specimen will be tracked. Each new specimen collected will be assigned a unique barcode identifier that can be linked to the original specimen collected and other relevant information within the inventory system. To ensure patient confidentiality, only containers used for the initial specimen collections will be labeled with patient identifiers.

Only the barcode identifier will be applied to all subsequent specimen containers. When specimens are processed and aliquoted, no patient information will be included on the new containers. Original specimen containers will be discarded. Only barcode-labeled specimens without patient identifiers will be shipped for analysis and/or storage. Specimen labels will indicate: CTEP protocol number, unique patient accession number, 3-digit sample number (see list below), collection time, and total volume collected, as appropriate. Samples from sets of at least three patients will be grouped for scientific analysis.

Standardized 3-digit sample collection numbers:
200 series: blood for PK
400 series: blood for circulating tumor cells (CTCs)
500 series: tumor biopsies

The inventory process contains other security provisions sufficient to safeguard patient privacy and confidentiality. Access to the inventory system and associated documents will be restricted to appropriate individuals. Requests to use specimens stored in the repository must be approved. The only patient information available in the inventory system will be the patient sex, diagnosis, and level of informed consent given. SOPs ensure that any changes in informed consent made by a patient and relayed to the PI will be reflected in the inventory system to ensure that specimens are destroyed as appropriate. All laboratory personnel will be trained to adhere to SOPs and will be monitored for high-quality performance.

Any new use of these samples will require prospective IRB review and approval. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e., broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

9.3 Human Data Sharing Plan

What data will be shared?
We will share human data generated in this research for future research as follows:
X De-identified data in an NIH-funded or approved public repository
X Identified data in BTRIS (automatic for activities in the Clinical Center)
X De-identified or identified data with approved outside collaborators under appropriate agreements

How and where will the data be shared?
Data will be shared through:
X An NIH-funded or approved public repository: clinicaltrials.gov
X BTRIS (automatic for activities in the Clinical Center)
X Approved outside collaborators under appropriate individual agreements
X Publication and/or public presentations

When will the data be shared?
X At the time of publication or shortly thereafter

10 STUDY CALENDAR

Baseline evaluations are to be conducted within 72 hours prior to start of protocol therapy. Scans and x-rays must be done ≤ 4 weeks prior to the start of therapy. Start of next cycle may be delayed for up to 1 week to accommodate scheduling conflicts. History and physical examination and laboratory evaluations can be performed up to 3 days before the start of the next cycle.

Study Procedure	Screen	Study Treatment								
		Cycle 1				Cycle 2 and subsequent cycles				Off Treatment
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4	
Talazoparib (BMN 673)[a]		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Informed consent	**X**									
Demographics	**X**									
Medical history	**X**									
Concurrent meds	**X**	**X**----------**X**								
Physical exam[b]	**X**		**X**			**X**				**X**
Vital signs	**X**		**X**			**X**				**X**
Height	**X**									
Weight	**X**					**X**				**X**
Performance status	**X**					**X**				**X**
CBC w/diff, plts[c]	**X**		**X**	**X**		**X**				**X**
Serum chemistry[c]	**X**		**X**	**X**		**X**				**X**
PT, INR, PTT[d]	**X**									
β-HCG[e]	**X**									
Adverse event evaluation	**X**	**X**----------**X**								
Tumor measurements	**X**	Tumor measurements are repeated every 2 cycles. Documentation (radiologic) must be provided for patients removed from study for progressive disease.								**X**
Tumor biopsy[f]	**X**		**X**							
Circulating tumor cells[g]	**X**	**X**	**X**			**X**				
Blood for PK[h]										

a. Talazoparib (BMN 673) will be administered orally at 1000 µg/day each day for 28 days.
b. Physical examination at the Clinical Center should be performed at the start of each cycle (up to 3 days before start of a new cycle and within 2 days of day 8 during cycle 1.
c. Serum chemistry (albumin, total bilirubin, calcium, creatinine, creatine clearance, phosphorus, magnesium, potassium, sodium, SGOT [AST], SGPT [ALT]); CBC w/diff, platelets at baseline, within 2 days of day 8, and during week 3 of cycle 1, then every 4 weeks at the start of each subsequent cycle (up to 3 days before start of a new cycle). If clinically indicated, labs may be obtained with more frequency with subsequent cycles.
d. PT/INR, PTT prior to biopsy.
e. Serum pregnancy test (women of childbearing potential) within 1 week prior to enrollment and as clinically indicated.
f. Tumor biopsies will be prior to treatment and 3-6 hrs after the talazoparib (BMN 673) dose on day 8. One optional tumor biopsy may also be obtained either on day 1 (± 2 days) of the cycle following any restaging at which a 10-19% increase in tumor volume is observed (according to RECIST criteria) if the patient has been on study for at least 4 cycles, or at disease progression.
g. CTCs will be obtained prior to drug administration; 3-6 hours and then approximately 24 hours post drug administration (prior to day 2 dose) on day 1, 3-6 hours post drug administration on day 8 in cycle 1, and 3-6 hours post drug administration on day 1 of cycle 2 (± 3 days for scheduling conflicts), on day 1 of every subsequent cycle (every 3 cycles for patients on study more than 12 months) before drug administration, and at time of disease progression
h ***Please note:*** *As of Amendment H (2/5/2018) blood for PK analysis will no longer be collected.*

11 MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated for response every 8 weeks (every 2 cycles). In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with talazoparib (BMN 673).

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit

objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

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

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

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

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with

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

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

11.2 Guidelines for Evaluation of Measurable Disease

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

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

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

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

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of

the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

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

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

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

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

11.3 Response Criteria

11.3.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

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

11.3.2 Evaluation of Non-Target Lesions

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

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

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

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

11.3.3 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.

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**

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

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

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

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

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

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

11.4 Duration of Response

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

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

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

12 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be collected in the Center for Cancer Research C3D database and will be transmitted to CTMS electronically at least once every 2 weeks.

Note: **All** adverse events that have occurred on the study, including those reported through CTEP-AERS, must be reported via the monitoring method identified above.

12.1.2 Responsibility for Data Submission

N/A

12.2 CTEP Multicenter Guideline

N/A

12.3 Collaborative Agreements Language

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

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this

protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from http://ctep.cancer.gov.

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

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

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

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

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164.

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

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

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an

additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

E-mail: ncicteppubs@mail.nih.gov

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

13 STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

Patients will receive talazoparib (BMN 673) orally at 1000 μg/day, each day, in 28-day cycles. Tumor biopsies will be mandatory predose and 3-6 hours post talazoparib (BMN 673) dose on cycle 1 day 8.

Up to 24 patients will be accrued to assure at least 16 patients with matched, evaluable baseline and day 8 biopsies (with 97% likelihood). The primary endpoint will be the percent of patients who achieve a sustained PD response, defined to be at least 4% nuclear area positive (NAP) γH2AX at the day 8 biopsy. In clinical testing, this level of γH2AX is seen less than 5% of the time at baseline (in the absence of an active agent) [38]. If we observe at least 3 out of the 16 (19%) patients with evaluable baseline and day 8 biopsies achieving such a sustained PD response, we will declare the agent promising by means of the PD assay. This design will give us 90% power to detect a true 30% sustained PD response rate, across patients with less than .04 probability of a false positive in the event that the agent has no effect and the true likelihood of such a sustained PD response, for an individual patient, is less than 5%. [*Note:* As of 3/24/2020, this study has closed to accrual. The PD response rate will be determined and tested against the null hypothesis of 5% (the rate of false positivity for the threshold value of 4% NAP γH2AX).]

13.2 Sample Size/Accrual Rate

A total of 16 patients with matched, evaluable baseline and day 8 biopsies will be enrolled. Patients who have at least 4% NAP at the pre-treatment biopsy will not be included in the primary analysis and for sample size calculations would not be considered evaluable. In order to allow for some patients who will not be evaluable, the accrual ceiling for the study is 24 patients. As of July, 2017, 9 patients have been enrolled with 6 having evaluable

matched biopsy pairs. Additional patients will be enrolled, up to an accrual ceiling of 15 (or 24 total patients), yielding a 99% likelihood of accruing 12 patients with evaluable biopsy pairs.

It is anticipated that 2-3 patients may be enrolled per month onto this study. It is expected that an additional 8-12 months (as of July, 2017) will be required to accrue the number of patients necessary to complete the trial.

13.3 Analysis of Exploratory Pharmacodynamic Endpoints

Mean and SD of change in % NAP, from pre-treatment baseline to day 8 among all patients and among patients who achieve a sustained PD response.
Mean and SD of ERCC1 at pre-treatment baseline and at day 8 among all patients and among patients who achieve a sustained PD response.

14 HUMAN SUBJECTS PROTECTIONS

14.1 Justification for Subject Selection

This study will be open to all individuals regardless of gender, ethnicity, or race, provided that the aforementioned inclusion and exclusion criteria are met. Patients for this study will be recruited through internal referral, our physician referral base, and through various cancer information hotlines (i.e., Clinical Studies Support Center, 1-800-4Cancer). To date, there is no information that suggests that differences in drug metabolism or effect on tumor would be expected in one ethnic group compared to another. Efforts will be made to extend accrual to each representative population, but a balance must be struck between participant safety considerations and limitations on the number of individuals exposed to potentially ineffective treatments on the one hand and the need to explore racial/ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to ethnic identity are noted, a follow-up study may be written to investigate those differences more fully.

Due to lack of knowledge of the effects of talazoparib (BMN 673) on the fetus or infants, as well as the possibility of teratogenic effects, pregnant and nursing women will be excluded from this trial. Patients with unstable or serious medical conditions are excluded due to the possibility that talazoparib (BMN 673) may worsen their condition and the likelihood that the underlying condition may obscure the attribution of adverse events to talazoparib (BMN 673). HIV-positive patients on combination antiretroviral therapy are excluded from the study because of possible PK interactions with talazoparib (BMN 673).

14.1.1 Participation of Children

This study includes patients 18 years of age and older. Because insufficient dosing or adverse event data are currently available on the use of talazoparib (BMN 673) in patients <18 years of age, children are excluded from this study, but may be eligible for future pediatric trials. Studies will be performed in patients <18 years of age when it is appropriate to do so.

14.2 Evaluation of Benefits and Risks/Discomforts

There may or may not be any clinical benefit to a patient from participation in this trial. Their participation will benefit future cancer patients. Potential risks include the possible occurrence of any of a range of side effects that are listed in the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients as described in Sections 5 and 6. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which participants are entitled under applicable regulations.

14.3 Consent and Assent Process and Documentation

An associate or principal investigator on the trial will inform patients of the purpose, alternatives, drug administration plan, research objectives, and follow-up of this trial. The patient will be provided an IRB-approved consent for review and signature and his/her questions will be answered. After a decision is made to enroll into the study, a signature will be obtained from the patient. The original signed consent goes to Medical Records; a copy will be placed in the research record. Patients will not be consented by telephone.

All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on study.

14.3.1 Participation of subjects unable to give consent

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation, all subjects ≥ age 18 at the NCI only will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MEC Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

14.4 Procedure for Protecting Against or Minimizing Any Potential Risks

All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. This study may involve risks to patients, which are currently unforeseeable. All patients will be monitored for side effects from taking study medication. This research represents a greater than minimal risk to participants, but presents the prospect of direct benefit to individual subjects.

The research component of this study required to obtain 3 CT tumor biopsies confers radiation exposure at an effective dose of 2.4 rem. This dose is below NIH RSC guidelines of less than 5.0 rem per year in adults, and represents a slightly greater than minimal risk to patients.

14.5 Patient Advocate

The patients' rights representative is available to patients receiving treatment on this protocol at the NIH Clinical Center at (301) 496-2626 in Building 10 of the Clinical Research Center, Room 1-3521, on the Bethesda NIH campus. Patients will be informed that they can contact the study PI or RN at any time with questions about their medical care, and that the patients' rights representative is also available to answer non-medical questions about the study.

15 REFERENCES

1. Ame, J.C., C. Spenlehauer, and G. de Murcia, *The PARP superfamily.* Bioessays, 2004. **26**(8): p. 882-93.

2. Tomoda, T., et al., *Enhanced expression of poly(ADP-ribose) synthetase gene in malignant lymphoma.* Am J Hematol, 1991. **37**(4): p. 223-7.

3. Shiobara, M., et al., *Enhanced polyadenosine diphosphate-ribosylation in cirrhotic liver and carcinoma tissues in patients with hepatocellular carcinoma.* J Gastroenterol Hepatol, 2001. **16**(3): p. 338-44.

4. Fukushima, M., et al., *Poly(ADP-ribose) synthesis in human cervical cancer cell-diagnostic cytological usefulness.* Cancer Lett, 1981. **14**(3): p. 227-36.

5. Alderson, T., *New targets for cancer chemotherapy--poly(ADP-ribosylation) processing and polyisoprene metabolism.* Biol Rev Camb Philos Soc, 1990. **65**(4): p. 623-41.

6. Wielckens, K., et al., *ADP-ribosylation of nuclear proteins in normal lymphocytes and in low-grade malignant non-Hodgkin lymphoma cells.* Eur J Biochem, 1980. **104**(1): p. 279-87.

7. Berger, N.A., et al., *Synthesis of DNA and poly(adenosine diphosphate ribose) in normal and chronic lymphocytic leukemia lymphocytes.* J Clin Invest, 1978. **62**(1): p. 111-8.

8. Hirai, K., K. Ueda, and O. Hayaishi, *Aberration of poly(adenosine diphosphate-ribose) metabolism in human colon adenomatous polyps and cancers.* Cancer Res, 1983. **43**(7): p. 3441-6.

9. Fernet, M., et al., *Poly(ADP-ribose) polymerase, a major determinant of early cell response to ionizing radiation.* Int J Radiat Biol, 2000. **76**(12): p. 1621-9.

10. Shall, S. and G. de Murcia, *Poly(ADP-ribose) polymerase-1: what have we learned from the deficient mouse model?* Mutat Res, 2000. **460**(1): p. 1-15.

11. Masutani, M., et al., *The response of Parp knockout mice against DNA damaging agents.* Mutat Res, 2000. **462**(2-3): p. 159-66.

12. Ame, J.C., et al., *PARP-2, A novel mammalian DNA damage-dependent poly(ADP-ribose) polymerase.* J Biol Chem, 1999. **274**(25): p. 17860-8.

13. Menissier de Murcia, J., et al., *Functional interaction between PARP-1 and PARP-2 in chromosome stability and embryonic development in mouse.* Embo J, 2003. **22**(9): p. 2255-63.

14. Schreiber, V., et al., *Poly(ADP-ribose) polymerase-2 (PARP-2) is required for efficient base excision DNA repair in association with PARP-1 and XRCC1.* J Biol Chem, 2002. **277**(25): p. 23028-36.

15. Memisoglu, A. and L. Samson, *Base excision repair in yeast and mammals.* Mutat Res, 2000. **451**(1-2): p. 39-51.

16. Ruscetti, T., et al., *Stimulation of the DNA-dependent protein kinase by poly(ADP-ribose) polymerase.* J Biol Chem, 1998. **273**(23): p. 14461-7.

17. Galande, S. and T. Kohwi-Shigematsu, *Poly(ADP-ribose) polymerase and Ku autoantigen form a complex and synergistically bind to matrix attachment sequences.* J Biol Chem, 1999. **274**(29): p. 20521-8.

18. Boulton, S., S. Kyle, and B.W. Durkacz, *Interactive effects of inhibitors of poly(ADP-ribose) polymerase and DNA-dependent protein kinase on cellular responses to DNA damage.* Carcinogenesis, 1999. **20**(2): p. 199-203.

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

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

21. Iglehart, J.D. and D.P. Silver, *Synthetic lethality--a new direction in cancer-drug development.* N Engl J Med, 2009. **361**(2): p. 189-91.

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

23. Fong, P.C., et al., *Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers.* N Engl J Med, 2009. **361**(2): p. 123-34.

24. Audeh, M.W., et al., *Phase II trial of the oral PARP inhibitor olaparib (AZD2281) in BRCA-deficient advanced ovarian cancer.* ASCO Meeting Abstracts, 2009. **27**(15S): p. 5500-.

25. Tutt, A., *Phase II trial of the oral PARP inhibitor olaparib in BRCA-deficient advanced breast cancer.* ASCO Meeting Abstracts, 2009. **27**(15S): p. 5500.

26. Shen, *LT-00673, a highly potent PARPIs, shows antitumor activity against tumor cells with DNA repair deficiencies.* AACR 101st Annual Meeting. AACR 101st Annual Meeting Washington DC Poster # 3514, 2010.

27. Wang, B., et al., *Novel PARP Inhibitors with Potent Anti-tumor Activity as Single-agent and Combination Therapies. Mol Cancer Ther 8 12 Supplement 1 (abstract # A121).* 2009.

28. Fernandez-Capetillo, O., et al., *H2AX: the histone guardian of the genome.* DNA Repair, 2004. **3**(8-9): p. 959-967.

29. Rogakou, E.P., et al., *DNA double-stranded breaks induce histone H2AX phosphorylation on serine 139.* Journal of Biological Chemistry, 1998. **273**(10): p. 5858-5868.

30. Paull, T.T., et al., *A critical role for histone H2AX in recruitment of repair factors to nuclear foci after DNA damage.* Current Biology, 2000. **10**(15): p. 886-895.

31. Bassing, C.H. and F.W. Alt, *H2AX may function as an anchor to hold broken chromosomal DNA ends in close proximity.* Cell Cycle, 2004. **3**(2): p. 149-153.

32. Redon, C., et al., *Histone H2A variants H2AX and H2AZ.* Current Opinion in Genetics & Development, 2002. **12**(2): p. 162-169.

33. Celeste, A., et al., *Genomic instability in mice lacking histone H2AX.* Science, 2002. **296**(5569): p. 922-927.

34. Kummar, S., et al., *Phase 0 clinical trial of the poly (ADP-ribose) polymerase inhibitor ABT-888 in patients with advanced malignancies.* J Clin Oncol, 2009. **27**(16): p. 2705-11.

35. Kummar, S., et al., *A phase I study of veliparib in combination with metronomic cyclophosphamide in adults with refractory solid tumors and lymphomas.* Clinical Cancer Research, 2012. **18**(6): p. 1726-34.

36. Allison Stewart, C., et al., *Dynamic variations in epithelial-to-mesenchymal transition (EMT), ATM, and SLFN11 govern response to PARP inhibitors and cisplatin in small cell lung cancer.* Oncotarget, 2017. **8**(17): p. 28575-28587.

37. Stark, T.W., et al., *Predictive value of epithelial-mesenchymal-transition (EMT) signature and PARP-1 in prostate cancer radioresistance.* Prostate, 2017. **77**(16): p. 1583-1591.

38. Wilsker, D.F., et al., *Evaluation of Pharmacodynamic Responses to Cancer Therapeutic Agents Using DNA Damage Markers.* Clin Cancer Res, 2019. **25**(10): p. 3084-3095.

APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: PATIENT'S MEDICATION DIARY

Today's Date _____Cycle #_____ Daily BMN 673 Dose_____µg

Patient Name_____(*initials acceptable)* **Patient Study ID _____**

INSTRUCTIONS

1. Complete one form for each cycle of treatment.
2. Swallow each capsule whole with a full glass of water with or without food. Do not chew or open the capsules. If capsule is broken and the powder of the capsules gets on skin, wash the exposed area with as much water as necessary. Inform investigator or nurse if that occurs.
3. Record the date and time you took the drugs.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring this form and your bottle of talazoparib (BMN 673) with when you return for your appointment.
6. In case of errors, please place a single slash mark through the error and initial it. Please do not white out any error or scribble it out with ink. Please do not write the correct information directly over the error, but on a separate line next to the error.

Day	Date	Time of dose	Number of capsules taken 250 µg	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				

Day	Date	Time of dose	Number of capsules taken 250 µg	Comments
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

Patient's signature: _____

APPENDIX C: PD/PK COLLECTION WORKSHEETS

Date:	**SAMPLE COLLECTION SHEET: Cycle 1 DAY 1/2**		
CTEP Protocol 9510 **Talazoparib (BMN 673) Dose:** **Patient ID:**	**Ht:** **Wt:** **BSA:**	**Page 102-12798 for Sample Pick-up** **Lab phone: 301-451-1169**	**Research Nurse:** Phone: **PI: A. P. Chen, MD** Phone: 301 768-2749

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
Day 1	**Prior to drug administration**	**PD 400** 2x 4 mL K3 EDTA Label tube: sample number, date and time			
Administer talazoparib (BMN 673); Time:_____					
Day 1	**3-6 hours after drug**	**PD 401** 2x 4 mL K3 EDTA Label tube: sample number, date and time			
Day 1	**24 hours after drug**	**PD 402** 2x 4 mL K3 EDTA Label tube: sample number, date and time			

Date:	**SAMPLE COLLECTION SHEET: Cycle 1 Day 8**		
CTEP Protocol 9510 **Talazoparib (BMN 673) Dose:** **Patient ID:**	**Ht:** **Wt:** **BSA:**	**Page 102-12798 for Sample Pick-up** **Lab phone: 301-451-1169**	**Research Nurse:** Phone: PI: **A. P. Chen, MD** Phone: 301 768-2749

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
Administer talazoparib (BMN 673); Time:_____					
Day 8	**3-6 hours after drug**	**PD 403** 2x 4 mL K3 EDTA Label tube: sample number, date and time			

Date:	**SAMPLE COLLECTION SHEET: Cycle 2 Day 1**				
CTEP Protocol 9510 **Talazoparib (BMN 673) Dose:** **Patient ID:**		**Ht:** **Wt:** **BSA:**	**Page 102-12798 for Sample Pick-up Lab phone: 301-451-1169**	**Research Nurse:** Phone: **PI: A. P. Chen, MD** Phone: 301 768-2749	
PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION					
Day	**Time**	**Instructions**	**Ideal Time**	**Actual Time**	**Record comments (i.e., if collection missed), and sign each time you collect a sample**
Administer talazoparib (BMN 673); Time:_____					
Day 1	**3-6 hours after drug**	**PD 404** 2x 4 mL K3 EDTA Label tube: sample number, date and time			

Date:	**SAMPLE COLLECTION SHEET: Cycle 3 and onwards Day 1/Per PI**		
CTEP Protocol 9510 **Talazoparib (BMN 673) Dose:** **Patient ID:**	**Ht:** **Wt:** **BSA:**	**Page 102-12798 for Sample Pick-up Lab phone: 301-451-1169**	**Research Nurse:** Phone: **PI: A. P. Chen, MD** Phone: 301 768-2749

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
Day 1	**Prior to drug administration**	**PD 40X** 2x 4 mL K3 EDTA Label tube: sample number, date and time			

Date:	**SAMPLE COLLECTION SHEET: Day of restaging follow-up or progression biopsy**		
CTEP Protocol 9510 **Talazoparib (BMN 673) Dose:** **Patient ID:**	**Ht:** **Wt:** **BSA:**	**Page 102-12798 for Sample Pick-up Lab phone: 301-451-1169**	**Research Nurse:** Phone: **PI: A. P. Chen, MD** Phone: 301 768-2749

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
Day 1	**Prior to drug administration**	**PD 40X** 2x 4 mL K3 EDTA Label tube: sample number, date and time			

APPENDIX D: PK SAMPLE HANDLING AND SHIPPING

Please note: *As of Amendment H (2/5/2018) blood for PK analysis will no longer be collected.*

Pharmacokinetic Blood Sampling and Plasma Sample Preparation

- Affix completed sample labels lengthways to vacutainer and cryovials. Each blood sample must be processed within 1 hour of draw.
- Collect approximately 5 mL of blood in K3 EDTA vacutainer tubes **at room temperature.**
- Invert vacutainer gently 8-10 times.
- Centrifuge at 1500 x g for 10 minutes **at room temperature**.
- Transfer 0.8 mL of plasma into each of three 2-mL cryovials. To avoid contamination, always use a new transfer pipette for each sample, and do not remove the plasma near the precipitate.
- Transfer plasma samples to -70^{o}C freezer (within 2 hours of collection).
- Ship 2 cryovials of plasma (primary samples) on dry ice (shipping instructions below). Ship backup samples on dry ice in a separate shipment.

PK Sample Shipping Log and Instructions

- Ship PK plasma samples every 3 months or when requested.
- Use an electronic manifest for each shipment (see below). Each manifest should indicate the subject ID, time points, and number of samples included in the shipment.
- Place samples grouped by subject in cryobox. Ensure the cryobox is closed and remains so in transit using shipping tape. Place the cryobox in a sealable Biohazard bag with an appropriate amount of absorbent.
- Each shipment should be prepared in accordance with IATA regulations. Samples must be shipped at least 3 days prior to US National Holiday.
- Frozen samples should be shipped via Fed Ex, Monday through Wednesday. **No shipments should be made later than Wednesday of any given week**. (Samples should arrive by Friday, not on the weekend, because it is closed on weekends.)
- For questions regarding sample shipment, contact Lara Graham, 610-296-3152, lgraham@alliancepharmaco.com.
- On the day of shipment, e-mail the completed electronic manifest, the tracking number and other appropriate paperwork to Lara Graham (lgraham@alliancepharmaco.com)

  Lara Graham
  Sample management
  Alliance Pharma
  17 Lee Blvd.
  Malvern, PA19355
  Ph: 610-296-3152
  lgraham@alliancepharmaco.com

Sample PK Shipment Manifest: Talazoparib (BMN 673) Plasma Samples from Study NCI/CTEP #9510
To: lgraham@alliancepharmaco.com

Sponsor: National Cancer Institute/CTEP **P9510**

Date Shipped:

No. of items shipped:

Shipped by:

Item No	Pt/Sample ID	Description	Day	Time Point	Cycle	Draw Date and Time	Unit	Quantity	Volume
1		Plasma PK					cryovial		
2		Plasma PK					cryovial		
3		Plasma PK					cryovial		
4		Plasma PK					cryovial		
5		Plasma PK					cryovial		
6		Plasma PK					cryovial		
7		Plasma PK					cryovial		
8		Plasma PK					cryovial		
9		Plasma PK					cryovial		
10		Plasma PK					cryovial		
11		Plasma PK					cryovial		
12		Plasma PK					cryovial		
13		Plasma PK					cryovial		
14		Plasma PK					cryovial		
15		Plasma PK					cryovial		
16		Plasma PK					cryovial		
17		Plasma PK					cryovial		
18		Plasma PK					cryovial		