Amendment

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Protocol Title: A Phase 2 Pilot Study of BMN 673 (Talazoparib), an Oral PARP Inhibitor, in Patients with Deleterious BRCA1/2 Mutation-Associated Ovarian Cancer who have had prior PARP Inhibitor Treatment

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* Signature signifies that investigators on this protocol have been informed that the collection and use of personally identifiable information at the NIH are maintained in a system of record governed under provisions of the Privacy Act of 1974. The information provided is mandatory for employees of the NIH to perform their assigned duties as related to the administration and reporting of intramural research protocols and used solely for those purposes. Questions may be addressed to the Protrak System Owner.

** I have reviewed this research project and considered the NIH Policy for Inclusion of Women and Minorities in Clinical Research. Taking into account the overall impact that the project could have on the research field involved, I feel the current plans adequately includes both sex/gender, minorities, children, and special populations, as appropriate. The current enrollment is in line with the planned enrollment report for inclusion of individuals on the basis of their sex/gender, race, and ethnicity and is appropriate and of scientific and technical merit.

IRB Meeting Date: Expedited

DEC Clearance Date: 09/01/2016

Protocol Version Date: 08/08/2016

NCI Protocol #: 9632

Local Protocol #: 15-C-0050, Amendment C

TITLE: A phase 2 pilot study of BMN 673 (Talazoparib), an oral PARP inhibitor, in patients with deleterious BRCA1/2 mutation-associated ovarian cancer who have had prior PARP inhibitor treatment

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A. *Obtain information by intervening or interacting with living individuals for research purposes*
B. *Obtaining identifiable private information about living individuals*
C. *Obtaining the voluntary informed consent of individuals to be subjects*
D. *Makes decisions about subject eligibility*
E. *Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes*
F. *Studying, interpreting, or analyzing de-identified data or specimens for research purposes*
G. *Some/all research activities performed outside NIH*

Investigational Agents:

Drug Name:	BMN 673 (Talazoparib), NSC 771561
IND Number:	119558
Sponsor:	CTEP
Manufacturer:	BioMarin Pharmaceutical Inc.

PRÉCIS

Background:

- Patients with germline BRCA1/2 mutations (gBRCAm) demonstrate repeated therapeutic susceptibility to DNA damaging agents, especially platinums, even if they have previously progressed on a similar (platinum-based) regimen.
- PARP inhibitors (PARPi) have clinical activity in gBRCAm-associated malignancies, although patients eventually develop progressive disease.
- BMN 673 (talazoparib) is a novel PARPi, with excellent oral bioavailability and greater anti-tumor activity *in vitro* and *in vivo* at lower concentrations than first generation PARPi.
- It is unknown whether secondary BRCA mutations or other potential mechanisms of clinical resistance portend cross-resistance to a highly potent PARPi.

Objectives:

- To determine the objective response rate (CR+PR) of single agent BMN 673 (talazoparib) in ovarian cancer patients with gBRCAm who have progressed on prior PARPi therapy.

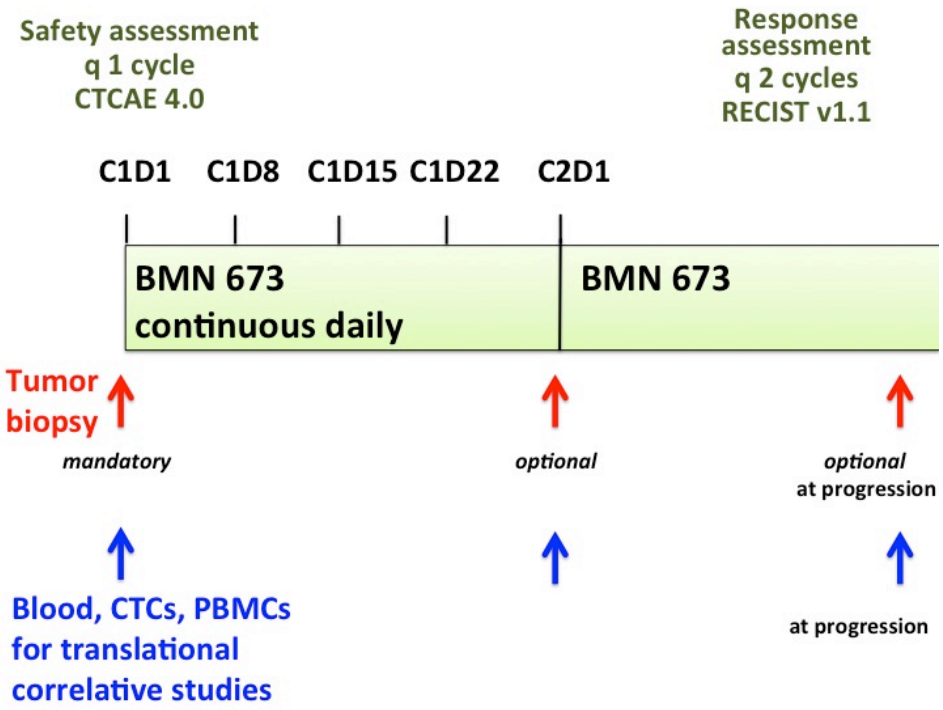
Eligibility:

- Women with recurrent and/or metastatic gBRCAm-associated ovarian cancer, with progression on PARPi monotherapy within the immediate prior 2 months of the time of screening visit.
- Patients should have responded to their prior PARPi therapy (CR, PR or SD>4months).
- Patients cannot have received another therapy between stopping their first PARPi therapy and initiating therapy on this trial, but must be off the prior PARPi for at least 4 weeks.
- ECOG performance status 0-2 and adequate organ and marrow function.

Design:

- This is an open label, single arm phase II trial to examine activity of BMN 673 (talazoparib).
- Patients will receive BMN 673 (talazoparib) at the RP2D of 1mg p.o. once daily on 28 day cycles.
- Research samples including whole blood, plasma, CTCs, and tumor biopsies will be obtained for PD endpoints at baseline, ~cycle 1 day 29 (prior to cycle 2 day 1), and/or at progression in all patients.
- Patients will be evaluated every two cycles for response using RECISTv1.1 criteria and every cycle for safety using CTCAEv4.0.

SCHEMA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Response assessment
q 2 cycles
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C1D8
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C1D22
C2D1
BMN 673
continuous daily
BMN 673
Tumor biopsy
mandatory
optional
optional
at progression
Blood, CTCs, PBMCs
for translational
correlative studies
at progression

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1 OBJECTIVES

1.1 PRIMARY OBJECTIVE

1.1.1 To determine the objective response rate (CR+PR) of the single agent BMN 673 (talazoparib) in ovarian cancer patients with germline BRCA1/2 mutations (gBRCAm) who have progressed on prior PARP inhibitor (PARPi) therapy.

1.2 SECONDARY OBJECTIVES

1.2.1 To determine the safety and toxicity of BMN 673 (talazoparib) in patients with gBRCAm-associated ovarian cancer in the second PARPi exposure setting.

1.2.2 To determine the progression-free survival (PFS) in patients with gBRCAm-associated ovarian cancer in the second PARPi exposure setting.

1.2.3 To compare PFS on BMN 673 (talazoparib) with the PFS from the first PARPi exposure.

1.2.4 To determine if a tumor gain-of-function mutation in BRCA1/2 occurred after initial PARPi exposure.

1.3 EXPLORATORY OBJECTIVE

1.3.1 To correlate biochemical changes in the DNA damage repair proteins and/or other pathways in tumor and blood with response to treatment.

2 BACKGROUND

2.1 STUDY DISEASE

Approximately 15% of high grade serous ovarian cancers are deficient in homologous recombination [1] DNA double strand break (DSB) repair due to germline *BRCA*1 and *BRCA*2 mutation (gBRCAm).[2] Patients with gBRCAm ovarian cancers have increased therapeutic susceptibility to platinums,[3] thus, often receive multiple lines of platinum-based chemotherapy and have a longer median survival time than those without gBRCAm.[3-6] They are also more sensitive than other ovarian cancers to DNA-damaging agents, such as pegylated liposomal doxorubicin, even after acquiring platinum resistance.[7] Our phase 1 study of olaparib and carboplatin (08-C-0092) also confirms that gBRCAm carriers with platinum resistant/refractory disease can have repeated clinical benefit from platinum-based regimens.[8] Our study yielded a clinical benefit rate of 70% in 20 gBRCAm patients with platinum resistant/refractory ovarian cancer. We observed a 25% PR and 45% SD, and with a median duration of response of 5 months (4^{+}-17) and 10.5 months (4-25), respectively. Poly(ADP-ribose) polymerase inhibitors (PARPi) have demonstrated promising results in preclinical and clinical studies, as a monotherapy or in combination therapy in gBRCAm-associated malignancies. Moderate response rates and prolonged time to progression have been seen, although patients eventually develop progressive disease, and require subsequent treatments. Retrospective studies have indicated that these patients do not lose susceptibility to other chemotherapeutic agents after treatment with a PARPi.[9] Thus, it is plausible to speculate that ovarian cancer patients with gBRCAm may have a second clinical response to another PARPi after prior progressive disease on the first PARPi.

Ang et al[10] recently reported gBRCAm carriers with ovarian cancer respond well to chemotherapy, including platinum-based regimens, after developing progressive disease on olaparib monotherapy; all patients received olaparib ≥200mg bid dosing, for at least 1 month. The overall objective response rate (ORR) was 36% (24/67 patients) by RECIST and was 45% (35/78) by RECIST and/or GCIG-CA125 criteria, with median progression-free survival (PFS) and overall survival (OS) of 17 weeks and 34 weeks, respectively. This response rate (RR) is similar to that seen in initially platinum-sensitive patients who have had a platinum-free interval of over 24 months.[11] This efficacy of post-olaparib chemotherapy in gBRCAm carriers was greater than expected given that ORR to second or advanced lines of chemotherapy in recurrent ovarian cancer is below 20%.[12] *BRCA1, BRCA2, TP53*, and *PTEN* were examined by massively parallel sequencing in 6 patient tumor samples from that study and there was no evidence of revertant mutations in *BRCA1*. This and other studies have led to an estimated frequency of such mutations, adjusted for sample size, to be a relatively uncommon event (12.5% [95%-CI: 0-37.5%]). [9] [13]

Preclinical data[14-16] suggest that exposure to PARPi may occur and if so, may compromise benefit to subsequent treatment. One documented mechanism is acquisition of secondary mutations of *BRCA1* and *BRCA2*. There are no comprehensive clinical studies to date examining the prevalence of secondary *BRCA1* and *BRCA2* mutations in patients who have received and progressed on PARPi, and whether they will respond to the subsequent PARPi. A retrospective study by Norquist et al[13] showed 13 of 46 women (23%) with gBRCAm-associated recurrent ovarian cancer had revertant mutations in *BRCA1* or *BRCA2*, restoring wild-type sequencing after multiple chemotherapies. Twelve (46.2%) of 26 platinum-resistant ovarian cancers within that group had secondary mutations after platinum-based chemotherapy, compared with one (5.3%) of 19 with platinum-sensitive disease ($p = 0.003$). Six patients with platinum-resistant recurrent ovarian cancer were then treated with olaparib-based therapy. One of three patients with known secondary mutations restoring BRCA1 and BRCA2 function had a partial response to olaparib-based therapy. Thus, it is unclear whether secondary *BRCA1* and *BRCA2* mutations do predict poor second clinical response to PARPi or platinum-based therapy. Additionally, it is unknown whether this predicts cross-resistance to a second PARPi, independently of PARPi potency. *Hence, we hypothesize that patients with gBRCAm-associated ovarian cancer may respond to a second, possibly more potent PARPi, after progressive disease on a PARPi*.

Investigating the clinical response, dissecting and defining mechanisms of clinical resistance to PARPi, and examining cross-resistance to another PARPi and other DNA damaging agents is critical. The PARPi-treated gBRCAm group is now emerging as a new patient population with unmet therapeutic needs. Our study will lead to optimal application and sequencing of PARPi administration, and create an opportunity for identification of predictive biomarkers for the subsequent use of another PARPi.

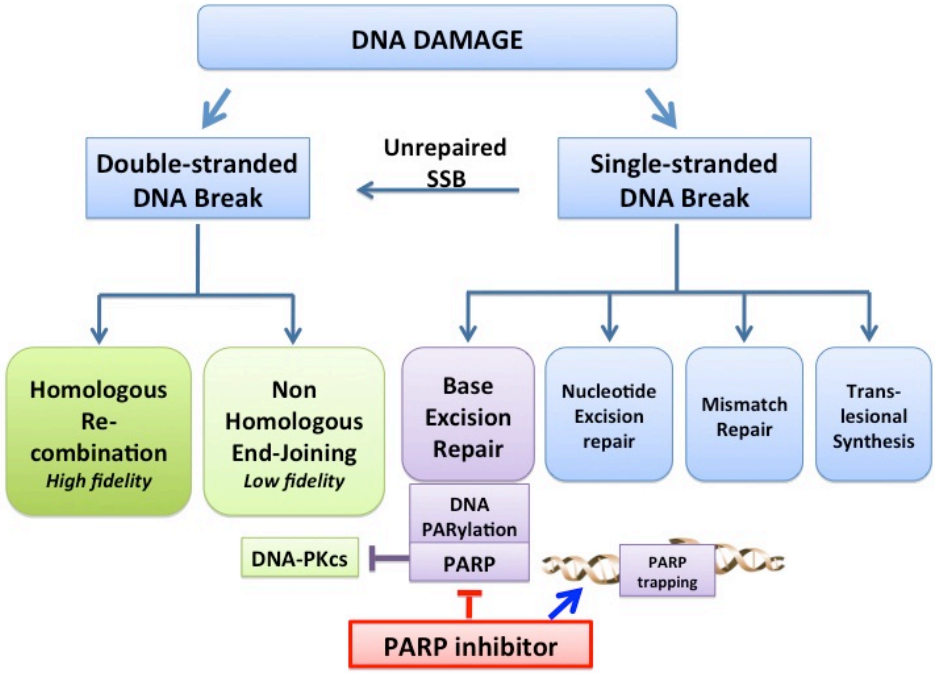

Figure 1. DNA double strand and single strand breaks repair pathways

PARPi were initially thought to mediate their antitumor effects as catalytic inhibitors of PARP-1 and PARP-2, and block repair of DNA single strand break (SSB). However, the mechanism(s) of action of PARPi are not fully understood (Figure1). Dr. Pommier's group in the Developmental Therapeutics Branch/CCR reported a new mechanism[14]. They showed that PARPi trap the PARP1 and PARP2 enzymes at damaged DNA sites, preventing DNA replication and transcription. Trapped PARP–DNA complexes were more cytotoxic than unrepaired SSBs caused by catalytic PARP inhibition. Moreover, there is different potency in PARP trapping among PARPi (niraparib and olaparib >> veliparib), which correlates with their different anti-tumor activities in early clinical studies. PARPi that bind to the catalytic domain can allosterically alter the binding affinity of PARP enzyme to DNA. BMN 673 (talazoparib) is the most potent PARP-trapping PARPi, and more cytotoxic at an equimolar concentration, than olaparib, in both BRCA mutated- and BRCA-wild type cell lines.[17] Trapping of PARP-DNA complexes also leads to replication fork damage but utilizes additional repair pathways including the Fanconi pathway (FA), template switching (TS), ATM, FEN1 (replicative flap endonuclease), and polymerase b proteins. BMN 673 (talazoparib)'s trapping activity could be another mechanism to further stress chromosomal instability and apoptosis in tumors with revertant mutations in *BRCA1* or *BRCA2*.

Approximately 95% of high-grade serous ovarian cancer (HGSOC) have p53 dysfunction. This leads cells to proceed prematurely into mitosis with incompletely replicated and broken chromosomes due to the absence of the G2/M checkpoints, ultimately arrest in prometaphase. More replication origins are activated than the replication apparatus can tolerate in early S phase, resulting in slowed and arrested DNA replication forks, and DNA DSB. Thus, it is postulated that PARP-DNA trapping alone can generate DNA damage and mitotic catastrophe in either HR-

competence or - incompetence HGSOC cells, despite the absence of DNA damage by external agents.

2.2 BMN 673 (TALAZOPARIB), A NOVEL, HIGHLY POTENT ORAL PARPI

2.2.1 Preclinical data

Preclinical studies of BMN 673 (talazoparib)[18] confirm that BMN 673 (talazoparib) is a highly potent PARP1/2 inhibitor (PARP1 IC_{50} = 0.57 nM), with anti-tumor cytotoxicity at lower concentrations than earlier generation PARPi (Table 1).

Table 1. In vitro activities of BMN 673 (Talazoparib) and other PARP inhibitors[18]

	PARP1 Enzyme Inhibition IC_{50} (nM)	Cellular PAR Synthesis EC_{50} (nM)	Capan-1 Cytotoxicity IC_{50} (nM)
Veliparib	4.73	5.9	>10,000
Rucaparib	1.98	4.7	609
Olaparib	1.94	3.6	259
LT-00628	1.82	4.5	8
BMN 673	0.57	2.5	5

Activities of BMN 673 (talazoparib), LT-00628, and three clinical PARPi, veliparib, rucaparib, and olaparib were compared in three *in vitro* assays: (i) IC_{50} for PARP1 enzymatic activity; [19] cellular PAR synthesis inhibition IC_{50} in human colon adenocarcinoma (LoVo) cells; and (iii) Capan-1 cell survival IC_{50} in a single-agent cytotoxicity assay. Values are average data from three to four independent experiments.

In vitro, BMN 673 (talazoparib) selectively targeted tumor cells with BRCA1/2 mutation or PTEN deficiency, with 20- to >200-fold greater potency than first generation PARPi. Several PARPi were screened for the concentration required to elicit a 20% reduction in cell survival (surviving fraction 80, SF_{80}). SF_{80} was achieved with a nanomolar concentration of BMN 673 (talazoparib) (12.5nM) in a moderately PARPi-resistant triple negative breast cancer cell line (CAL51), compared to the micromolar concentrations of other PARPi. Further, SF_{50} data also indicate BMN 673 (talazoparib) is highly potent in BRCA1/2 and PTEN deficient cell lines (Table 2). It has single-agent cytotoxicity in *BRCA1* mutant MX-1 breast cancer cells (IC_{50} 0.3 nM) and *BRCA2* mutant CAPAN-1 cells (IC_{50} 5nM).

Table 2. BMN 673 (Talazoparib) is highly potent in BRCA1/2 and PTEN deficient cell lines[18]

	SF_{50} (μM)								
	MX-1 (BRCA1 deficient)	SUM149 (BRCA1 deficient)	Capan-1 (BRCA2 deficient)	MB-468 (PTEN deficient)	LNCap (PTEN deficient)	PC-3 (PTEN deficient)	SW620	MDA-MB-231	MRC-5 (Normal)
Veliparib	ND	0.818	>10	ND	ND	ND	ND	ND	>10
Rucaparib	0.0053	0.0079	0.609	0.220	0.737	0.293	ND	5.53	8.53
Olaparib	0.0232	0.0198	0.259	0.368	0.589	0.787	ND	6.41	5.83
BMN 673	0.0003	8.57E-6	0.005	0.006	0.003	0.004	0.13	1.85	0.31

A variety of cultured human tumor cell lines were treated with veliparib, rucaparib, olaparib, or BMN 673 (talazoparib), and tumor-killing effects were assessed either by colony formation assays (SUM149) or two-dimensional cytotoxicity assays (all other cell lines). Survival curves were plotted and the IC_{50} was calculated. Known deficiency of HR DNA repair genes is indicated in parenthesis. Cells with BRCA1/BRCA2 mutations or PTEN deficiency were more sensitive to all PARPi than cells lacking these mutations.

Further, three PARPi including BMN 673 (talazoparib), olaparib and rucaparib were examined in wild type, and BRCA2-truncated mutant ($BRCA2^{tr/-}$) genetically engineered avian B-lymphoblast DT40 cells.[20] Cell viability assays showed markedly reduced ATP concentrations in both HR-deficient ($BRCA2^{tr/-}$) and wild type DT40 cells by PARPi (Figure 2A). Three PARPi were also examined by cell viability assay in both human Ewing's sarcoma (EW8) and prostate cancer (DU145) cell lines. These cell lines are known to be susceptible to PARP inhibition due to interaction between PARP1 and ERG to inhibit ETS gene fusion protein activity. Inhibition of PARP1 was reported to reduce ETS-positive, but not ETS-negative, prostate cancer xenograft growth.[21] Olaparib and rucaparib were again less cytotoxic than BMN 673 (talazoparib) in EW8 and DU145 cells (Figure 2B). These results show a greater PARP-mediated cytotoxicity of BMN 673 (talazoparib) than olaparib and rucaparib in comparable molar concentrations, leading to the possibility that there may be greater potency with at least similar if not improved outcome.

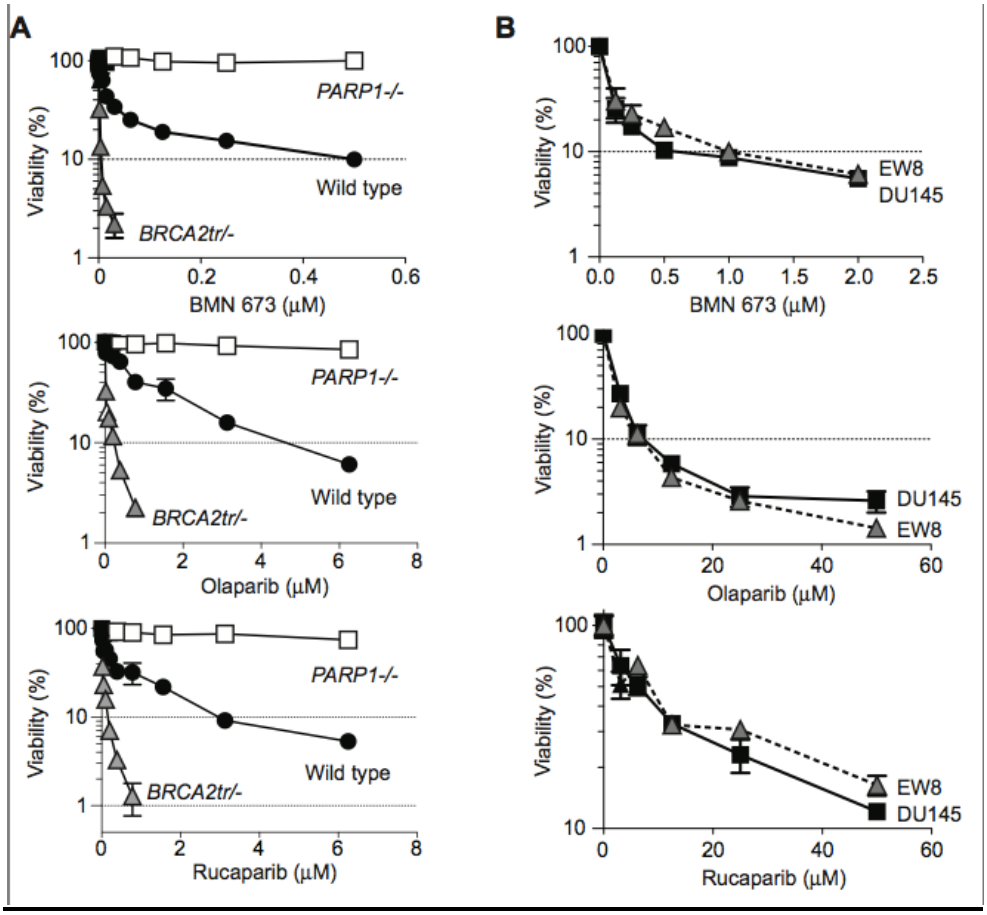

Figure 2. Cell viability with PARPi in *in vitro* models. Survival curves of wild type, PARP1$^{-/-}$, and BRCA2$^{tr/-}$ DT40 cells (A: left), and DU145 and EW8 cells (B: right).[22]

For all experiments, viability curves were derived after continuous treatment for 72 hours with the indicated PARPi in the indicated cell lines.

BMN 673 (talazoparib) is readily orally bioavailable, with >50% absolute oral bioavailability in rats when dosed in carboxylmethyl cellulose. Xenografted tumors carrying defects in DNA repair due to BRCA1/2 mutation or PTEN deficiency are profoundly sensitive to oral BMN 673 (talazoparib) treatment at doses well tolerated in mice. Once daily oral dosing of BMN 673 (talazoparib) at 0.33 mg/kg/day results in complete response in the MX-1 tumor model (Figure 3). At the lower dose of 0.1mg/kg, oral BMN 673 (talazoparib) have only a small effect on tumor growth after extended treatment (>21days), but is still more effective than olaparib dosed orally at 100mg/kg once daily. BMN 673 (talazoparib) is well tolerated at these doses (0.33mg/kg and 0.1 mg/kg), with no animal lethality or significant weight loss observed after 28 consecutive, daily, oral doses. Pharmacodynamic studies also demonstrate potent PARP inhibition by BMN 673 (talazoparib) in mouse tumor biopsies.

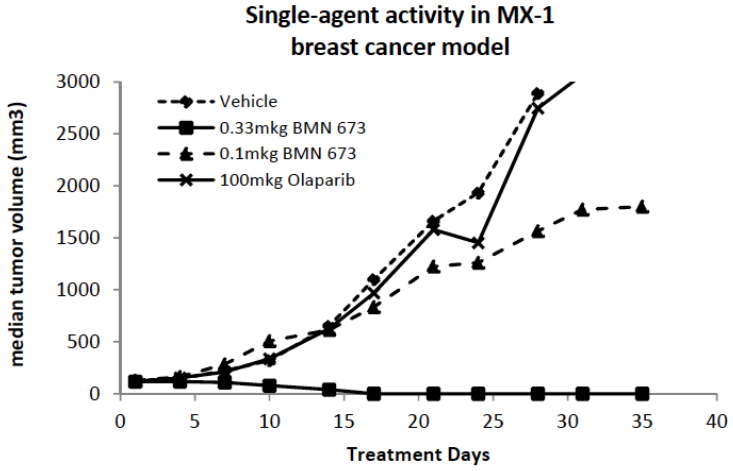

Figure 3. *In vivo* anti-tumor activity of BMN 673 (Talazoparib)[18]

BMN 673 (talazoparib) exhibits antitumor activity against a BRCA-mutant tumor model in mice. MX-1 human mammary xenografts were inoculated subcutaneously in female athymic nu/nu mice. When tumors reached an average volume of approximately 150 mm^3 (range, 100–196 mm^3), mice were randomized into various treatment groups, and were treated orally, once daily for 28 consecutive days, with BMN 673 (talazoparib) (0.33 or 0.1 mg/kg/d), olaparib (100 mg/kg/d), or empty vehicle. Median tumor volume was plotted against days of treatment (first day of treatment is defined at day 1).

Hence, this highly active agent is the ideal agent to examine in ovarian cancer patients with prior PARPi exposure due to its a) increased molar activity, b) greater PARP trapping activity, c) oral bioavailability, d) manageable drug class side effects, and e) novelty.

2.2.2 Preliminary clinical data

Dose

Two phase I dose escalation studies are ongoing (study PRP-001; NCT01286987, and study PRP-002; NCT01399840, 2013 IB). The first-in-human phase 1 (PRP-001; Table 3) is a 2-part, single-arm study in patients with advanced solid tumors considered to have defects in DNA-repair pathways, particularly those with BRCA and PTEN dysfunction. Preliminary PRP-001 study results indicate BMN 673 (talazoparib) is well tolerated with anti-tumor activity in patients with gBRCAm, yielding a single agent recommended phase II trial dose of 1000 µg/d continuous daily dosing in 4-week cycles. 39 patients (33F/6M) were enrolled in 9 cohorts dosed from 25 to 1100 µg/d, defining a MTD of 1000 µg/d. Inhibition of PARP activity in PBMCs was observed at doses ≥ 100 µg/d. The expansion cohort included tumors with gBRCAm, including 17

gBRCAm ovarian/primary peritoneal, 6 gBRCAm breast, 1 gBRCA2m pancreas, and 1 gBRCA2m prostate cancers.

Table 3. Dose Levels (DLs): phase I studies of BMN 673 (Talazoparib) in advanced cancer patients (total 47 patients)

Study Number	Dose	Number of Patients	Duration of Exposure (Range, Days)
PRP-001	25 µg/day	3	35-98
	50 µg/day	3	34-205
	100 µg/day	3	65-253
	200 µg/day	3	35-435
	400 µg/day	3	97-268
	600 µg/day	6	58-289
	900 µg/day	6	34-252
	1000 µg/day	14[b]	1-92
	1100 µg/day	6	15-126

[a] Includes data from ongoing trials (2013 IB).

[b] One patient received a single dose at 1100 µg/day prior to that dose level being deemed above the MTD.

BMN 673 (talazoparib) has also been examined in subjects (PRP-002) with advanced hematological malignancies (arm 1) or with other defects in DNA-repair pathways, including RAD51 or ATM dysfunction (arm 2). The initial cohort of patients was treated with 100 µg BMN 673 (talazoparib) once daily. At the time of the Investigational Brochure Ver. 3 (dated 11 March 2013) update, 29 patients have been enrolled dosed up to 1350 µg/day.

Adverse events interim summary

Dose-limiting toxicities (DLTs) were thrombocytopenia in 1 of 6 and 2 of 5 patients at 900 and 1100 µg/d, respectively, in patients on the PRP-001 study. No DLTs have occurred in arm 1 of the PRP-002 study. In arm 2 of a PRP-002 study, dose-limiting events of grade 4 neutropenia occurred in 2 of 5 patients receiving 900 µg/day, with one of the patients experiencing neutropenic sepsis.

The most common grade 3/4 adverse events [19] related to BMN 673 (talazoparib) were hematologic toxicities, consistent with known PARPi class effects:

- Seven patients have reported grade 3 anemia. One patient experienced an SAE of grade 3 anemia; other six events were not drug-related.
- Seven patients have reported AEs of grade 3/4 thrombocytopenia (4 in PRP-001, and 3 in PRP-002). All events were considered to be non-serious.
- Eight patients have reported AEs of grade 3/4 neutropenia. One patient experienced an

SAE of grade 3 neutropenic sepsis; all other events have been reported as non- serious.

A total of 50 serious adverse events (SAEs) were reported occurring in 30 of 76 patients (39.5%) in both studies, including febrile neutropenia (4), and anemia (2). Only two SAEs were described as related to BMN 673 (talazoparib): grade 3 anemia, and neutropenic sepsis.

No treatment-related deaths were reported. Nine patient deaths occurring on the study PRP-001 were attributed to either rapid disease progression (7), or other causes, including pneumonia (1), and renal impairment (1).

Other drug-related and dose-related AEs have included alopecia, fatigue, and gastrointestinal side effects.

Pharmacokinetics

Interim PK data were available from 39 patients across the dosing range of 25 - 1100 µg (study PRP-001; 2013 IB). Patients received a single dose on day 1 and were followed for PK assessments for 7 days. On day 8, patients started daily dosing through day 35 (Figure 4). On day 35, patients were followed for 7 days without additional dosing for washout PK assessments. Overall, BMN 673 (talazoparib) plasma concentrations peaked 1-2 hrs post-dose, and exposure increased dose proportionally. Most patients obtained steady-state plasma concentrations by the end of the second week of daily dosing (day 22).

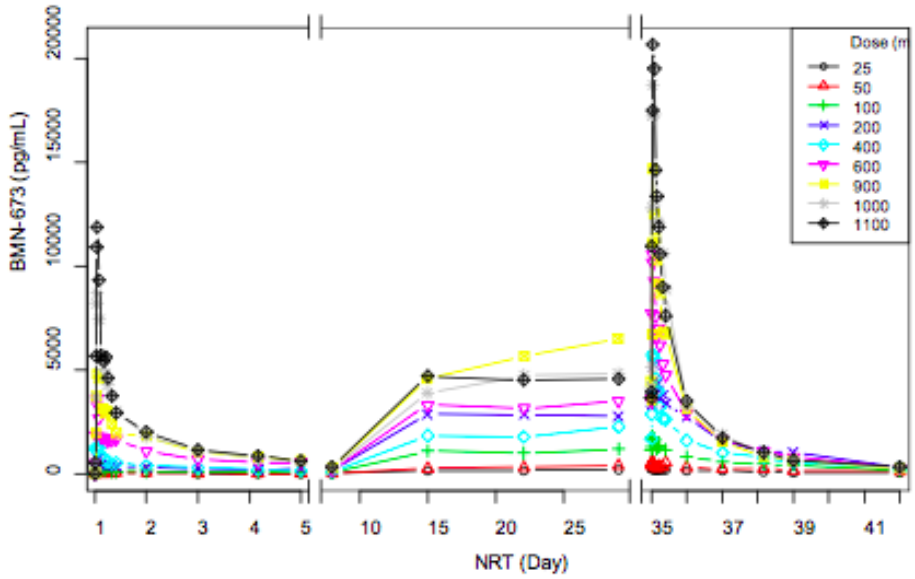

Figure 4. Mean PK profiles by dose of BMN 673 (Talazoparib)

Mean BMN 673 (talazoparib) plasma concentration by dosing through cycle 1 of part 1 of PRP-001

NRT: normal relative time

Following a single dose, mean plasma C_{max} and $AUC_{0\text{-}24hr}$ ranged from 788 to 13,200 pg/mL and from 9,140 to 92,100 pg-hr/mL, respectively, over the 200 to 1100 µg dose range. Steady state was apparent in most patients by two weeks with daily dosing. Following single doses, BMN

673 (talazoparib) C_{max} and $AUC_{0\text{-}24hr}$ were linear between 400 and 1100 µg. Following multiple doses, BMN 673 (talazoparib) C_{max} and $AUC_{0\text{-}24hr}$ were linear between 25 and 1100 µg/day. Table 4 shows a summary of the resulting PK parameters (2013IB).

Table 4. PK parameters: phase I studies of BMN 673 (Talazoparib) in advanced cancer patients

Dose (µg)	Day (N[a])	$AUC_{0\text{-}24}$ (pg-hr/mL)	C_{max} (pg/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	Vz/F (L)	CL/F (L/hr)	C_{min} (pg/mL)	AF
200	1 (N=3)	9140 (3550)	788 (369)	1 [1, 2]	216 (134)	676 (219)	2.60 (1.36)	--	--
	35 (N=3)	83200 (49300)	5620 (3530)	2 [1, 3]	49.7 (14.1)	249 (212)	3.11 (1.91)	2740 (1510)	9.14 (4.56)
400	1 (N=3)	13500 (5170)	1830 (699)	2 [0.75, 3]	100 (22.7)	1040 (399)	7.01 (1.85)	--	--
	35 (N=3[c])	54800 (11800)	6560 (1500)	1 [0.75, 2]	69.2 (23.7)	637 (245)	6.49 (2.05)	1610 (629)	5.57 (3.30)
600	1 (N=6)	37700 (12900)	4100 (1400)	0.75 [0.75, 2]	61.7 (17.8)	449 (146)	5.00 (0.86)	--	--
	35 (N=6)	119000 (20000)	11300 (3230)	0.88 [0.75, 6]	50.3 (8.15)	379 (114)	5.15 (0.89)	2870 (592)	3.34 (0.78)
900	1 (N=6)	58300 (24200)	6100 (3060)	2 [1, 10]	59.8 (10.4)	458 (163)	5.45 (2.09)	--	--
	35 (N=5)	157000 (24100)	15400 (1540)	1 [1, 2]	51.8 (12.1)	440 (133)	5.86 (0.93)	3030 (852)	3.69 (2.40)
1000	1 (N=5)	84100 (27600)	10600 (4220)	1 [0.75, 2]	53.5 (14.1)	415 (172)	5.33 (1.53)	--	--
	35 (N=6)	203000 (54800)	21000 (7990)	1 [0.75,	40.4 (14.2)	311 (155)	5.23 (1.40)	3520 (1270)	2.42 (0.32)

				2]					
1100	1 (N=7)	92100 (33100)	13200 (3220)	1 [0.75, 2]	66.1 (15.2)	515 (205)	5.33 (1.63)	--	--
	35 (N=4)	189000 (28100)	23400 (4810)	1.5 [1, 2]	49.5 (9.19)	419 (76.3)	5.91 (0.80)	2910 (803)	2.53 (0.48)

[a] One patient (1217-0807), received a 1100 µg dose on Day 1 and 1000 µg from Day 8 onwards.

[b] N=2 for AUC_{0-24}, $t_{1/2}$, Vz/F, and CL/F due to missing postdose samples beyond 10 hours postdose and an indeterminate lambda-z for patient 1217-0101

[c] N=2 for AUC_{0-24} due to missing predose sample for patient 1217-0503

Values are presented as mean (SD), expect for T_{max} which is represented as median [min, max]

Table 5 also shows the comparison of *in vitro* and plasma concentration of BMN 673 (talazoparib) with other PARPi.

Table 5. Plasma concentration and *in vitro* concentration of BMN 673 (Talazoparib) and other PARPi.

		Olaparib(AZD2281)	**Veliparib(ABT888)**	**BMN 673 (Talazoparib)**
Biologically active dose		400mg oral twice daily	300mg oral twice daily	0.025 to 1.1mg oral daily (RP2D 1mg daily)
Physiologically attainable blood level in patients	$C_{max\ ss}$	1.45 to 11.0 µg/mL (3.34 to 25.3 µM) with 50 to 400mg (Astra Zeneca IB)	0.9µmol/L with 50mg (Kummar et al JCO 2009)	0.3 to 25.4 ng/mL (=0.79 to 66.8 nM)
	AUC_{0-24SS}	6.56 – 122 ug-hr/mL.	Not available	3.96 – 203 ng-hr/mL
IC_{50} in vitro		Up to 20µM in BRCAwt (0.2 to 4 µM in gBRCA1/2^{m} breast and ovarian cancer cell lines)	> 20µM in BRCA wild-type and gBRCA2m ovarian cancer (1.9 to 4.4 µM in gBRCA1/2m breast and ovarian cancer cell lines)	0.3 to 5nM

Preliminary activity data

As of this writing, one patient with platinum resistant ovarian cancer achieved a complete response. RECIST and/or CA-125 responses occurred in 19/28 (68%) gBRCAm ovarian/peritoneal cancer patients (RECIST response only 11/25 [44%]). Objective responses occurred in 7/18 (38%) gBRCAm breast cancer patients.

2.3 POTENTIAL BIOMARKERS AND MECHANISMS OF PARP INHIBITOR CLINICAL RESISTANCE

It has been demonstrated that increased DNA repair capacity in tumor cells is associated with resistance to platinums, alkylators, or radiation, and significantly limits the efficacy of these agents in most diseases.[23] Potential mechanisms of clinical resistance to PARPi include but not limited to (1) restoration of BRCA function due to secondary *BRCA1* and *BRCA2* mutations as discussed above; (2) increased activity of RAD51; (3) loss of 53BP1; and, (4) downregulation of DNA-PKcs or KU 80, key proteins in non-homologous end joining (NHEJ) activity.

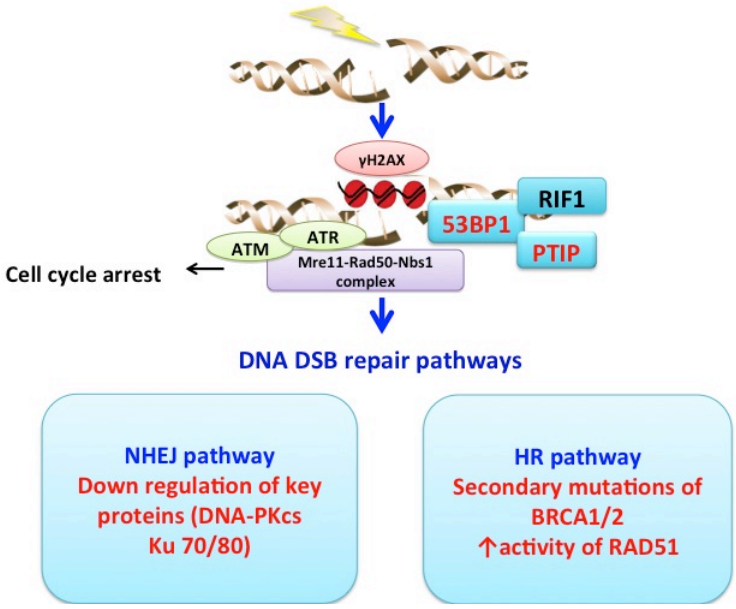

Figure 5. Potential mechanisms of resistance to PARP inhibitors: (1) increased RAD51 repair activity (2) loss of 53BP1 or loss PTIP (3) down regulation of key proteins (DNA-PK or Ku80) in NHEJ

For *BRCA2*, secondary mutation was in part due to intragenic deletion of the c.6174delT mutation with restoration of an open reading frame and production of functional protein.[24] Reconstitution of BRCA2-deficient cells with these revertant *BRCA2* alleles abrogated PARPi sensitivity and HR deficiency, shown by recovery of RAD51 foci formation in response to treatment with PARPi and radiation.[15] BRCA2-mutated breast cancer cell lines and the CAPAN1 pancreatic cancer cell line; both situations were cross-resistant to PARPi. Subsequently, selected BRCA2 mutation carriers with recurrent ovarian tumors with acquired cisplatin resistance were found to have undergone secondary mutation with reversion of its *BRCA2* functional loss.[16] This and other studies have led to an estimated frequency of such mutations are relatively uncommon event (12.5-23%). [9 13] Hence, if patients acquire mutations in *BRCA2* that restore HR functionality, they may develop clinical resistance to PARPi treatment, whereas platinum-resistant BRCA2-mutated tumors without secondary *BRCA2* mutations may remain sensitive to

PARPi.[13,15,16] However, the recent publication[10] demonstrated no evidence for secondary *BRCA* mutations in patients who developed resistance to olaparib. Therefore, alternative mechanisms of clinical resistance need to be sought.

Some BRCA1 deficient tumors were found to overexpress RAD51, which might lead to partial restoration of repair capacity. A recent *in vitro* study investigated the potential resistance mechanism(s) of the combination of temozolomide and veliparib. Colorectal carcinoma HCT116 cells resistant to this drug combination (HCT116R) had increased expression of the HR genes *RAD51, FANCA, FANCG, BLM, BRCA1*, and *BRCA2*. Recently, Cardnell et al reported, using small cell lung cancer (SCLC) preclinical models, the correlation of PARPi sensitivity and a 17 DNA damage repair protein panel, including but not limited to RAD51 and 53BP1.[25] The SCLC cell lines with higher expression of the DNA repair protein panel, measured by reverse phase protein array (RPPA)[26], were more sensitive to PARP inhibition. Conversely, cell lines with a relatively higher expression of PI3K pathway proteins demonstrated a strong inverse correlation with PARPi sensitivity. These data suggest clinical resistance to PARPi may develop through multiple mechanisms independent of revertant BRCA1 or 2 mutation, such as loss of 53BP1 or increased protein expression of NHEJ or PI3K pathway. [25]

We examined potential predictive biomarkers to PARPi-based therapy in our phase 1 study of olaparib and carboplatin (08-C-0092/ NCT00647062, Figure 6)[8]. Our exploratory proteomic analysis of paired tumor biopsies indicated increased pretreatment FOXO3a expression was significantly related to a longer duration of response (≥ 6 months; p=0.0002, R^2=0.94)

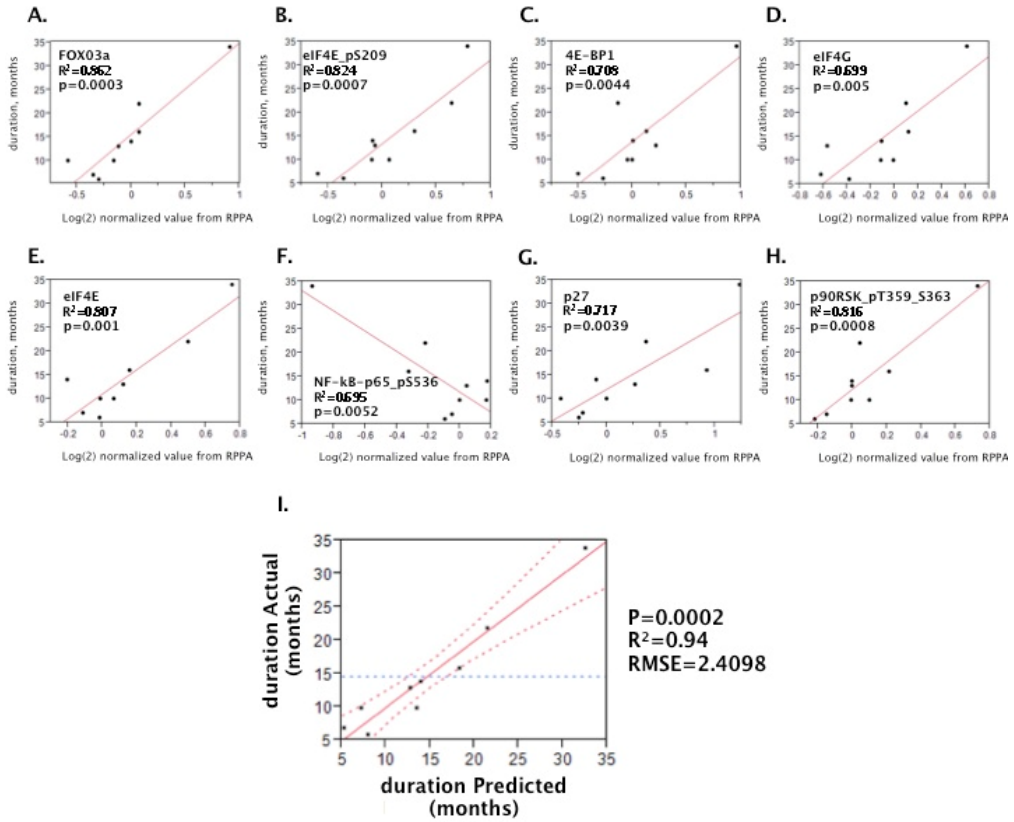

Figure 6. The relationship between pretreatment biopsy protein expression and response duration[8]. A cut off of R^2=0.8 was used to select the top potential predictive biomarkers. **A-H**: 8 proteins were statistically significantly correlated with PFS ≥6 months. **I**: pS209-eIF4E and FOXO3a were isolated as drivers for the PFS outcome ($p<0.001$, R^2=0.94, RMSE=2.41). RPPAs were analyzed for correlations between pretreatment protein levels and duration of response with a two tailed ANOVA analysis and controlled for false discovery rate of 0.05. RPPA: reverse phase protein microarray. RMSE: root mean square error.

IHC confirmed the finding and demonstrated a significant difference in expression of FOXO3a between the stromal and tumor cells, confirming the FOXO3a signal came from the tumor cells (Figure 7C). Further, the IHC FOXO3a positive cells were significantly reduced after 1 cycle of treatment in the responders and the number of FOXO3a+ cells/HPF correlated with clinical response (Figure 7A and B).

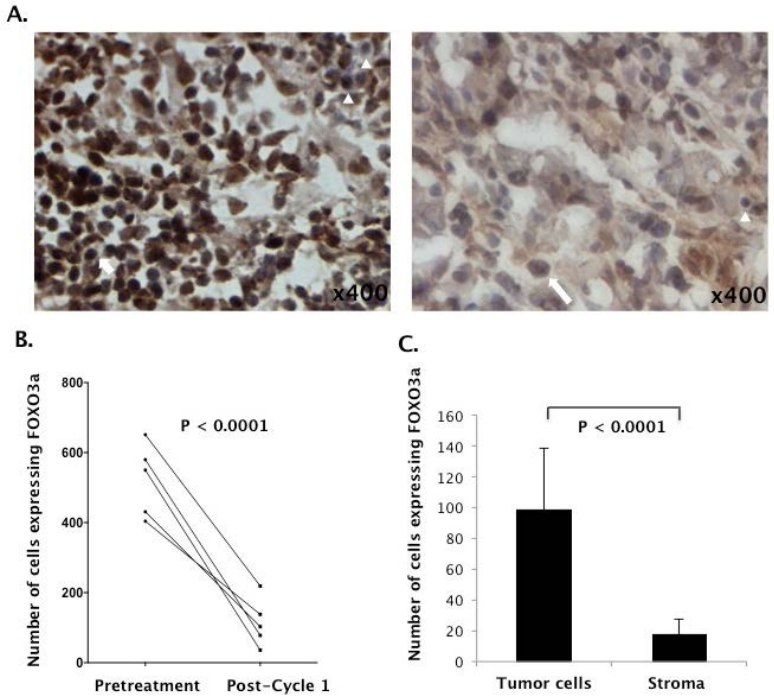

Figure 7. Validation of FOXO3a using immunohistochemistry.[8] **A**. Example paired FOXO3a stained biopsy set (400x magnification). Left: pretreatment biopsy; Right: after cycle 1. Arrowheads: negatively stained nuclei, note similar intensity in pre and post-C1 samples; short arrows: tumor cells with positively stained nuclei; long arrow: tumor cell with positively stained cytosol. **B.** FOXO3a-positive tumor cell nuclei are reduced after one cycle of treatment. Paired samples sets for 5 patients were available for enumeration. The mean of FOXO3a positive cells at baseline: 427.73 (range 181-758, SD 198.96, 95% CI 229.77-625.69) v. 112 (range 19-358, SD 90.89, 95% CI 20.78-202.58)], $p<0.0001$. **C.** Tumor cells are the source of the FOXO3a signal ($p<0.001$). Tumor and stromal cells with positively stained nuclei were counted per 5 HPF. The median of IHC results between tumor and stromal cells were compared using a two-tailed paired Student t-test.

FOXO3a was originally reported as a tumor suppressor gene associated with cell cycle regulation through Fas-mediated death.[27] Multiple preclinical studies have shown that FOXO3a promotes phosphorylation of ATM at Ser1981 and prompts the ATM–Chk2–p53-mediated apoptotic program following DNA damage.[28,29] We will examine the pretreatment FOXO3a expression in this study, to examine its behavior as a potential biomarker in response to subsequent PARPi-based therapy after first PARPi exposure.

Another possible resistance mechanism to PARPi was reported by Dr. Nussenzweig's group, Laboratory of Genome Integrity/CCR and others.[30-33] His laboratory showed 53BP1 inhibits HR repair in BRCA1-deficient cells; whereas, loss of 53BP1 increased HR capacity, and rescued RAD51 focus formation after radiation treatment.[31] Breast cancers arising in gBRCA1m carriers frequently show low levels of 53BP1 expression.[30] This finding may explain why the frequency and duration of response to PARPi is overall less in breast cancers than in ovarian cancer. Consistent with this, 53BP1 was found to be lost in a fraction of BRCA1-deficient mouse mammary tumors that acquired PARPi resistance in vivo.[33] To further define other resistance mechanisms related to loss of 53BP1, Dr. Nussenzweig and his colleagues identified and recently published the interaction of 53BP1 and PTIP, the Pax2 transactivation domain interaction protein.[32] His group has shown that PTIP is a regulator of 53BP1 at DNA damage sites.[34] PTIP promotes genome instability in BRCA1-knockout lymphocytes by inhibiting double strand DNA break (DSB) resection. PTIP recruitment to DSBs was reported to be 53BP1 and ATM independent.[35,36] Callen et al[32] showed loss of PTIP reverses the HR defect in BRCA1-knockout B cells as shown by reaccumulation of RAD51 foci, and subsequent resection of DSB. There has yet been no investigation of the role of PTIP in clinical PARPi resistance, thus, making it important to define the expression of PTIP in PARPi sensitive and resistance clinical samples. We will collaborate with Dr. Nussenzweig to investigate these molecular events in our patients.

Lastly, Patel et al reported that a key mechanism of PARP-1 is to maintain a brake on NHEJ. They showed that PARPi induced phosphorylation of DNA-PK and stimulated error-prone NHEJ selectively in HR-deficient cells.[19] Inhibition or downregulation of Ku80 or DNA-PK increased resistance to PARPi in PEO1 ovarian cancer and CAPAN1 pancreatic cancer cells, both BRCA2-deficient.[19] Therefore, resistance to PARPi can be acquired from altered expression of key regulatory proteins of the complex HR pathway. This mechanism has not been examined in clinical samples.

A key to progress is understanding this difference and subsequent identification, development and validation of biomarkers to identify the subgroup of patients who become clinically resistant to platinums and/or PARPi. Hence, it is necessary to elucidate PARPi resistance mechanisms in clinical samples, and to identify and investigate potential biomarkers to help define susceptibility of gBRCAm ovarian cancer patients to re-exposure to PARPi. PARPi after PARPi (PAP) therapy will provide initial findings with which to lead to randomized trials examining the role of repeat PARPi therapy in patients with gBRCAm, and with tissue and blood acquisition, will allow further characterization of resistance pathways and development of potential biomarkers.

2.4 RATIONALE

This phase 2 pilot study will test our hypothesis that ovarian cancer patients with gBRCAm will have a second clinical response to a second, highly potent, PARPi after sustaining progressive disease while receiving a first PARPi. Our scientific rationale is based on the following:

1) gBRCAm carriers' well-recognized clinical behaviors: gBRCAm carriers demonstrate repeated therapeutic susceptibility to DNA damaging agents, especially platinums, even if they have progressed on a similar, prior (platinum-based) regimen.

2) BMN 673 (talazoparib) is a novel, potent PARP inhibitor, which has excellent oral bioavailability. BMN 673 (talazoparib) has yielded greater anti-tumor activity *in vitro* and *in vivo* at lower concentrations than earlier generation PARPi.

3) Olaparib is now being tested in phase III maintenance registration trials for gBRCAm-associated ovarian cancer at the first and subsequent remission (2 studies; Study of OLaparib in Ovarian cancer [SOLO] 1 and SOLO2). Both niraparib and rucaparib are being tested in phase III trials for women with recurrent platinum-sensitive high grade serous ovarian cancer (ARIEL and NOVA). These women will need subsequent therapeutic opportunities and have already been clamoring for second access to a PARPi. Thus, the PARP inhibitor-treated exposed gBRCAm patient community is now emerging as a new patient population with unmet therapeutic needs. Reintroduction of a PARPi in this setting has not been studied, and will be an important question to guide patient- and resource-efficient use of this important new class of drug.

3 PATIENT SELECTION

3.1 ELIGIBILITY CRITERIA

3.1.1 Recurrent, and/or metastatic germline BRCA 1/2 mutation-associated ovarian cancer, with progression on a PARP inhibitor monotherapy after attaining a response to that PARPi (CR, PR, or SD≥4mo)

3.1.1.1 Progression should have occurred within the immediate prior 2 months of the time of screening visit, with no intervening anti-cancer therapy.

3.1.2 Patients must be at least 4 weeks from the last dose of prior PARP inhibitor.

3.1.3 All patients must have at least one lesion deemed safe to biopsy and be willing to undergo mandatory baseline biopsy. It is preferred that this lesion be a lesion that progressed or arose while on the prior PARP therapy.

3.1.4 Histopathologic diagnosis of ovarian cancer (including primary peritoneal and fallopian tube cancers) must be confirmed in the Laboratory of Pathology, NCI.

3.1.5 Age ≥18 years.

3.1.6 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A, Section **16.1**).

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

- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL

- total bilirubin ≤ 1.5X upper limit of normal, unless known Gilbert's syndrome
- AST(SGOT)/ALT(SGPT) ≤3 × institutional upper limit of normal
- creatinine < 1.5 X upper limit of normal

  OR
- measured creatinine clearance >60 mL/min/1.73 m^2 for patients with serum creatinine levels > 1.5 x upper limit of normal.
- hemoglobin ≥ 10 mg/dL (in the absence of transfusion within 24 hours prior to dosing).

3.1.8 All patients must have measurable disease by RECIST v1.1.

3.1.9 Use of raloxifene for bone health is allowed.

3.1.10 Patients must be at least 1 week from the last dose of complementary or alternative medications.

3.1.11 Patients who have had major surgery must be fully recovered and ≥4 weeks post-operative prior to enrolling on study.

3.1.12 Women of child-bearing potential 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 at least three months following the last dose of experimental therapy and must have a negative urine or serum pregnancy test within 7 days prior to the start of the study.

3.1.13 Patient must be able to swallow pills.

3.1.14 Integral biomarkers: all patients who are eligible for the study due to a history of positive BRCA1/2 mutation must provide documented evidence of their deleterious germline mutation status, obtained in a CLIA-certified laboratory, including but not limited to Myriad Genetics prior to study enrollment. Variants of uncertain significance (VUS) of BRCA1/2 and BRCA1/2 somatic mutations are not considered deleterious germline BRCA1/2 mutations. Due to the long acceptance of BRCA 1 and BRCA 2 mutation testing through Myriad, Myriad results will be acceptable. If testing for BRCA 1 and BRCA 2 mutation is done by other organizations, a genetic consultation report from a qualified medical professional confirming that the laboratory results showed a recognized germ line deleterious BRCA 1 or BRCA 2 mutation or deleterious BRCA 1 rearrangement is required.

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

3.2 EXCLUSION CRITERIA

3.2.1 Patients who have had prior BMN 673 (talazoparib) therapy.

3.2.2 Patients with known brain metastases diagnosed within 1 year will be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other

adverse events. Exception: patients with brain metastases diagnosed greater than 1 year prior to study entry may be considered if they received sterilizing therapy to the CNS (resection or radiation) and have been CNS progression-free for the 1-year period.

3.2.3 Lack of recovery of prior cancer therapy-related adverse events to Grade ≤1 (NCI CTCAE v4.03; except alopecia). Stable persistent grade 2 peripheral neuropathy may be allowed as determined on a case-by-case basis at the discretion of the PI. Patients with platinum-related grade 2 or greater hypomagnesemia (on replacement) will be eligible.

3.2.4 Uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, clinically significant GI bleeding or hemoptysis within 28 days prior to the start of the study, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.5 Patients with active infection will not be eligible, but may become eligible once infection has resolved and they are at least 7 days from completion of antibiotics.

3.2.6 Another previous or current invasive malignancy within the last 2 years, with the exception of curatively treated stage Ia cervical carcinoma, or resected stage Ia endometrial cancer, and noninvasive nonmelanoma skin cancers.

3.2.7 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with BMN 673 (talazoparib). HIV- positive patients who are not on cART and have CD4 counts > 500 are eligible.

3.2.8 History of allergic reactions attributed to compounds of similar chemical or biologic composition to BMN 673 (talazoparib)

3.2.9 Patients who are receiving any other investigational or commercial agents with the intent to treat the malignancy.

3.2.10 Patients with gastrointestinal conditions that might predispose for drug intolerability or poor drug absorption.

3.2.11 Use of nasogastric or G-tube administration.

3.3 INCLUSION OF WOMEN AND MINORITIES

Women of all races and ethnic groups are eligible for this trial.

4 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office [37] 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 to the research team. A recorder is available during non-working hours.

5 TREATMENT PLAN

This is an open label, single arm, non-randomized phase II trial to examine activity of BMN 673 (talazoparib) in patients with gBRCAm-associated ovarian cancers who have had prior PARPi therapy. Patients will be evaluated at baseline and prior to each cycle by history and physical examination (H&P; only pretreatment full H&P must be noted in the research record), and every two cycles by imaging studies (CT scans). Reassessment noninvasive imaging to document response will be performed every 2 cycles (~8 wks). See Section **11** for study calendar.

5.1 SCREENING EVALUATION

- Complete history and physical examination are required prior to initiation of study. They will include but are not limited to: height, weight, and ECOG performance score, documentation of 1) mutation status and family history where appropriate; 2) measurable/evaluable disease, 3) narcotic use and pain assessment (if applicable), 4) medication history, and 5) prior therapies (hormonal, surgical, radio therapeutic, and cytotoxic).
- Confirmation of Diagnosis in NCI Laboratory of Pathology.
- Laboratory studies (See Section **11** for study calendar) will be done within 1 week of consent. CBC with differential and platelet count must be repeated the day of consent.
- Serum chemistry - Bilirubin, hemoglobin, AST, ALT, creatinine or creatinine clearance.
- Serum beta-hCG or urine pregnancy test in women of childbearing potential.

5.2 BASELINE EVALUATION

- Baseline history, physical examination, and documentation of concomitant medications are to be conducted within 1 week of consent.
- Laboratory studies (See Section **11** for study calendar) will be done within 1 week of consent. CBC with differential and platelet count must be repeated the day of consent.
- On-study tumor documentation may be done within 17 days prior to consent.
- Treatment must begin within 1 week after consent, allowing for the required biopsies and research samples to be obtained. If a patient is coming off another intramural study where a biopsy on post-progression is optional, and she agrees to undergo this optional biopsy on that study, she may allow extra cores to be taken to fulfill the on-study biopsy requirements of this study and avoid the risks of back-to-back tissue acquisition. The patient may be off-treatment and on follow-up on another therapeutic trial.

5.3 AGENT ADMINISTRATION

- Patients will receive oral BMN 673 (talazoparib) at the RP2D of 1mg/day daily for 28-day cycles, until progressive disease, limiting toxicity, intercurrent medical issues, or patient withdrawal of consent.
- Treatment will be administered on an outpatient basis. BMN 673 (talazoparib) can be administered with and without a meal. Reported adverse events and potential risks are described in Section **7.3.1**. 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.

5.3.1 CCR Self-Administered Study Drugs Policy

All oral self-administered investigational agents will be properly accounted for, handled, and disposed in accordance with existing federal regulations and principles of Good Clinical Practice. All oral study drugs will be recorded in patient diaries (See Appendix D, Section **16.4**). This will be used as a memory aide for subjects. A clinical research team maintains the primary source record.

5.4 General Concomitant Medication and Supportive Care Guidelines

Based on *in vitro* data (2013 IB), BMN 673 (talazoparib) is not likely to inhibit metabolism via human cytochrome P450 (CYP 450) enzymes. The case report form will capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies due to potential interaction with other concomitantly administered drugs.

5.4.1 Nausea/Vomiting

Anti-emetics will not be administered routinely prior to BMN 673 (talazoparib). 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, anti-emetics 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 anti-emetics within 24 hours.

5.4.2 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 p.o. after the first unformed stool with 2 mg p.o. 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.

5.4.3 Hematologic toxicity

See Section **6.1.1** for details.

5.5 Duration of Therapy

Prior to documenting removal from protocol therapy, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- 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.
- Positive pregnancy test

5.6 DURATION OF FOLLOW UP

PFS2 (the time between initiation of BMN 673 (talazoparib) and disease progression on a subsequent therapy) will be obtained during follow-up. For this, participants will be followed for 3 years by clinic visit or by phone until death or progression on subsequent therapy after removal from study treatment, whichever occurs first. Participants' vital status will be followed every 6 months either at a scheduled clinic visit or by phone following removal from the study treatment. Date and cause of death should be provided for participants who become deceased within the 3-year interval following removal from the study treatment.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs will be reported up to 30 days following the last dose of study drug.

Participants removed from study treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event to grade 1 or better, by a monthly scheduled clinic visit or by phone.

5.7 OFF-STUDY PROCEDURE

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off-study. An off-study 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.

6 DOSING DELAYS/DOSE MODIFICATIONS

Table 6. Dose Levels of BMN 673 (Talazoparib)

Dose Level (DL)	*BMN 673 (talazoparib), oral, once daily*
Starting dose, DL1	*1000mcg (1mg)*
DL-1	*750mcg (0.75mg)*
DL-2	*500mcg (0.5mg)*

DL-3	*250mcg (0.25mg)*

Table 7. Treatment modifications of BMN 673 (Talazoparib) for Drug-related hematologic toxicities*

Grade	*Occurrence*	*Immediate Action*	*Resumption of Therapy*
1	All	None	no interruption
2	All	None	No interruption, with the exception of thrombocytopenia. In the case of the first thrombocytopenia, therapy will resume at the same dose level once platelet counts > 100,000/L. In the case of recurrent grade 2 thrombocytopenia, therapy will resume at the next lower dose level if toxicities have resolved to platelet counts > 100,000/L.
3	1st**	Hold therapy until Grade ≤ 2	Initiate appropriate medical therapy and, with the exception of thrombocytopenia, reinitiate BMN 673 (talazoparib) at the same dose level if toxicities have resolved to Grade 2 or less. In the case of thrombocytopenia, therapy will resume at the next lower dose level once platelet counts ≥ 100,000/L.
	2nd**	Hold therapy until Grade ≤ 2	Initiate appropriate medical therapy and, with the exception of thrombocytopenia, reduce to the next lower dose level if toxicities have resolved to Grade 2 or less. In the case of thrombocytopenia, therapy will resume at the next lower dose level once platelet counts ≥ 100,000/L.
4	1st**	Hold therapy until Grade ≤ 2	Initiate appropriate medical therapy and, with the exception of thrombocytopenia, reduce to the next lower dose level prior to re-initiation of BMN 673 (talazoparib) if toxicities have resolved to Grade 2 or less. In the case of thrombocytopenia, therapy will resume at the next lower dose level once platelet counts ≥ 100,000/L within the 3-week period.

	2nd	Hold therapy until Grade ≤ 2	Terminate therapy BMN 673 (talazoparib). Follow patient until resolution/stabilization of toxicity.

*For adverse events that are at least possibly, probably, or definitely attributable to BMN 673 (talazoparib) alone
**If no resolution occurs within the 3-week period, the study drug will be discontinued.

6.1.1 Hematologic Toxicity

- Hold BMN 673 (talazoparib) until hematologic toxicities resolve to grade 2 or better prior to starting the next cycle. In the case of thrombocytopenia, therapy will resume once platelet counts > 100,000/L. Treatment may be delayed for a maximum of 3 weeks after holding the treatment for toxicities that develop and do not resolve as defined above (exemptions: lymphopenia, or leukopenia in the absence of grade 3 or higher neutropenia).
- Beyond three weeks, the patient will not receive further therapy on this protocol. They will be taken off treatment, and will be followed for resolution of toxicities or bone marrow biopsies to evaluate the other causes of bone marrow suppression such as myelodysplastic syndrome on treatment follow up period.
- 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 2-5 days later.

6.1.1.1 Neutropenia

- Growth factors to prevent neutropenia will not be administered prophylactically, but can be used during a drug hold to assist the recovery.
- Filgrastim/PEG filgrastim will be used only if the patient has neutropenia with sepsis for the purpose of facilitating recovery of the neutropenic sepsis[38].

6.1.1.2 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.
- In the case of Grade 1 or the first Grade 2 thrombocytopenia, therapy will resume at the same dose level once platelet counts > 100,000/L.
- In the case of recurrent Grade 2 or Grade 3 or Grade 4 thrombocytopenia, therapy will resume at the next lower dose level once platelet counts ≥ 100,000/L.

6.1.1.3 Anemia

- Symptomatic anemia should be treated with red blood cell transfusion and is recommended if the hemoglobin falls below 8 g/dL or the patient is symptomatic.

- 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).

6.1.2 Non-hematologic Toxicity

Grade 3-4 Drug-related non-hematologic toxicities: Doses of BMN 673 (talazoparib) will be held until toxicities recover to Grade 1 or less prior to re-initiating treatment at the next lower dose level. Dose modifications for nausea, vomiting, and diarrhea will be made only if they are refractory to treatment. Asymptomatic electrolyte abnormalities will not require dose reduction if resolution to Grade 1 or less is documented within 72 hours.

6.1.2.1 Nausea/Vomiting

See Section **5.4.1**

6.1.2.2 Diarrhea

See Section **5.4.2**

6.1.2.3 The patient will be removed from the study if grade 3 or 4 non-hematologic toxicity recurs (see below for exemptions) after resumption of study drug at the lower dose level. Exemptions:

- Asymptomatic hyperuricemia/hypouricemia/hypophosphatemia/hyponatremia with optimal repletion
- Asymptomatic hypomagnesemia with optimal repletion
- Asymptomatic hypocalcemia, or hypokalemia with optimal repletion

However, asymptomatic grade 4 hypokalemia not corrected to grade 1 or 0 within 48 hours despite optimal repletion will result in discontinuation of study drug.

Subsequent grade 3 asymptomatic electrolytes toxicities that could be controlled with standard medications will not have dose reduction. However, asymptomatic grade 3 hypokalemia not corrected to grade 1 or 0 within 48 hours despite optimal repletion will result in dose reduction.

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

7.1.1 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 above.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of at least possibly related to the agent/intervention should be recorded and reported as per sections **7.2**, **7.3**, **7.4**, **7.5**, **7.6**, and **7.7**.

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.

7.1.2 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.

7.1.3 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.

7.1.4 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.

7.1.5 Serious Adverse Event

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.

7.1.6 Disability

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

7.1.7 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.

7.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

7.1.9 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.

7.1.10 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; **AND**
- 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.

7.2 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 **7.3**) and the characteristics of an observed AE (Section **7.4**) will

determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

7.3 COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LIST (CAEPR)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The SPEER is a list of events that are protocol-specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse_events_adeers for further clarification. Also refer to the Investigator's Brochure for frequency data.

NOTE: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously via CTEP-AERS. 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.

7.3.1 CAEPRs for CTEP IND Agent: BMN 673 (Talazoparib) (NSC 771561)

Comprehensive Adverse Events and Potential Risks list (CAEPR)

for

BMN 673 (talazoparib, NSC 771561)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via AdEERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 219 patients.* Below is the CAEPR for BMN 673 (talazoparib).

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 2.0, July 24, 2015[1]

Adverse Events with Possible Relationship to BMN 673 (talazoparib) (CTCAE 4.0 Term) [n= 219]			**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			
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
Nausea			***Nausea (Gr 2)***
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
INVESTIGATIONS			
	Neutrophil count decreased		***Neutrophil count decreased (Gr 2)***
	Platelet count decreased		***Platelet count decreased (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		

[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.

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

CARDIAC DISORDERS - Atrial flutter

GASTROINTESTINAL DISORDERS - Abdominal pain; Flatulence; Toothache

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Fever

INFECTIONS AND INFESTATIONS - Lung infection; Sepsis

INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Anorexia; Hypokalemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Musculoskeletal and connective tissue disorder - Other (muscle cramps); Musculoskeletal and connective tissue disorder - Other (muscle spasm); Pain in extremity

NERVOUS SYSTEM DISORDERS - Headache; Peripheral sensory neuropathy

PSYCHIATRIC DISORDERS - Anxiety

RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Pleural effusion

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Rash maculo-papular

Note: BMN 673 (talazoparib) 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.

7.4 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 for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section **7.3.1**) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in Section **7.6**.
- **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.

7.5 EXPEDITED ADVERSE EVENT REPORTING TO CTEP

7.5.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event 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 **7.5.2**).

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.

7.5.2 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 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. 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

7.6 ROUTINE ADVERSE EVENT REPORTING TO CTEP

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

7.7 NCI-IRB REPORTING

7.7.1 NCI-IRB Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report to the NCI-IRB:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received by the NCI-IRB within 7 working days of PI awareness via iRIS.

7.7.2 NCI-IRB Requirements for PI Reporting at Continuing Review

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.

7.7.3 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.

7.8 SECONDARY MALIGNANCY

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

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/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.

7.8.2 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.

7.9 DATA AND SAFETY MONITORING PLAN

7.9.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis weekly when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS and to the Sponsor.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 PHARMACEUTICAL INFORMATION

8.1 CTEP IND AGENT: BMN 673 (TALAZOPARIB) (IND# 119558; NSC 771561)

8.1.1 **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)

8.1.2 Other Names: BMN 673 ts

8.1.3 **Classification***:* poly(ADP-ribose) polymerase (PARP) inhibitor

8.1.4 **CAS**: 1207456-01-6

8.1.5 **Molecular Formula:** $C_{26}H_{22}F_2N_6O_4S$ (BMN 673 ts) **M.W.:** 552.5624 (BMN 673 ts)

8.1.6 **Mode of Action**: 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.

8.1.7 **Description:** BMN 673 free base is the active moiety of the BMN 673 ts (tosylate salt) formulation.

8.1.8 **How Supplied:** BMN 673 capsules are supplied by BioMarin Pharmaceutical, 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.

BMN 673 capsules may be repackaged from the manufacturer-supplied HDPE bottle into a pharmacy-supplied HDPE bottle for dispensing purposes BMN 673.

8.1.9 **Storage:** Store BMN 673 capsules at room temperature (15-30°C/59-86°F) and protected from light.

8.1.10 **Stability:** Shelf-life stability studies of BMN 673 capsules are ongoing.

8.1.11 **Route of Administration:** Oral administration. Take BMN 673 with or without food.

8.1.12 **Potential Drug Interactions**: Based on in vitro data, 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.

8.1.13 **Availability:** BMN 673 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

8.2 AGENT ORDERING AND AGENT ACCOUNTABILITY

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

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.3 AGENT INVENTORY RECORDS

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

The overall goal of the correlative studies is to identify potential predictive biomarkers of subsequent PARPi response and further elucidate the PARPi clinical resistance mechanisms in BRCA1/2 mutation-associated malignancies. Patients will undergo a mandatory biopsy at baseline. Optional research biopsies will be performed on C1D28 (before C2D1) of treatment and/or at progression to assess the effect of response to BMN 673 (talazoparib) therapy at minimal risk. Blood samples will be collected at baseline, on approximately C1D28 (before C2D1), and at progression. Supernatants and/or pellets may be collected from patients who undergo either therapeutic or diagnostic thoracentesis or paracentesis while on study. The following tests will be performed on patients' specimens, in order of priority (Tables 6 and 7).

All patients on the study are requested to submit a block of tissue or 20 paraffin-capped unstained slides from a recent resection or barring that, from the original surgery. All efforts will be made to obtain these samples to achieve the secondary objectives.

Table 8. Integrative Biomarkers

Integrated biomarkers name	**Assay**	**Tissue/Body Fluid Tested and Timing of Assay**
Secondary mutation of BRCA 1 and BRCA 2 (Lee, WMB; with Dr. Elizabeth Swisher at University of Washington)	Next Generation Sequencing to elucidate the secondary mutations of BRCA 1 and 2	Tissue/ Baseline (mandatory biopsy) and at progression (optional)
FOXO3a, 53BP1 and RAD51 (Lee, WMB; MDAnderson RPPA core)[26]	Reverse phase protein microarray (RPPA)[26]	Tissue/ Baseline (mandatory biopsy), C1D29 (optional, prior to C2D1) and at progression (optional)

Table 9. Exploratory Biomarkers

Exploratory Biomarker name	**Assay**	**Tissue/Blood Tested and Timing of Assay**
Secondary mutations of BRCA1/BRCA2 and p53 mutation in circulating tumor (ct)DNA (Lee, WMB: with James D. Brenton at Cancer Research UK Cambridge Institute, University of	Next Generation Sequencing: Correlation of baseline of BRCA1/BRCA2 secondary mutation, and correlation of baseline or changes of p53 mutation in ctDNA with clinical response.	Peripheral blood/ Baseline, prior to C2D1, and at progression

Cambridge, UK		
Enumeration of circulating tumor cells (CTCs) (Lee, WMB; with Jane Trepel, Preclinical Development Research Core/CCR/NCI)	Ferrofluidic enrichment and multi-parameter flow cytometric: Correlation of baseline or changes in CTCs with clinical response[39].	Peripheral blood/ Baseline, prior to C2D1, and at progression
gH2AX/Mre11 by flow cytometry (Lee, WMB; Dr. Lee's laboratory team)	Multi-parameter flow cytometry: Correlation of baseline with clinical outcome	PBMC/Baseline only
Immune subsets (Lee, WMB; with Jane Trepel, Preclinical Development Research Core/CCR/NCI)	Multi-parameter flow cytometry Correlation of baseline or changes in immune subsets with clinical response.	Peripheral blood/ Baseline, prior to C2D1, and at progression
PTIP mRNA quantitative PCR (Lee, WMB; Dr. Nussenzweig's group)	mRNA expression by quantitative PCR in tumor samples	Tissue/Baseline
SLFN11 (SCHLAFEN 11) mRNA quantitative PCR (Lee, WMB; Dr. Pommier's group, DCTB/CCR/NCI)	mRNA expression by quantitative PCR in tumor samples	Tissue/Baseline

9.1 TUMOR BIOPSIES

9.1.1 Rationale

The on-study biopsy and the optional second/third biopsies are necessary for the execution of the critical translational endpoints evaluating proof of concept and demonstration of mechanism and activity. The primary purpose of the pretreatment biopsy is for genetic analysis for secondary mutations that may reinstate a functional BRCA1 or BRCA2 protein. Tumor biopsies will be evaluated for, but not limited to DNA damage response and resistance markers such as γH2AX, phosphoATM/ATR, FOXO3a, RAD51, 53BP1, PTIP, and SLFN11.

9.1.2 Tissue acquisition

- Our collaborators in Interventional Radiology will obtain core biopsies of a sentinel lesion. Where ever safe, the sentinel lesion is preferred to be one that has either progressed on the prior PARPi therapy or developed de novo while on the prior PARPi. If this is not safe or feasible, biopsy of another lesion is permissible.
- Biopsy procedures are for research purposes and will be done after protocol consent is obtained, and always prior to drug initiation. Second (optional, but highly encouraged) biopsy will be requested prior to C2d1.
- Biopsies from a new lesion or site of progression will be requested at the time of drug discontinuation (optional).

9.1.3 Timing

Biopsies will be performed at the following times:

- Mandatory – after consent, prior to treatment on cycle 1 day 1
- Optional, highly encouraged - cycle 1 day 28 of treatment (prior to cycle 2 day1)
- Optional - at the time of progression

Attempts will be made to obtain four cores if safe and feasible, which will be frozen for research studies. Inability to get tissue with a reasonable attempt will not preclude treatment and the patient will remain eligible for all other translational components. Members of the interventional radiology team will decide the type of imaging used to facilitate biopsies. Should CT scans be needed for biopsy, a limit of 10 scans for each procedure will be observed to minimize radiation exposure to the patient.

The biopsies are to be immediately embedded, frozen, and stored in the Lee lab at -80^{0}C on site according to our laboratory SOP (Appendix B, Section **16.2**). The schedule for the biopsies will be made with Special Procedures (Dr. Brad Wood). Members of the Lee lab will be on call to receive and embed biopsies on site in special procedures: Phone (301) 496-3776, beeper 102-11155.

Each patient sample set will be assigned a unique patient identifier. The protocol scientific investigator(s) handling the samples will be blinded as to the patient identification, patient data and outcome.

Biopsy material will be prioritized for genomic sequencing and proteomics. The remaining tissue will be released for additional testing prioritized to other DNA damage repair pathways analyses, and immunohistochemistry, in that order.

9.2 SECONDARY MUTATIONS OF BRCA 1 AND BRCA 2

Biopsy materials from the pretreatment biopsy will be prioritized for secondary BRCA mutation testing. Next generation sequencing [40,41] or massively parallel sequencing[42] has been applied to study the secondary mutations of BRCA 1 and 2 in tumor or blood samples. We will collaborate with Dr. Elizabeth Swisher's group at University of Washington for DNA sequencing to

elucidate the secondary mutations of *BRCA1* and *BRCA2* patients who developed progression on the first PARPi-based therapy. Anonymized patient samples will be batched to

Elizabeth Swisher, MD
Professor, Dept. Ob/Gyn
University of Washington
1959 NE Pacific St
Seattle, WA 98195
(206) 543-3669
Email: swishere@uw.edu"

9.3 TISSUE LYSATE ARRAY PROTEOMIC ANALYSIS

Reverse phase protein array (RPPA) is a high-throughput antibody-based technique developed for functional proteomics studies to evaluate protein activities in signaling networks. RPPA will be employed to quantitate activated and inactive signaling components of the DNA damage repair pathways and the presence or absence of 53BP1 and RAD51 before therapy.[25] Analysis of specific proteins and their activation status target proteins are listed on MD Anderson RPPA core facility website (http://www.mdanderson.org/education-and-research/resources-for-professionals/scientific-resources/core-facilities-and-services/functional-proteomics-rppa-core/index.html. MD Anderson has ongoing real time quality control and identifies those proteins and/or samples that do not meet standards.

9.4 LASER CAPTURE MICRODISSECTION AND SANGER SEQUENCING ANALYSES FOR SECONDARY MUTATIONS OF BRCA1 AND BRCA2

Reversion mutation events may be difficult to identify by next generation sequencing, which sequences short DNA pieces in which it is difficult to differentiate wildtype sequence coming from contaminating non-tumor cells from wildtype sequence in tumor DNA secondary to reversion of the mutant allele. Swisher laboratory is currently developing and testing bioinformatic algorithms for BROCA-HR that will identify these reversion events by comparing variant reads at the mutation site with careful allele ratio assessments of the nearby chromosomal region. Laser capture microdissection (LCM) on a pure neoplastic cell population[13] will complement BROCA-HR sequencing. Swisher group will also assess the mutation site with Sanger sequencing. If a reversion event is suspected, allelotyping is performed at informative intragenic SNPs. In this study, Swisher laboratory will assess for secondary somatic mutations using the LCM and Sanger sequencing and compare that to predictions provided by a new reversion algorithm with BROCA-HR done without LCM.

Coded patient samples will be batched to

Elizabeth Swisher, MD

Professor, Dept. Ob/Gyn

University of Washington
1959 NE Pacific St
Seattle, WA 98195
(206) 543-3669
Email: swishere@uw.edu

Requirements for the assay:

1. One H&E section and three 8 micron sections of the biopsy specimen on membrane slides (LCM0522, Applied Biosystems). Can be shipped at room temperature.

2. Information of the specific mutation to be evaluated (unless already obtained from BROCA-HR)

Methods: Neoplastic DNA is obtained by LCM and isolated with the PicoPure DNA extraction kit. Sanger sequencing is performed around the known mutation site. When a reversion mutation is suspected, further sequencing of informative intragenic SNPs (which are identified through BROCA-HR sequencing of germline DNA) is performed to confirm that detected wildtype sequence is truly coming from the mutant allele.

The results of molecular studies conducted using tissue specimens are for research purposes only and will not be disclosed to individual subjects. The exception to this is potential incidental findings that are deemed medically significant and actionable. The policy for this disclosure is outlined below and in the consent form for this study.

- Subjects will be given the opportunity to choose whether or not they would like to be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for the purpose of this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists)
- Subjects that have opted to have findings returned and who still remain on the study will be contacted at this time with a request to provide a blood sample to be sent to a CLIA certified laboratory. If the research findings are verified in the CLIA certified lab, the subject will be referred to genetics counseling for the disclosure of the results. Funding for a CLIA laboratory confirmation will be decided after discussion with the patients, their health insurance companies, or other appropriate funding resources at CCR/NCI.
- This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.
- Contact information must be maintained on subjects that have opted to have their results returned. If a subject's participation in the study ends prior to the primary analysis, they

should be enrolled on study 96-C-0071, a follow up protocol, in order to allow for post study contact for the dissemination of any incidental findings and the maintenance of contact information.

9.5 DATA SHARING PLANS

9.5.1 Human Data Sharing Plan

What data will be shared?

I 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__ De-identified data in BTRIS (automatic for activities in the Clinical Center)

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__ Publication and/or public presentations.

When will the data be shared?

_X__ At the time of publication or shortly thereafter.

9.5.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

9.6 PTIP mRNA QUANTITATIVE PCR

Nussenzweig's group[32] recently showed loss of PTIP reverses the HR defect in the BRCA1-knockout B cells shown by reaccumulation of RAD51 foci, and subsequent resection of DSB. We will collaborate with Dr. Nussenzweig to develop the protocol to measure mRNA expression by quantitative PCR in tumor samples. This will be done in an exploratory fashion.

9.7 SLFN11 (SCHLAFEN 11) mRNA QUANTITATIVE PCR

SLFN11 is a gene recently identified as a determinant of cell death and cell cycle arrest in response to DNA targeted agents including topoisomerase inhibitors, DNA cross-linking agents, such as platinums. Zoppoli et al.[43] reported SLFN11 expression in ovarian and colorectal cancers and normal corresponding tissues from The Cancer Genome Atlas database and high SLFN11 expression independently predicts overall survival in a group of ovarian cancer patients treated with cisplatin-containing regimens. Pommier's group also recently reported SLFN11 expression is causally linked to cancer cell death response to BMN 673 (talazoparib) (AACR 2014). We will collaborate with Dr. Pommier to develop the protocol to measure mRNA expression by

quantitative PCR or protein by IHC in tumor samples. This will be done in an exploratory fashion.

9.8 TESTS ON PERIPHERAL BLOOD SAMPLES

The following tests will be performed on patients' peripheral blood samples, in order of priority. These correlative studies will be done in an exploratory fashion.

Blood samples will be collected prior to treatment on cycle 1 day, cycle 1 day 28 of treatment (prior to cycle 2 day1), and at the time of progression

9.8.1 Secondary mutations of *BRCA1* and *BRCA2* in circulating tumor (ct) DNA

Dr. James D. Brenton's group, Cancer Research, UK showed very low frequency mutational changes can be detected in ctDNA, 0.2-1% frequency within all DNA reads, for *TP53* missense mutations using HiSeq 2000 sequencing or digital PCR[44]; this may underestimate the ability to observe a unique mutational change such as the defined revertant mutations. Revertant mutations of *BRCA1* and *BRCA2* may be identified using highly sensitive ctDNA NGS methods. Identification of novel *BRCA*1/2 transcripts in ctDNA may be sufficient to suggest a revertant mutation has occurred. A successful ctDNA assay will allow demonstration of tumor reacquisition of HR function in a noninvasive modality. Additionally, we will also follow *TP53* missense mutation changes on treatment as a reference mutation. For this, I will collaborate with Dr. Brenton to apply his validated system to this question (See Appendix C, Section **16.3**; SOP for the sample collection).

- Samples will be collected in Two-9mL EDTA tubes (lavender top tubes) at baseline, cycle 1 day 29 (prior to cycle 2 day1), and at progression.
- The key is to maximize removal of contaminating cells and genomic DNA from these cells as large genomic DNA fragments hinder plasma DNA analysis.
- **CRITICAL STEP**: Time between blood draw and processing should be **less than 1 hour**. Gently invert tubes after blood draw. Do not shake or vortex tubes as cellular lysis could occur.
- Notification and Handling of Samples: members of the Lee lab on call to receive specimens: Phone (301) 496-3776, beeper 102-11155.

9.8.2 Enumeration of circulating tumor cells (CTCs)

Multiple clinical studies done using CTC enumeration shows that presence of CTC is a strong prognostic factor for overall survival in patients with metastatic breast, colorectal or prostate cancer.[41,45] The predictive role of CTCs in ovarian cancer is not well defined. Previous antibody-based methods resulted in low CTC detection rates, and the majority of CTCs detected in these previous studies may not have been viable.[46] [47] We will collaborate with Jane Trepel at Preclinical Development Research Core/CCR/NCI correlate baseline or changes in CTCs with clinical response. [26]

- Blood will be collected to correlate baseline or changes in CTCs[39] with clinical response. CTCs will be investigated using ferrofluidic enrichment and multi-parameter flow cytometric detection. CTCs are identified by positive for expression of epithelial markers

including but not limited to EpCAM and negative for expression of the pan-hematopoietic markers including but not limited to CD45.

- Collection of Specimen(s): Two 9-mL EDTA tubes (lavender top tubes) will be collected from each patient at the following time points: baseline, and C1d29, and at the time of progression.
- Immediately after collection, invert the blood tubes 3-4 times.
- Notification and Handling of Samples: as soon as possible after the patient is scheduled please send email notification to the Trepel lab: Jane Trepel at trepel@helix.nih.gov; Min-Jung Lee at leemin@mail.nih.gov that the sample is scheduled. As soon as the sample is drawn, please call the Trepel lab at 301-496-1547 to communicate that the sample is ready. Keep the sample on the unit at room temperature. The sample will be picked up by the lab and processed for CTC enumeration.

9.8.3 gH2AX and/or MRE11 by flow cytometry

γH2AX and MRE11 have been employed individually as surrogate measures of DNA DSB damage and repair, respectively, but neither alone has been proven a predictive biomarker. Our preliminary data suggest high γH2AX and low MRE11 expression in patient PBMCs prior to initiation of olaparib and carboplatin correlated with poor response to PARPi therapy in gBRCAm-associated cancers[48] (Lee et al, manuscript submitted).

- PBMC samples will be collected and archived for flow cytometric determination of DNA damage and repair using flow cytometric γH2AX and MRE11 dual-labeling assay.
- Samples will be collected in Two-8ml BD Vacutainer CPT (blue/black tubes) *at baseline only*.
- The specimens must be processed to cryopreserve PBMC aliquots within 2-3 hours of collection. The sample will then be separated into plasma and divided into aliquots and frozen. Plasma will be separated immediately upon receipt and aliquots frozen at -80^0C (no greater than 1 ml aliquots) in Jane Trepel's lab in building 10.
- Notification and Handling of Samples: as soon as possible after the patient is scheduled please send email notification to the Trepel lab at trepel@helix.nih.gov; Min-Jung Lee at leemin@mail.nih.gov and yusuke.tomita@nih.gov and call the Trepel lab at 301-496-1547 to arrange for immediate pick-up when the sample is drawn.

9.8.4 Immune Subsets

Emerging data suggest there is an interplay between chemotherapies and the host immune system[49,50]. Further, tumors with high genomic instability, such as ovarian cancer, may trigger host immune reaction, which may correlate with patient clinical outcome[51]. Hence, monitoring immune subsets in ovarian cancer patients may facilitate the establishment of personalized therapy in ovarian cancer.
PBMCs will be assessed using multiparameter flow cytometry for immune subsets including but not necessarily limited to Tregs, MDSC, effector and exhausted CD8+ T-cells and their functional markers, i.e. PD-1, TIM3, CTLA-4 and/or CD40.

- Collection of Specimen(s): Two 8-ml BD Vacutainer CPT (blue/black tubes) will be

collected from each patient at the following time points: baseline, and C1d29 (prior to C2d1), and at time of progression.

- Immediately after collection, mix the blood sample by gentle inversion several times. The date and exact time of each blood draw should be recorded on the tube.
- Notification and Handling of Samples: as soon as possible after the patient is scheduled please send email notification to the Trepel lab at trepel@helix.nih.gov; Min-Jung Lee at leemin@mail.nih.gov and yusuke.tomita@nih.gov and call the Trepel lab at 301-496-1547 to arrange for immediate pick-up when the sample is drawn.

9.9 SAMPLE STORAGE, TRACKING AND DISPOSITION

Each patient sample set will be assigned a unique patient identifier in the recipient lab with bar coding in the Clinical Pharmacology Program (CPP) laboratories and the scientific investigator handling and performing analyses on the samples will be blinded as to the sample source, patient data, and outcome. There will be no date identifiers on the samples. Samples will be grouped for scientific analyses. If a patient needs to have a malignant effusion tapped for diagnostic or therapeutic purposes, a sample will be collected for research. At the end of the protocol, samples will be stored for potential further analysis as new information becomes available (only for those subjects who consented to future optional studies). Any new use of identified or coded samples, specimens, or data will undergo prospective and continuing IRB review and approval. The PI will report any loss or destruction of samples to the IRB.

Samples, and associated data, will be stored in the locations listed above unless the patient withdraws consent. If researchers have samples remaining once they have completed all studies associated with the protocol, they must be returned to Dr. Lee's laboratory or to the CPP repository. Samples can only be saved at completion of study for future use if subjects consent. 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.

Samples will be ordered and tracked through the CRIS Screens. Should a CRIS screen not be available, the NIH form 2803-1 will be completed and will accompany the specimen and be filed in the medical record. Samples will not be sent outside NIH without IRB notification and an executed MTA.

9.10 PROTOCOL COMPLETION/SAMPLE DESTRUCTION

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described above. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed. Once primary

research objectives for the protocol are achieved, intramural researchers can request access to remaining samples providing they have an IRB approved protocol and patient consent.

The PI will report any loss or destruction of samples to the NCI IRB as soon as he is made aware of such loss. The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples or other problems associated with samples will also be reported to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.

10 DATA REPORTING / REGULATORY REQUIREMENTS

10.1 DATA REPORTING

10.1.1 Method

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDUS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site

(http://ctep.cancer.gov/reporting/cdus.html).

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

10.2 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:

Email: ncicteppubs@mail.nih.gov

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

10.2.1 A Sample Transfer Agreement with the University of Washington will be executed prior to the shipment of any samples from NCI to the collaborator(s) at the University of Washington for the purpose of biomarker, correlative, and/or special studies.

10.3 DATA COLLECTION

The investigators will be responsible for the collection, maintenance, quality control of the study data. Clinical data will be entered into the NCI C3D electronic database at least once every 2 weeks when patients are enrolled on the trial. Protocol specific electronic Case Report Forms (eCRFs) will be developed for this trial in C3D.

End of study procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breech in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

10.3.1 Source documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, patients' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, X-rays. The investigator will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s), providing direct access to source documents.

10.3.2 Case Report Forms

Data may be entered from the source documents directly into eCRFs in C3D for each patient enrolled in this study. The principal investigator or research nurse will review the eCRFs for completeness and accuracy. Independent audits may also be conducted by NCI personnel to ensure completeness and accuracy of data in C3D.

11 STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and X-rays must be done within 17 days prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Procedure	Screening	Pre-study Baseline	Cycle 1				Cycle 2 and after				Off Treatment[c]
			Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4	
Administration of BMN 673 (talazoparib)			A	A	A	A	A	A	A	A	
Informed consent		X									
Demographics		X									
Medical history	X	X									
Concurrent meds		X	----------→								
Physical exam	X		X				X				X
Vital signs	X		X				X				X
Height	X										
Weight			X				X				X
Performance status	X		X				X				X
CBC w/diff, plts	X	X	X	X	X	X	X	X[f]	X[f]	X[f]	X
PBMCs for correlative studies			X								
CTC analysis			X				X				X
Serum chemistry[a]	X	X	X				X				X
B-HCG	X[b]										
EKG (as indicated)		X									
Confirmation of Diagnosis in NCI Laboratory of Pathology	X										
Adverse event evaluation		X	X	X	X	X					X
Tumor biopsy[d]		X					X				X
CT scans [e]		X					X				
Reassessment noninvasive imaging			Re-staging every 2 cycles								

A: BMN 673 (talazoparib) at the RP2D of 1000 μg/day daily of a 28d cycle.

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

b: Serum pregnancy test (women of childbearing potential).

c: Off-therapy evaluation.

d: Mandatory tumor biopsy will be done at baseline, and optional biopsies will be performed on C1D29 (prior to C2D1) and at progression.

e: Scans must be done within 17 days prior to the start of therapy.

f: As clinically indicated.

12 MEASUREMENT OF EFFECT

12.1 ANTITUMOR EFFECT – SOLID TUMORS

For the purposes of this study, patients should be re-evaluated for response every two cycles. In addition to a baseline scan, confirmatory scans should also be obtained within four 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).[52] 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.

12.1.1 Definitions

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

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.

12.1.2 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).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

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.

12.1.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, 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. 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.[52]

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.

12.1.4 Response Criteria

12.1.4.1 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.

12.1.4.2 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).

12.1.4.3 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		

12.1.4.4 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.

13 HUMAN SUBJECTS PROTECTIONS

13.1 RATIONALE FOR SUBJECT SELECTION

Women from all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. To date, there is no information that suggests that differences in drug metabolism or disease response would be expected in one group compared to another. Efforts will be made to extend accrual to a representative population, but in this preliminary study, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic and/or ineffective treatments on the one hand and the need to explore ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to ethnic identity are noted, accrual may be expanded or a follow-up study may be written to investigate those differences more fully. This study will be recruited through internal referral, our local physician referral base, and will be posted on clinicaltrials.gov.

13.2 PARTICIPATION OF CHILDREN

Subjects under 18 are excluded because the incidence of ovarian cancers including primary peritoneal, fallopian tube cancers in this population are extremely rare. The study medication is also investigational and has not been studied in pediatric populations.

Men are excluded because ovarian cancer in males does not exist.

13.3 Evaluation of Benefits and Risks/Discomforts

The potential benefit to a patient who enters study is a reduction in the bulk of her tumor, which may or may not have a favorable impact on symptoms and/or survival. Potential risks include the possible occurrence of any of a range of side effects that are listed in Section **7.3.1** and the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients on a regular basis as described earlier.

13.4 Risks/Benefits Analysis

13.4.1 Potential Risks

13.4.1.1 Risk of serial biopsies: All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection and visceral injury) that will be explained fully during informed consent. If patients suffer any physical injury as a result of the biopsies, immediate medical treatment is available at the NIH's Clinical Center in Bethesda, Maryland. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

13.4.1.2 Radiation Risks: CT scans will be performed as clinically indicated. CT-guided biopsies will also be clinically indicated in most cases. In addition, one mandatory and two optional CT-guided biopsies will be performed for research purposes Such "research-purpose" CT guided biopsies involve exposure to radiation**.** This radiation exposure is not required for medical care and is for research purposes only. The amount of radiation received in this study is 0.54 rem which is below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. More information about radiation is available in the pamphlet, An Introduction to Radiation for NIH Research Subjects.

13.4.1.3 Risk of Treatment: Details of the risk of drug therapy are detailed in Section **8.1**.

13.5 Consent and Assent Process and Documentation

An associate or principal investigator on the trial will inform patients of the purpose, alternatives, treatment 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 at a subsequent visit. Original consents will be placed in the Medical Record.

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.

13.5.1 Consent via telephone

When re-consent is required due to an amendment, the patient can be consented via telephone if needed for logistical reasons. The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the

opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented on a progress note by the consenting investigator and a copy of the informed consent document and note will be kept in the subject's research record

14 STATISTICAL CONSIDERATIONS

14.1 STUDY DESIGN/ENDPOINTS

The primary objectives of this trial are to establish whether BMN 673 (talazoparib) is able to be associated with at least a minimal response rate in patients with gBRCAm-associated ovarian cancer that have progressed on PARPi therapy.

In patients with ovarian cancer who were treated with a PARPi and progressed, the study will be conducted using an optimal two-stage phase II trial design[53] in order to rule out an unacceptably low 5% ORR (p0=0.05) in favor of an improved RR of 25% (p1=0.25). With alpha=0.10 (probability of accepting a poor treatment=0.10) and beta = 0.10 (probability of rejecting a good treatment=0.10), this study will initially enroll 9 patients with RECIST v1.1 measurable disease, who have previously been treated with a PARPi alone, and if 0 of the 9 have a response, then no further patients will be accrued. If 1 or more of the first 9 patients has a response, then accrual would continue until a total of 24 patients have been enrolled. As it may take several weeks to determine if a patient has experienced a response, a temporary pause in the accrual to the trial may be necessary to ensure that enrollment to the second stage is warranted. If there are 1 to 2 responses in 24 patients, this would be an uninterestingly low response rate. If there were 3 or more responses in 24 patients (12.5%), this would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (5% response rate), the probability of early termination is 63.0%.

If there is at least one response in the first 9 ovarian cancer patients on the trial who were previously treated with only a PARPi, then an amendment will be submitted to open a second cohort of patients to be evaluated for clinical response consisting of recurrent or metastatic ovarian cancer patients with gBRCAm who were previously treated with PARPi combination therapy, and progressed. In these patients with ovarian cancer who were treated with PARPi combination therapy, and progressed, the study will also be conducted using the same optimal two-stage phase II trial design in order to rule out an unacceptably low 5% ORR (p0=0.05) in favor of an improved RR of 25% (p1=0.25). That is, with alpha=0.10 (probability of accepting a poor treatment=0.10) and beta = 0.10 (probability of rejecting a good treatment=0.10), this arm of the study will initially enroll 9 patients with measurable disease, with ovarian cancer who have previously been treated with PARPi combination therapy, and if 0 of the 9 have a response, then no further patients will be accrued. If 1 or more of the first 9 patients has a response, then accrual would continue until a total of 24 patients have been enrolled. As it may take several weeks to determine if a patient has experienced a response, a temporary pause in the accrual to

the trial may be necessary to ensure that enrollment to the second stage is warranted. If there are 1 to 2 responses in 24 patients, this would be an uninterestingly low response rate. If there were 3 or more responses in 24 patients (12.5%), this would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (5% response rate), the probability of early termination is 63.0%.

Toxicity and safety will be monitored in all patients enrolled on this trial and will be tabulated according to maximum grade of toxicity of a given type observed per patient. The results will be published for all patients as well as separately by type of disease.

As a secondary endpoint, progression free survival (PFS) will be estimated using a Kaplan-Meier curve based on all patients who were evaluated for response. The PFS at selected points will also be reported, along with associated 80% and 95% confidence intervals. The median time to progression after receiving BMN 673 (talazoparib) will be compared informally to the time to progression for the same patients after receiving an initial PARPi exposure. Analysis by type of cancer will also be performed.

Other secondary endpoints will focus on the ability of biomarkers including but not limited to 53BP1 by RPPA, to be associated with response in patients with ovarian cancer. Patients will be divided into groups based on whether they responded (PR+CR) or not, or were progression free at 6 months or not, and values of the biomarkers at baseline will be compared between each of the groups defined both ways using a Wilcoxon rank sum test. Changes in biomarkers from baseline will also be compared between the two groups defined both ways, but as a less important evaluation. As these will all be considered exploratory analyses, the results will not be formally adjusted for any multiple comparisons but will be considered in the context of the hypothesis generating nature of the evaluations. In practice, only results with very small p-values such as $p<0.005$ may be interpreted as being potentially statistically significant. Other secondary endpoints relating to development of mutations, biochemical changes in the DNA damage repair pathways, CTCs or immune subsets will be evaluated in a descriptive fashion.

14.2 SAMPLE SIZE/ACCRUAL RATE

It is expected that 10-12 patients per year may enroll onto this trial. In order to have 24 total evaluable patients with ovarian cancer who were treated with a PARPi alone, and 24 with PARPi combination therapy, if there is a response in the first 9 patients on the PARPi alone cohort. In this case, an amendment will be submitted to open the separate cohort for PARPi combination cohort.

It is anticipated that 1-2 years may be required for accrual. To allow for a very small number of non-evaluable patients for response (4), the accrual ceiling will be set at 28 patients.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**

Hispanic or Latino	2	+	0	=	2	
Not Hispanic or Latino	26	+	0	=	26	
Ethnic Category: Total of all subjects	28 (A1)	+	0 (B1)	=	28	(C1)
Racial Category						
American Indian or Alaskan Native	0	+	0	=	0	
Asian	2	+	0	=	2	
Black or African American	7	+	0	=	7	
Native Hawaiian or other Pacific Islander	0	+	0	=	0	
White	19	+	0	=	19	
Racial Category: Total of all subjects	28 (A2)	+	0 (B2)	=	28	(C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)	

Accrual Rate: 1-2 pts/month **Total Expected Accrual:** Min 9 Max 28

14.3 REPORTING AND EXCLUSIONS

14.3.1 Evaluation of Toxicity

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

14.3.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease

progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

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16 APPENDICES

16.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

16.2 APPENDIX B. LABORATORY STANDARD OPERATING PROCEDURE- TISSUE CORE COLLECTION

Lee Laboratory Standard Operating Procedure for Tissue Core Collection-

Needle Biopsy – Cryopreservation in OCT

Principle:

Core needle biopsies are used to sample tissue from a specific, defined location. These biopsies may consist of normal, pre-malignant and malignant tissue due to the multi-level tissue sample that is obtained. This type of sample is ideal for studying the micro-tumor environment.

Rapid freezing of the sample is required to prevent degradation of the proteins or RNA. Optimal Cutting Temperature (OCT) compound is an alcohol polymer that is liquid at room temperature and a solid at –20oC. This polymer is used to cryo-protect the tissue and provide a medium for cryo-sectioning.

Materials:

Cryomolds (Sakura Finetek Ca.t # 4728)

OCT (Sakura Finetek Cat. # 4583)

Dry ice

Ultra cold freezer (-70^0 to -80^0C)

Needle: 16 or 18 gauge

Permanent marker

Sterile forceps

Sterile Glass slides

Aluminum foil or 50ml Falcon tubes

Procedure:

1. Prepare all supplies prior to the biopsy procedure to avoid delay once the specimen has been obtained.

2. Label the handle and the front surface of the cryomold with the sample or patient's identifying information.

3. Perform core needle biopsy.

4. Pick the core from the biopsy needle onto a sterile glass slide.

5. Fill cryomold about 1/3 full with OCT. Place the cryomold in dry ice to partially freeze the OCT. The OCT should be jelly-like, not completely frozen.

6. Carefully lift the core biopsy by both ends with sterile forceps. **Do not stretch the biopsy or it will break.**

7. Lay the biopsy as straight as possible in the OCT. Once the sample touches the OCT, you cannot reposition it or the sample will break apart.

8. Quickly add OCT on top of the biopsy, completely covering the sample.

9. Ensure the sample is level and freeze immediately in dry ice.

10. Store wrapped in aluminum foil or in a 50ml Falcon tube at –70ºC.

Note:

Do not lay the biopsy on frozen OCT and cover it with liquid OCT. The OCT will not fuse and will split into two sections when cutting the frozen tissue sections.

Frozen Section Slides

1. Frozen sections for proteomic analysis should be cut at 5-8um on plain, uncoated glass microscope slides.

2. The tissue section should be placed as close as possible to the center of the slide. Do not place the frozen section at the end of the slide.

3. Two tissue sections from the same biopsy may be placed on the same glass slide if space permits.

4. Do not allow the tissue section to air on the slide. Freeze immediately on dry ice or at –80ºC.

16.3 APPENDIX C: LABORATORY STANDARD OPERATING PROCEDURE- PLASMA AND BUFFY COAT COLLECTION FOR CIRCULATING TUMOR DNA

Lee Laboratory Standard Operating Procedure for Plasma and Buffy coat collection for circulating tumor DNA (modified from Brenton Laboratory SOP at Cancer Research UK Cambridge Institute)

1. Required consumables

- Two S-Monovette 9ml EDTA tubes (Sarstedt: 02.1066.001)
- 2ml screw-capped micro-tubes (Sarstedt: 72.694.006)
- 2ml non-screwcapped Non-Stick RNase-free Microfuge Tubes (Applied Biosystems: AM12475)
- Transfer pipette (Fisher Scientific: 2655116)

2. Recommended procedure for the Plasma collection, processing, storage and transport of plasma for ctDNA and/or circulating nucleic acid studies

1.**IMPORTANT:** Blood samples should be centrifuged as soon as possible after collection to avoid fragmentation, degradation and leukocyte lysis. Samples should be spun **within 1 hour of collection.**
2. Collect blood into EDTA tubes. Label the tube with appropriate Study/Patient Number Identifiers. Record the time of collection and whether the blood was drawn using a peripheral venous access device (eg. cannula or butterfly) or a central venous access device (CVAD).
3. After collection, gently invert tubes 8-10 times to mix and leave tubes upright prior to centrifugation. As soon as possible, and **within 1 hour after collection**, centrifuge samples at 1600g for 10 minutes at room temperature using a "swing out" rotor. (NB. Centrifuge with the brake off). Record the time of centrifugation.
4. Transfer 1ml aliquots of plasma to sterile 2ml micro-tubes (non-screw capped RNase-free tubes can be used at this stage).

* Take care to avoid any buffy coat layer in this step. See "Procedure for the collection of buffy coat samples for circulating nucleic acid studies" in section 3 below for separate collection of buffy coat for germline DNA.

5. Centrifuge the plasma aliquots in a bench top centrifuge at 14,000rpm for 10 minutes to pellet any remaining cellular debris.
6. Carefully transfer 1ml aliquots of supernatant to sterile 2ml screw-capped micro-tubes, and discard the pellet.
7. Label tubes with appropriate barcode labels as required by the Study. Freeze aliquots in a -80^{0}C freezer in appropriately labeled storage boxes.

3. Recommended procedure for the collection of Buffy coat samples for ctDNA and/or circulating nucleic acid studies

1. Following Step 2 in the plasma collection protocol detailed above, carefully transfer the buffy coat layer into a separate sterile micro-tube tube using a transfer pipette or standard pipette. It may help to use a gentle swirling action to remove the buffy coat layer, taking care to avoid plasma and the red blood cell layer wherever possible.

2. Label tubes with appropriate barcode labels as required by the Study. Freeze aliquots in a -80^0C freezer in appropriately labelled storage boxes.

** Electronically record all appropriate collection details (study and anonymized patient identifier), collection date, sample volume, and sample/biorepository identifiers into study log records, as defined by study requirements. Record box number/row/column position, and if there were any sample handling or quality issues (e.g. if samples were hemolyzed).

16.4 APPENDIX D: PATIENT DRUG ADMINISTRATION DIARY

Patient Name _____ Study ID _____

Cycle Number _____

1. Please 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 a capsule is broken and the powder of the capsules gets on your skin, wash the exposed area with as much water as necessary. Inform the study doctor or nurse if that occurs.
3. Record the date and time you took the drugs.
4. If you miss or vomit the dose, please make a note of this in your diary and contact your study doctor or nurse immediately to receive further instructions.
5. If you have any comments or notice any side effects, please record them in the Comments column.
6. Please bring this form and your bottles of BMN 673 (talazoparib) with when you return for your appointments.
7. 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.

You will take: **BMN 673 (talazoparib)** Dose: _____

DAY	DATE	TIME TAKEN	COMMENTS (side effects or missed doses)
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			

Number of pills taken:	**Number of pills returned:**

Patient Signature:_____/Date:_____

Research Staff Signature:_____/Date:_____

INSTITUTE: National Cancer Institute

STUDY NUMBER: 15-C-0050 PRINCIPAL INVESTIGATOR: Jung-min Lee, M.D.

STUDY TITLE: A phase 2 pilot study of BMN 673 (Talazoparib), an oral PARP inhibitor, in patients with deleterious BRCA1/2 mutation-associated ovarian cancer who have had prior PARP inhibitor treatment

Continuing Review Approved by the IRB on 11/02/15
Amendment Approved by the IRB on 10/05/16 (C) Date posted to web: 10/12/16

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

The purpose of this study is to test the response to the study drug called BMN 673 (talazoparib) in ovarian cancer patients that were born with a BRCA mutation whose disease has gotten worse on previous treatment with a similar type of drug.

BMN 673 (talazoparib) is a PARP inhibitor. PARP inhibitors are thought to work by preventing DNA repair in tumor cells and trapping PARP into DNA that may cause toxic effects to tumor cells. BMN 673 (talazoparib) is reported to have a greater PARP-DNA trapping activity compared with other PARP inhibitors in experimental cancer cells. Also, ovarian cancer patients with BRCA mutations tend to have repeat response to platinum-based chemotherapy after they progress on a similar platinum-based regimen. It is unknown whether they have second response to another PARP inhibitor after they progressed on their first PARP inhibitors. We hope this greater PARP-DNA trapping activity yields second benefits in patients that were treated successfully but progressed on their first PARP inhibitors. BMN 673 (talazoparib) is an experimental drug that has shown some anti-cancer effects against tumor cells in experimental animals and in patients with defects in their DNA-repair pathways. This drug is in the beginning stages of being tested in humans. Although we hope this experimental therapy will decrease the size of your tumor, we cannot promise or predict the benefits of the treatment at this time.

You are being asked to take part in this study because you have ovarian cancer. You have already been treated with PARP inhibitors and your disease is now growing. People who are not in a study are usually treated with standard chemotherapies. Approximately 28 people will take part in this study.

What are the study groups?

All study participants will get the study drug BMN 673 (talazoparib).

How long will I be in this study?

You will receive the study drug until your disease gets worse or you experience intolerable side effects. After you finish receiving treatment, your doctor will continue to watch you for side effects and follow your condition for up to 4 weeks. Afterward, the doctor will continue to be in touch with you to check on your health by phone every 6 months for up to 3 years.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra tests, and/or procedures that you will need to have if you take part in this study.

Before you begin the study:

You will need to have the following examinations, tests, or procedures to find out if you can be in the study. Most of these examinations, tests, or procedures are part of your regular cancer care

and may be done by your health care team, even if you do not join the study. If you have had them recently, they may not need to be repeated. This will be up to your study doctor. You will have the examinations, tests, and procedures listed below to see if you can take part in the study (this is called the screening or baseline evaluation).

- **Complete medical history.**
- **Physical examination:** including height, weight, blood pressure, pulse, and temperature.
- **Standard blood tests:** (requiring about 1 tablespoon of blood in total), which include measurement of your white blood cells, red blood cells, platelets, blood sugar and electrolytes, how your liver and kidneys work, and how well your blood clots.
- **EKG:** A test that checks for problems with the electrical activity of your heart.
- **Pregnancy test:** A blood test will be done to check for pregnancy in women who are able to become pregnant.

During the study:

If you are accepted and you choose to take part, you will begin receiving BMN 673 (talazoparib). You will take BMN 673 (talazoparib) by mouth once per day. The drug is given in cycles; each cycle is 28 days (4 weeks) long. You can take the drug with or without food. You will continue to take the study drug until your disease gets worse or you experience intolerable side effects.

You will be asked to maintain a diary to document the exact time you took the study drug, and to report any side effects you may have. If you miss or vomit the dose, please make a note of this in your diary and contact your team immediately to receive further instructions. Please bring the study diary, pill bottle, and any remaining medication with you to each clinic visit.

You will also have tests and procedures done because you are in the study to see how BMN 673 (talazoparib) is affecting your body. This will include repeating some of the imaging studies (e.g., CT scans, a computerized x-ray examination) every 8 weeks to find out if your cancer has responded. Descriptions of the tests and procedures that will be performed during the study are listed below. Please see the Study Chart below for more details.

Clinical Center Visits: We will ask that you come to the Clinical Center at the beginning of cycle 1, and weeks 1, 2, and 3 during cycle 1; and at the beginning of week 1 for all other cycles. While you are at the Clinical Center we will perform study tests and procedures to see how the study drug is affecting your body. If you develop any side effects, you may be asked to visit more often.

Standard procedures being done because you are in this study; these may be done more often because you are in the study:

- **Clinic visit:** to ask how you are feeling and to evaluate you with a physical examination during week 1 of cycle 1 and week 1 for all subsequent cycles.
- **Vital signs and physical examinations:** will be performed during the clinic visits.
- **Blood tests:** Measurement of your white blood cells, red blood cells, platelets, blood sugar, electrolytes, and of how your liver and kidneys work will be done during weeks 1-4 of cycle 1; at the beginning of all subsequent cycles; and additional weeks as needed to follow up on any side effects you may develop. Approximately 1 tablespoon (15 mL) of blood will be drawn per visit.
- **CT scans** (or other imaging tests): such as ultrasound (an examination using sound waves) or MRI (an examination using magnetic field and radio waves) that detect your tumor will be done before the study and every 8 weeks while you are receiving study drugs. This is done so that any benefit of the treatment can be determined, and if your cancer is not responding to the treatment, the study team can tell you and discuss other treatment options (discussed further below).

Tests and procedures that are either being tested in this study or being done to see how the drug is affecting your body:

- **Research blood samples:** We will collect blood samples to find out the effects of the drug on any tumor cells in the blood. These blood samples are mandatory and will be collected at the beginning of the study, cycle 2, and at disease progression. Please see the study chart for more details. The total blood for all these tests will be about 6 tablespoons (95 mL).

- **Tumor biopsy:** After you are accepted to take part in the study, you will be asked to undergo imaging-directed biopsy of your tumor (removal of a small bit of tissue for microscopic examination) once before you receive the study drug. This first biopsy is mandatory for participation in this study to examine the potential resistance mechanisms to PARP inhibitors. Additionally, you will be asked to undergo two optional biopsies after you have taken the drug on day 28 and at disease progression. We are collecting optional biopsy samples to study the effects of BMN 673 (talazoparib) on your tumor. Biopsies are an important part of this trial and are done for research purposes.

  Tumor biopsies are only collected by trained personnel. Biopsies are collected using a small needle under imaging guidance (CT, MRI, or ultrasound as deemed appropriate by the interventional radiologist performing the biopsy). Imaging helps the specialized radiologist know that the needle has been placed into the tumor mass.

Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, pain at the biopsy site, which can be treated with regular pain medications, and bruising. Rarely, an infection can occur which will be managed with antibiotics.

When you are finished taking the drugs

When you have finished taking BMN 673 (talazoparib), your study doctor will watch you carefully for up to 30 days after the last treatment or until another treatment is started. You will need these tests and procedures at that time:

- Vital signs and a physical examination
- Blood tests
- CT scans or other imaging tests such as ultrasound or MRI

You will be followed for 30 days after taking the last dose of study drugs. We will call you between days 27-30 to ask about any side effects that were ongoing when you stopped therapy, or any new side effects that might be related to the study therapy. If you have side effects that might be related to the study drugs that have not gotten better after 30 days, we will call you every 2 weeks until the side effects have become stable or gotten better. Afterward, the doctor will continue to be in touch with you to check on your health by phone every 6 months for up to 3 years.

Study Chart

The study drug is given over 28-day periods of time called cycles. The chart below and on the next page shows what will happen to you during cycle 1 and future cycles after you sign the consent form and start the study. Each cycle is numbered in consecutive order. The left-hand column shows the day in the cycle and the right-hand column shows what will happen on that day.

Day	**What to do and what will happen to you**
Before starting study drug	• Check in at the Outpatient Clinic • Get routine blood tests • Pregnancy test for women who are able to become pregnant • Have a history taken of how you feel and undergo a physical examination by a Health Care Provider • CT scan will be done • Tumor biopsy will be taken • Blood sample for research will be taken
Cycle 1,	• Visit the Clinical Center

Day	What to do and what will happen to you
Day 1	• Have a history taken of how you feel and undergo a physical examination by a Health Care Provider • Get routine blood tests • Begin taking BMN 673 (talazoparib) by mouth • Blood sample for research will be taken
Cycle 1, Day 8	• Get routine blood tests • Continue taking BMN 673 (talazoparib)
Cycle 1. Day 15	• Get routine blood tests • Continue taking BMN 673 (talazoparib)
Cycle 1. Day 22	• Get routine blood tests • Continue taking BMN 673 (talazoparib)
Cycle 2 and onwards, Day 1	• Check in at the Outpatient Clinic • Have a history taken of how you feel and undergo a physical examination by a Health Care Provider • Get routine blood tests • CT scan to determine how your tumor is responding to the treatment will be done every 2 cycles (8 weeks) • Blood sample for research will be taken before taking BMN 673 (talazoparib) (before start of cycle 2 day 1 and at disease progression) • Continue taking BMN 673 (talazoparib) • Optional tumor biopsies will be taken before start of cycle 2 day 1 and at progression

What tests will be done on my samples?

Your tissue (tumor and normal tissue) and blood that are collected will be used to look for specific changes in your BRCA gene and possibly other genes associated with DNA repair or other pathways in tumors.

This analysis could be used to develop new ways of diagnosing and treating cancer. In order to examine the tumor and normal tissue, we may use several different techniques depending on the type of tissue we collect. Also, we will look for changes of DNA damage repair markers, circulating tumor cells, and immune cells in the blood. We will study whether these changes link to your health outcomes.

When we are conducting these tests, it is possible that we could identify possible changes in other parts of your DNA that are not related to this research. These are known as "incidental medical findings." However, the analyses that we perform in our laboratory are for research purposes only; they are not nearly as sensitive as the tests that are performed in a laboratory that

is certified to perform genetic testing. Changes that we observe unrelated to our research may or may not be valid.

Therefore, we do not plan to inform you of the results of testing on your tissue and blood that is performed in our research lab. However, in the unlikely event that we discover a finding that is believed to be clinically important based on medical standards at the time that we first analyze your results, we will, if you agree, contact you. This could be many years in the future. We will ask you to have an additional tube of blood drawn to verify the findings we have seen in our lab. If the results are verified, you will be re-contacted and offered a referral to a genetic healthcare provider to discuss the results.

[ ] Initials: _____ I DO NOT want to be contacted if incidental findings with potential health implications are discovered.

[ ] Initials: _____ I DO want to be contacted if incidental findings with potential health implications are discovered. (You will be given a choice to learn or not learn about a genetic change that we find).

Release of genetic information

Your privacy is very important to us and we will use many safety measures to protect your privacy. However, in spite of all of the safety measures that we will use, we cannot guarantee that your identity will never become known. Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them.

While the databases developed for this project are not open to everyone and also will not contain information that is traditionally used to identify you, such as your name, address, telephone number, or social security number, people may develop ways in the future that would allow someone to link your genetic or medical information in our databases back to you. For example, someone could compare information in our databases with information from you (or a blood relative) in another database and be able to identify you (or your blood relative). It also is possible that there could be violations to the security of the computer systems used to store the codes linking your genetic and medical information to you.

Your individual genomic data and health information may be put in a controlled access database. This means that only researchers who apply for and get permission to use the information for a specific research project will be able to access the information. Your genomic data and health information will not be labeled with your name or other information that could be used to

identify you. Researchers approved to access information in the database have agreed not to attempt to identify you.

Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives.

It is possible also that someone could get unauthorized access or break into the system that stores information about you. Every precaution will be taken to minimize this risk. There also may be other privacy risks that we have not foreseen. There also may be other privacy risks that we have not foreseen.

Since some genetic variations can help to predict future health problems for you and your relatives, this information might be of interest to health care providers, life insurance companies, and others. However, Federal and State laws provide some protections against discrimination based on genetic information. For example, the Genetic Information Nondiscrimination Act (GINA) makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. However, GINA does not prevent companies that sell life insurance, disability insurance, or long-term care insurance from using genetic information as a reason to deny coverage or set premiums. GINA also does not apply to members of the United States military, individuals covered by the Indian Health Service, or veterans obtaining health care through the Veteran's Administration. Lastly, GINA does not forbid insurance medical underwriting based on your current health status though the Affordable Care Act limits consideration of pre-existing conditions by insurers.

Who else besides the investigators on this study will know the results of my sample testing?

Once we obtain any of the samples listed above, the investigators take all your personal information off those samples and label them with a study code number. Only the investigators on this study know who the sample came from. The key linking your personal information with the code number is kept in a secure computer data base, with access only to the 2-3 research staff who will be discussing this study with you. Once the sample has been labeled with a code, it is sent to a variety of NIH laboratories for storage and testing. No one testing your samples will be able to link the results to you personally. Specimens obtained during your participation in this study may be sent for testing to investigators outside of NCI or the NIH. All samples will be coded to protect your privacy and no personal information will be included. Other investigators on this study will have access to limited clinical and biologic data such as age, gender and disease status.

How long will your samples be stored?

The samples collected during this study will be stored for as long as the study is open. When this study is closed, we would like to keep the samples for future research. We will request your permission to do so, later in this consent.

What possible risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss.

The BMN 673 used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

The risks of the study drug, BMN 673 (talazoparib), are as follows:

COMMON, SOME MAY BE SERIOUS In 100 people receiving BMN 673, more than 20 and up to 100 may have:
• Nausea • Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving BMN 673, from 4 to 20 may have:
• Anemia which may require blood transfusion • Constipation, diarrhea, vomiting • Bruising, bleeding • Dizziness • Hair loss

RARE, AND SERIOUS In 100 people receiving BMN 673, 3 or fewer may have:
• Infection, especially when white blood cell count is low

Potential Risks Related to Research-Related Imaging Studies:

This research study involves exposure to radiation from up to 3 CT scans (used in biopsy collections). This radiation exposure is not required for your medical care and is for research purposes only. The amount of radiation you will receive in this study is 0.54 rem, which is below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If you would like more information about radiation, please ask the investigator for a copy of the pamphlet, "An Introduction to Radiation for NIH Research Subjects." While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer.

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer.

Please tell your doctor if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

If you are pregnant you will not be permitted to participate in this research study.

What possible benefits can I expect from taking part in this study?

We do not know if you will receive personal, medical benefit from taking part in this study. The aim of this study is to see if this experimental treatment will cause your tumors to shrink. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

Alternative Approaches or Treatments

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices.

- Getting treatment or care for your cancer without being in a study
- Taking part in another study, if one is available
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment

- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you

In this case, you will be informed of the reason therapy is being stopped.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to the manufacturer/Sponsor/collaborators or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH).
- The BMN 673 (talazoparib) will be supplied at no charge while you take part in this study. The cost of getting the BMN 673 (talazoparib) ready and giving it to you is also provided at no charge. It is possible that the BMN 673 (talazoparib) may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require

doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor and qualified representative(s) of any drug company supporting the study.
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

The National Institutes of Health and the research team for this study are using BMN 673 (talazoparib) developed by BioMarin Pharmaceutical Inc., through a joint study with your researchers and the company. This means it is possible that the results of this study could lead to payments to NIH scientists and to the NIH. By law, government scientists are required to receive such payments for their inventions. You will not receive any money from the development of BMN 673 (talazoparib).

Optional Biopsy

This biopsy to be performed is exclusively for research purposes and will not benefit you. The description of the biopsy procedure is provided above. It might help other people in the future. Even if you sign "yes" to have the biopsy you can change your mind at any time. Please read each sentence below and think about your choice. After reading each sentence, circle and initial the answer that is right for you. The decision to participate in this part of the research is optional, and no matter what you decide to do, it will not affect your care.

I agree to have the tumor biopsy for the research tests in this study.

Yes No Initials_____

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Jung-min Lee, M.D., Building 10, Room 12N226, Telephone: 301-443-7735. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 301-496-4251.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:	
A. Adult Patient's Consent I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study. _____ _____ Signature of Adult Patient/ Legal Representative Date _____ Print Name	**B. Parent's Permission for Minor Patient.** I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study. (Attach NIH 2514-2, Minor's Assent, if applicable.) _____ _____ Signature of Parent(s)/ Guardian Date _____ Print Name
C. Child's Verbal Assent (If Applicable) The information in the above consent was described to my child and my child agrees to participate in the study. _____ _____ _____ Signature of Parent(s)/Guardian Date Print Name	
THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM NOVEMBER 02, 2015 THROUGH NOVEMBER 01, 2016. _____ _____ _____ _____ Signature of Investigator Date Signature of Witness Date _____ _____ Print Name Print Name	