BROWN
Oncology Research Group

TITLE: BrUOG 390: Neoadjuvant treatment with Talazoparib for women with newly diagnosed, advanced ovarian cancer associated with a mutation in BRCA1 or BRCA2 (mBRCA): A Phase 2 Feasibility Trial

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Study Monitor & Central Coordinating Group: Brown University Oncology Research Group

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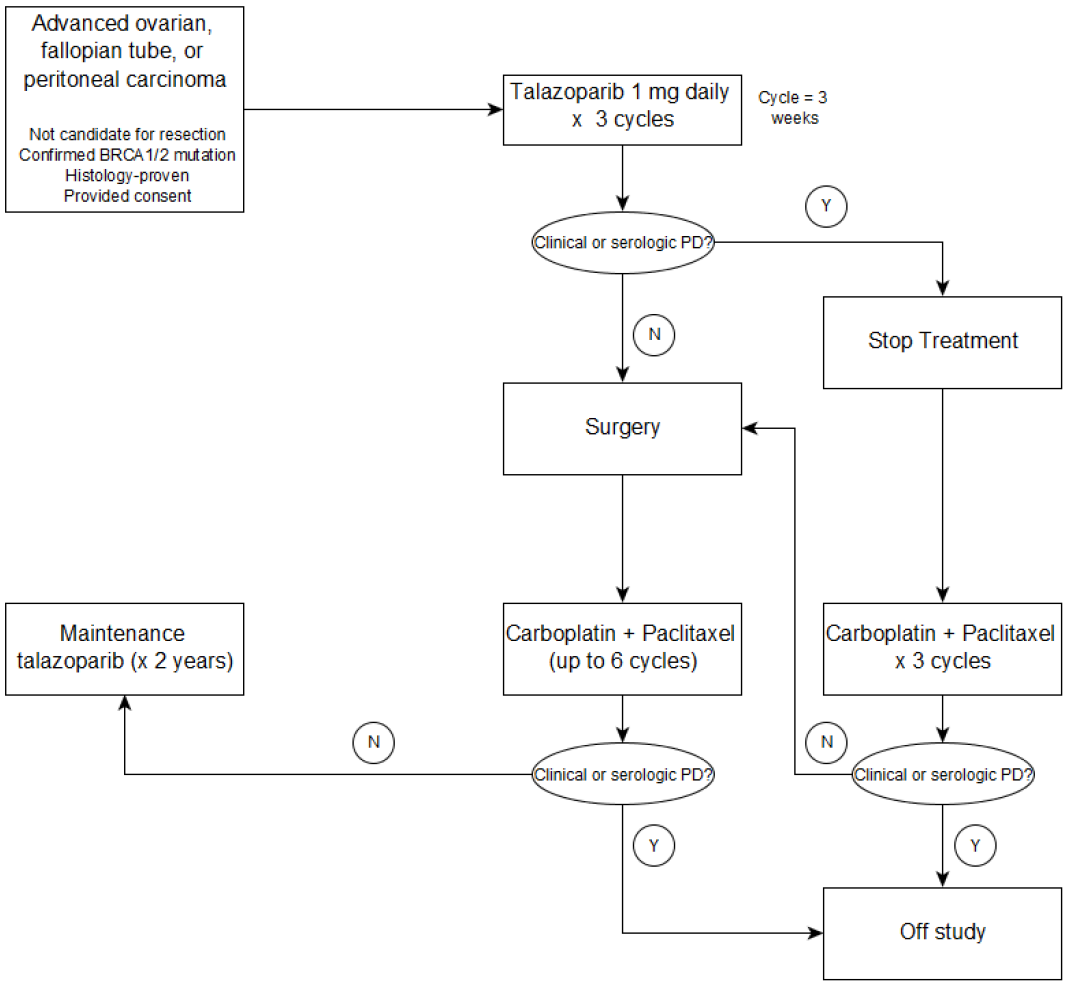
1 SCHEMA.


Advanced ovarian, fallopian tube, or peritoneal carcinoma
Not candidate for resection
Confirmed BRCA1/2 mutation
Histology-proven
Provided consent
Talazoparib 1 mg daily x 3 cycles
Cycle = 3 weeks
Clinical or serologic PD?
Y
N
Stop Treatment
Surgery
Maintenance talazoparib (x 2 years)
Carboplatin + Paclitaxel (up to 6 cycles)
Carboplatin + Paclitaxel x 3 cycles
N
Clinical or serologic PD?
N
Clinical or serologic PD?
Y
Y
Off study

2 OBJECTIVES

2.1 Primary Objective

To determine **feasibility as defined by:**

- Enrollment of 30 volunteers within two years of trial activation
- No more than three volunteers experiencing disease progression on talazoparib
- No more than two volunteers experiencing >grade 3 toxicity

2.2 Secondary Objectives

To determine preliminary effectiveness of talazoparib in this population by:

- Assessing the clinical objective response rate after nine weeks of talazoparib
- Define the rate of optimal cytoreduction and resection to no residual disease (R0) following talazoparib treatment.

2.3 Exploratory objective

The Chemotherapy Response Score (CRS) has been proposed as a reproducible measure of neoadjuvant carboplatin and paclitaxel, specifically in high grade serous carcinoma. We will collect the CRS scores in this trial to determine if it is useful in this setting.

All volunteers will be expected to undergo adjuvant chemotherapy using carboplatin and paclitaxel; however, for patients who have no evidence of disease at the time of interval cytoreduction (CRS3) the options to forego chemotherapy and continue on talazoparib can be considered following discussion with the Co-Principal Investigators. Following this, all volunteers who did **not** progress during talazoparib during the neoadjuvant period will be offered the option to reinitiate talazoparib to complete a two-year adjuvant course. For those who opt for talazoparib following adjuvant chemotherapy, we will measure the proportion who are progression-free at 3 years (3y PFS), measured from day 1 of maintenance treatment.

3 BACKGROUND AND RATIONALE

3.1 Ovarian cancer

Ovarian cancer is the most fatal gynecologic cancer; in the US alone an estimated 22,000 women will be diagnosed in 2019, with over 13,000 dying of the disease.[2] Approximately half of epithelial ovarian cancers (EOC) exhibit defective DNA repair through alterations in the homologous recombination (HR) pathway, with 14% accounted for by germline mutations in BRCA genes (mBRCA); this goes up to about one in five (20%) women when one includes tumor-associated (somatic) mBRCA.[3]

For women presenting with advanced ovarian cancer (Stage II to IV disease), neoadjuvant chemotherapy (NACT) has become a more widely accepted approach in treating advanced disease (stage III and IV). The adoption of NACT is based on multiple phase III trials showing similar benefits in terms of OS when NACT is compared with the usual standard of primary surgery followed by adjuvant chemotherapy.

Despite this more routine acceptance of NACT for the patient presenting with advanced ovarian cancer, the optimal treatment of these patients after planned interval cytoreduction remains unresolved. In other words, it may be that the lack of any survival advantage with NACT is related to the administration of the same chemotherapy prescription after the interval cytoreduction (i.e., in the adjuvant setting); the results of two randomized trials support the idea that the administration of a similar regimen in the neoadjuvant and adjuvant settings may result in a lack of survival advantage.[4,5]

Current pathology practice includes reporting pathologic assessment of disease response on surgical cancer specimens after NACT, called the Chemotherapy Response Score (CRS). This is a reproducible three-tier score, and demonstrates prognostic significance for progression-free survival (CRS 1 and 2 v 3: median, 15 v 19 months; p=0.016).[1]

3.2 Ovarian cancer associated with mutations in BRCA1 or BRCA2 (mBRCA)

The approach to women with mBRCA-associated ovarian cancer has heralded precision treatment in our field with the availability of PARP inhibitors. Now indicated as treatment for women with documented mBRCA (genomic or somatic), it also has shown significant benefits for women with recurrent EOC who respond to platinum-based therapy when administered as maintenance treatment. These data have led to the FDA approval of three PARP inhibitors for use in EOC, though indications slightly differ (Table 1). The results of the SOLO-1 trial led to the FDA approval of olaparib as a maintenance therapy after upfront chemotherapy for women with mBRCA-associated ovarian cancer.[6] In that trial, almost 400 women with newly diagnosed stage III-IV high grade serous or endometrioid cancers who had a clinical complete or partial response to platinum-based therapy were randomly assigned in 2:1 fashion to olaparib (300mg BID) or placebo. Compared to placebo, maintenance olaparib significantly prolonged 3-year progression-free survival (60 vs 27%, respectively, HR 0.30, p<.001).

Continued efforts aim to maximize the impact of PARP inhibitors for women with ovarian cancer, with or without an mBRCA, and multiple trials are ongoing in the upfront and recurrent disease setting.

Recently, Litton, et al. reported the results of a feasibility trial in which she aimed to enroll volunteers with a known mBRCA and operable breast cancer (clinical stage I to III, tumor size ≥1 cm) to neoadjuvant talazoparib.[7] The treatment course was to be for 8 weeks after which standard neoadjuvant anthracycline/taxane chemotherapy was to be administered. Her aim was to prove she could enroll 20 volunteers in 2 years. She was able to enroll 13 volunteers in 8 months, and impressively, all volunteers experienced a response with a mean tumor volume reduction of 88% (range, 30 to 98%). For women with triple-negative breast cancer, residual cancer burden was recorded as 0 or 1 at surgery. The study continues with an aim to enroll a cohort of 20 women with treatment using talazoparib for up to 6 months before definitive surgery. This study marks the first trial of true precision therapy in women with mBRCA-associated breast cancer.

Agent	**Trial**	**Volunteer and Study criteria**				**Efficacy**	**Toxicity**
		ROC	HGS	gBRCA	Maint		
Niraparib	NOVA[8] (n=546)	√	√		√	+++PFS in gBRCA+ and gBRCA-	Nausea, Thrombocytopenia, Fatigue, Anemia
Olaparib	SOLO-2[9] (n=295)	√	√	√	√	+++PFS	Nausea, Fatigue, Anemia, Emesis
	Phase 2[10] (n=193)	√	√	√		30%ORR 40%SD8w	Fatigue, Nausea, Anemia, Abdominal pain
Rucaparib	ARIEL-3[11]	√ ≥3 lines	√		√	+++PFS in gBRCA+, LOH+, ITT	Nausea, Fatigue, Anemia, Constipation
	Phase 2[12] (n=106)	√ ≥2 lines	√	√ Somatic allowed		54% ORR 9m mDOR	Nausea, Fatigue, Anemia, Abdominal pain

Table 1. FDA Indications of 3 available PARP Inhibitors for ovarian cancer

3.3 Talazoparib

Talazoparib (PF-06944076, formerly BMN 673, MDV3800) is a potent, orally bioavailable, small molecule poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor (PARPi) that is in development for the treatment of a variety of human cancers. PARPis exert antitumor activity via both inhibition of PARP catalytic activity (including inhibition of poly-ADP-ribosylation [PARylation]) and PARP trapping.

In vitro pharmacology studies with talazoparib demonstrated potent and selective inhibition of PARP1 (50% inhibitive concentration [IC50] = 0.7 nM) and PARP2 (IC50 = 0.3 nM) catalytic activity in a biochemical assay. Robust cytotoxicity following talazoparib treatment was observed in a panel of breast, prostate, pancreatic, and colorectal cancer cell lines with defects in DNA damage repair pathways. Evaluation of

PARP trapping in breast and prostate cancer cell lines treated with talazoparib resulted in increased trapping in the presence of single-strand break inducing agent methyl methane sulfonate (MMS). The effects were clearly evident in the BRCA1-mutant MDA-MB-436 breast cancer, which is sensitive to talazoparib-induced cytotoxicity, compared to the less sensitive BRCA1-mutant breast cancer HCC1954 line. PARP trapping has also been shown for the BRCA2-mutant DU145 prostate cancer cell line. Additionally, a multiparametric DDR assay in the DU145 cell line also showed that talazoparib treatment induced S-phase cell-cycle arrest, increased S-phase specific and total dsDNA breaks (measured by H2AX), increased early apoptosis (measured by cleaved caspase 3 [CC3]), and decreased cell population growth, compared to vehicle treated cells. The reduced population growth and cytotoxicity observed in the DDR assays are consistent with the proposed mechanisms of action for talazoparib: catalytic activity inhibition and PARP trapping.

In vivo, antitumor efficacy of single agent talazoparib was better than carboplatin in a breast cancer PDX model when dosed orally QD at 0.3 mg/kg. Breast cancer PDX models (one each with mutated BRCA1 and mutated BRCA2, and 3 models with wild type BRCA1/2) evaluated with talazoparib dosed BID at 0.07 mg/kg or 0.15 mg/kg showed that talazoparib elicited the strongest, statistically significant (compared to vehicle), dose dependent TGI response (100% TFS) in the BRCA1-mutated PDX model, but also elicited statistically significant TGI responses in the BRCA2-mutated model and BRCA1/2 wild type models. While activity was most robust in the BRCA1 mutated model, talazoparib was also active in the BRCA2 mutant and in the presence of wild type BRCA1/2, possibly due to other unknown DDR-related mutations.[13]

3.3.1. Summary of nonclinical studies

Talazoparib is a potent inhibitor of PARP1 and PARP2 catalytic activities and has demonstrated potency and selectivity toward PARP1 and PARP2 in vitro, as well as robust cytotoxicity in a panel of cell lines with defects in the DDR pathways. Evaluation of the potency and selectivity of talazoparib in a PARP inhibition enzyme assay was conducted with a panel of 13 PARP enzymes and demonstrated IC_{50} values for PARP1 and PARP2 of 0.7 nM and 0.3 nM, respectively.

Talazoparib also had activity toward PARP3 (IC50, 22 nM), TNKS1 (PARP5a; IC50, 13.5 nM), and TNKS2 (PARP5b; IC_{50}, 4.7 nM). Assessment of talazoparib for cytotoxic activity in a panel of breast, prostate, and pancreatic cancer cell lines harboring defects in DDR pathways, demonstrated mean IC_{50} values of $\leq$5 nM.

PARP trapping was measured in breast cancer cell lines treated with talazoparib over a concentration range that approximately covered an order of magnitude difference from the free C_{av} exposure achieved in volunteers and the IC_{90} for PARylation inhibition. Results showed increased trapping in the presence of MMS, an alkylating agent that induces ssDNA break, in the BRCA1-mutant MDA-MB-436 cell line, which was highly sensitive to talazoparib cytotoxicity and reduced trapping in the less sensitive BRCA1-mutant HCC1954 cell line. Multiparametric DDR assays in the BRCA2 mutated DU145

prostate cancer cell line were conducted using a range of clinically relevant talazoparib concentrations in the presence and absence of the DNA alkylating agent TMZ, which is used as a tool to further evaluate the functional effects of talazoparib. Talazoparib induced S phase cell cycle arrest, increased in S-phase specific dsDNA breaks (measured by H2A histone family, member X, gamma subunit, γH2AX), increased early apoptosis (measured by CC3), and resulted in decrease in cell proliferation compared to vehicle treated cells.

In vivo, antitumor efficacy of single agent talazoparib administered at 0.3 mg/kg QD was higher than carboplatin treatment in a breast cancer PDX model. Additional breast cancer PDX models (one with a BRCA1 mutation, one with a BRCA2 mutation, and 3 models with wild type BRCA1/2) were evaluated with talazoparib dosed at 0.07 mg/kg or 0.15 mg/kg BID for 34 or 35 days. Talazoparib treatment was most effective in the BRCA1 mutant model, resulting in percent ratio between the mean tumor volume of the treated group and the mean tumor volume of the control group (T/C%) of 0.39% for the 0.15 mg/kg dose level where 100% of the mice had complete tumor regressions at study termination (TFS). The BRCA2 mutant model showed statistically significant T/C% of 3.48% and 60% TFS, as did one of the 3 wild type BRCA1/2 models (T/C% = 0.32%, TFS = 80%) at 0.15 mg/kg, while the other 2 models exhibited modest effects. For the PDX models, the mean unbound C_{av} values at 0.07 and 0.15 mg/kg were approximately dose proportional and were 0.852 nM and 1.86 nM, respectively.

In secondary pharmacology assessments, no activity greater than 50% of a maximal response was observed for talazoparib indicating there is minimal potential for secondary (off-target) pharmacology at clinically relevant exposures. In addition, there were no talazoparib-related effects on respiratory or CNS parameters following a single oral administration to rat in safety pharmacology studies, and there were no effects in a hERG assay at concentrations up to 100 μM (38035 ng/mL) or 6966-fold above the observed unbound human clinical exposure at 1 mg QD human dose based on mean unbound steady state C_{max} of 5.46 ng/mL.

Further details of the nonclinical evaluation of talazoparib are available in the IB. [13]

3.3.2. Pharmacology of Talazoparib

Talazoparib activity was assessed with a panel of 13 PARP enzymes using a biochemical assay that measures incorporation of biotin-NAD+ in ADP-ribose polymers onto histone proteins (Study PF-06944076_02Nov17_092045). Talazoparib shows activity below 10 nM for PARP1 (0.7 nM), PARP2 (0.3 nM) and Tankyrase-2 (TNKS2, 4.7 nM), inhibition below 25 nM for PARP3 and TNKS1 and weak to no inhibition for the remainder of the enzymes tested.

Talazoparib was assessed for cytotoxic activity in cancer cell lines harboring defects in DNA repair pathways (Study BMN673-10-093). Talazoparib was cytotoxic to BRCA-deficient Capan-1 and MX-1 cells in culture, with IC_{50} values of 5.0 nM and 0.3 nM, respectively. Talazoparib was also highly cytotoxic to PTEN-deficient MDA-MB-468,

LNCaP, and PC-3 cells with IC_{50} values of 3.7 nM, 4.3 nM, and 4.4 nM, respectively, and MLH1 mutated hematocrit (HCT)-116 (IC_{50} = 10.6 nM). In contrast, the IC_{50} values of talazoparib in normal human primary cell line MRC-5 and other tumor cell lines (LoVo, MDA-MB-231, and A549) without reported DNA repair-related mutations were much higher (>250 nM to >1000 nM).

Talazoparib antitumor activity was benchmarked against carboplatin (Study MDVT-20160830B [MDV3800P058]) in a breast cancer PDX model. The 3 test groups (n = 7/group) received vehicle, talazoparib administered orally QD at 0.3 mg/kg, or carboplatin administered IP at 30 mg/kg once weekly. Talazoparib treatment resulted in statistically significant TGI (108%; p = 0.031) versus carboplatin treatment (TGI 67%; p = 0.178).

For in vivo studies, the oral route of exposure was selected for these studies since it is the intended route of clinical administration. To evaluate potential effects on the CNS, talazoparib was administered as a single oral dose to male rats at 0, 0.3, 1, and 3 mg/kg. The rats were volunteered to a modified Irwin battery to detect potential effects on central and peripheral nervous systems at baseline and up to 24 hours post-dose. There were no talazoparib-related effects on the parameters evaluated in modified Irwin battery of neurological assessments including home cage, hand-held, open-field or elicited response observations at doses up to 3 mg/kg. In addition, no microscopic pathology changes were seen in the brain in any of the repeat-dose toxicity studies. Toxicokinetic parameters were not measured in this study, but based on the 5-day rat study, maximum mean unbound plasma concentration at 3 mg/kg/day was 62.6 ng/kg, which is 11.4x the observed unbound human C_{max} concentration at the 1 mg QD clinical dose (5.46 ng/mL).

Talazoparib was administered as a single oral dose to male rats at 0, 0.3, 1 or 3 mg/kg to assess potential effects on the respiratory system over a 5.5-hour period using whole body plethysmography at baseline and then starting at 0.5 and 24 hours postdose. Tidal volume was decreased as much as 12% (relative to control) in all dose groups administered talazoparib. These generally nondose dependent decreases in tidal volume were offset by the non-statistically significant increases in respiration rate so that there was no overall change in minute volume. Toxicokinetic parameters were not measured in this study, but based on the 5-day rat study, maximum mean unbound plasma concentration at 3 mg/kg (the highest dose tested) was 62.6 ng/mL and is 11.4x the observed unbound human C_{max} concentration at the 1 mg QD clinical dose (5.46 ng/mL). Furthermore, there were no talazoparib-mediated adverse clinical signs associated with the respiratory system in the repeat-dose toxicity studies of up to 13-weeks duration in rats and dogs.

To evaluate the potential effect on the cardiovascular system, talazoparib was evaluated for its effect on binding to the hERG potassium channel stably expressed in human embryonic kidney (HEK-293) cells. Talazoparib inhibited the hERG current 6.7%, 14.2% and 33.4% at concentrations of 10, 30, and 100 µM. Due to solubility limitations the highest dose that could be tested was 100 µM and an IC_{50} could not be calculated since 50% inhibition was not achieved at the concentrations tested. Thus, the IC_{50} for hERG inhibition is considered >100 µM (38000 ng/mL) and is approximately >6996x the

observed unbound human clinical exposure at 1 mg QD human dose based on mean unbound steady state C_{max} of 5.46 ng/mL.

To further evaluate the potential for talazoparib to affect the cardiovascular system in vivo, ECG assessments were added on to the repeat GLP dog studies. No effects on ECGs were noted at doses of up to the highest dose tested (0.1 mg/kg) with mean unbound plasma exposures corresponding to 3.5x above human clinical exposure at 1 mg QD dose based on mean unbound steady state C_{max} of 5.46 ng/mL.

Further details of the pharmacology of talazoparib are available in the Investigator's Brochure. [13]

3.3.3. Summary of studies in human volunteers

The single dose PK of talazoparib have been evaluated in a total of 7 clinical studies, of which 6 were conducted in volunteers with cancer (Studies PRP-001, PRP-002, MDV3800-01, MDV3800-03, MDV3800-04, and MDV3800-14) and 1 in healthy volunteers (Study 673-103).

After administration of a single 1 mg dose of talazoparib capsules to volunteers with cancer, the median time to reach maximum plasma concentration (T_{max}) was ranging from 1.0 to 2.0 hours across studies. The median T_{max} was 0.5 hour following administration of talazoparib solution in Study MDV3800-03. The geometric mean C_{max} ranged from 4.35 to 8.79 ng/mL and the geometric mean area under concentration-time curve from time 0 to infinity (AUC_{inf}) ranged from 116 to 220 ng•h/mL. Talazoparib was eliminated slowly with a mean t½ ranging from 62.4 to 98.1 hours. It should be noted that the t½ value obtained from Study PRP-001 might be an underestimate as the PK sampling time was only up to 168 hours versus 504 hours in Study MDV3800-03.

The talazoparib geometric mean apparent volume of distribution (Vz/F) values estimated ranged from 447 to 847 L, which is significantly greater than total body water (42 L), indicating that talazoparib extensively distributes to peripheral tissues. The geometric mean apparent oral clearance (CL/F) values estimated for talazoparib ranged from 4.55 to 7.71 L/hour. The geometric mean renal clearance (CLr) ranged from 2.76 to 3.44 L/hour, indicating that urinary excretion was a major route of elimination for talazoparib.
The talazoparib geometric mean CL/F value after administration of a single 0.5 mg talazoparib dose to healthy volunteers in Study 673-103 was 7.99 L/hour and 8.19 L/hour in the fasted and fed conditions, respectively. This value was generally in a comparable range with that observed in volunteers following a single dose of talazoparib at various dose levels (4.55 to 7.71 L/hour). In addition, the t½ of talazoparib in healthy volunteers ranged from 81.3 to 208 hours (Study 673-103), which is within the mean range observed across studies conducted in volunteers receiving a single dose of talazoparib at various dose levels (52.9 to 229 hours, Study PRP-001). These results collectively indicate that the PK of talazoparib was comparable between volunteers with cancer and healthy volunteers.

The PK of talazoparib following multiple oral daily doses was evaluated in a total of 6 studies in volunteers with cancer (Studies PRP-001, PRP-002, 673-201, 673-301, MDV3800-01, and MDV3800-14). Following repeated 1 mg QD dosing to steady state, talazoparib was rapidly absorbed with a median T_{max} ranging from approximately 1.0 to 2.0 hours across studies. Talazoparib was eliminated slowly, with a geometric mean CL/F ranging from 4.80 to 5.53 L/hour. The mean plasma t½ was 57.8 hours (Study PRP-001), which may be an underestimate as the last PK sampling time was at 168 hours postdose. The geometric mean CLr was 3.34 L/hour, 3.32 L/hour and 2.74 L/hour in Studies PRP-001, PRP-002, and MDV3800-01 (Group A), respectively.

The talazoparib geometric mean C_{max} values ranged from 11.4 to 19.1 ng/mL and the geometric mean area under the concentration-time curve for a dosing interval (AUCγ) values ranged from 126 to 208 ng•h/mL. The talazoparib geometric mean steady-state pre-dose plasma concentration (C_{trough}) values ranged from 2.99 to 4.95 ng/mL. [13]

3.3.4. Absorption, Distribution, Metabolism, and Excretion

Based on the urinary excretion data from a Phase 1 mass-balance and metabolism study of talazoparib (MDV3800-03 [C3441003]), the absolute bioavailability is at least 54.6% with fraction absorbed of at least 68.7%. The talazoparib median T_{max} values ranged from 1.0 to 2.0 hours after single and multiple 1 mg oral dosing of talazoparib capsules in volunteers.

Study 673-103 evaluated the effect of food on the talazoparib plasma PK following administration of a single 0.5 mg dose of talazoparib oral capsule formulation in 18 healthy volunteers. Food intake (a high-fat, high-calorie meal) had no impact on the AUC while reduced the C_{max} by 46%. The ratios of adjusted geometric means following administration under fed compared to fasted conditions were 97.62% (90% CI: 92.48%, 103.05%) for AUC_{inf} and 53.88% (90% CI: 48.12%, 60.34%) for C_{max}. Consistent with findings from the food effect study, population PK analysis using data from Studies 673-301, 673-201, PRP-001, and PRP-002 showed food intake decreased absorption rate but had no impact on the extent of the absorption. The reduction in the rate of absorption with food is not expected to be clinically relevant as efficacy is generally driven by total exposure. Therefore, talazoparib can be taken without regard of food.

Radioactivity in whole blood versus plasma was approximately 1, indicating that there is no preferential distribution of talazoparib into RBC. Based on population PK analysis, the talazoparib apparent steady-state volume of distribution (Vss/F) was estimated to be 420 L, which is significantly greater than total body water (42 L), indicating that talazoparib extensively distributes to peripheral tissues.

In vitro experiments with human hepatocytes and liver microsomes indicated that talazoparib undergoes minimal hepatic metabolism. Following oral administration of a single 1 mg dose of ^{14}C-talazoparib to humans in Study MDV3800-03, no major circulating metabolites were identified in plasma, and talazoparib was the only circulating

drug-derived entity identified in plasma. No metabolites that individually represented more than 10% of the administered dose were recovered in the urine or feces. The identified metabolic pathways of talazoparib in humans include: 1) mono-oxidation; 2) dehydrogenation; 3) cysteine conjugation of monodesfluorotalazoparib; and 4) glucuronide conjugation.

Based on population PK analysis, the talazoparib CL/F was estimated to be 6.45 L/hour. In 6 female volunteers with advanced solid tumors given a single oral dose of 14C-talazoparib (Study MDV3800-03), a mean of 68.7% and 19.7% of the total administered radioactive dose was recovered in urine and feces, respectively. Excretion of unchanged talazoparib in urine was the major route of elimination accounting for 54.6% of the administered dose, while unchanged talazoparib recovered in the feces accounted for 13.6%. [13]

3.3.5. Drug-drug interactions

A Phase 1, open-label, 2-arm, fixed-sequence study (MDV3800-04 [C3441004]) was conducted to evaluate the effects of multiple doses of P-glycoprotein (P-gp) inhibitor itraconazole and P-gp inducer rifampin on the single-dose PK of talazoparib in volunteers with advanced solid tumors. In Arm A, coadministration of multiple daily doses of itraconazole 100 mg BID and a single 0.5-mg talazoparib dose increased the area under the concentration-time curve from 0 to infinity (AUC_{inf}) and C_{max} of talazoparib by approximately 56% and 40%, respectively, relative to a single 0.5-mg talazoparib dose administered alone. In Arm B, coadministration of multiple daily doses of rifampin 600 mg and a single 1-mg talazoparib dose increased talazoparib C_{max} by approximately 37%, whereas AUC_{inf} was not affected relative to a single 1-mg talazoparib dose administered alone. Consistent with the findings from the DDI study, population PK analysis indicated that concomitant administration of strong P-gp inhibitors with talazoparib increased talazoparib exposure by 44.7% relative to talazoparib administered alone. If a strong P-gp inhibitor must be coadministered to volunteers, the dose of talazoparib should be reduced to 0.75 mg. The overall talazoparib exposures observed when talazoparib was administered alone and with rifampin suggested that the effect of rifampin on talazoparib exposure in Study MDV3800-04 was minimal. Therefore, no talazoparib dose adjustments are recommended upon coadministration with P-gp inducers.

Population PK analysis indicated that coadministration of acid-reducing agents including proton-pump inhibitor (PPI), histamine receptor 2 antagonist (H2RA), or other acid-reducing agents had no significant impact on the absorption of talazoparib. [13]

3.3.6. Population pharmacokinetics

The population PK analysis for talazoparib was conducted based on 6207 PK observations of 490 volunteers with advanced cancer from 4 clinical trials, Studies PRP-001, PRP-002, 673-201 and 673-301. Talazoparib PK was well characterized by a 2-compartment model with first order absorption. In the base model, the estimated population mean value for CL/F was 6.45 L/h, for apparent central volume of distribution

(V2/F) was 157 L, for apparent peripheral volume of distribution (V3/F) 263 L, for apparent inter-compartmental clearance (Q/F) was 9.57 L/hour, for first-order absorption rate constant (ka) was 0.991 L/hour, and for lag time for absorption (Tlag) was 0.242 hour. Thus, the Vss/F was 420 L. [13]

3.3.7. Safety profile

Aggregate safety data from 5 open-label, including 1 randomized, company-sponsored clinical studies (PRP-001, 673-201, 673-301, MDV3800-13, and MDV3800-14; N = 502 volunteers) evaluating talazoparib monotherapy at the proposed dose of 1 mg/day (Talazoparib 1 mg/day Population) as of 31 January 2018 provide the basis for the reported treatment-emergent adverse events (TEAEs). In the ongoing Phase 2, open-label, extended treatment, safety study (MDV3800-13 [C3441010]), which provides access to talazoparib monotherapy for volunteers with solid tumors who were previously treated with talazoparib as a single agent or in combination with another agent in qualifying originating company-sponsored clinical studies, volunteers received varying doses of talazoparib, however, only the 55 volunteers who initiated treatment with talazoparib 1 mg/ QD in either the originating or extension study are included in the aggregate safety data (Talazoparib 1 mg/day Population).

The overall safety profile of talazoparib is based on pooled data from the 502 volunteers who received talazoparib at the proposed dose of 1 mg/day for solid tumors in 673-301, 673-201, MDV3800-13, PRP-001, and MDV3800-14. This is summarized in Table 2. [13]

3.4 Rationale

Given the effectiveness of PARP inhibitors in mBRCA-associated ovarian cancer, we propose a similar feasibility neoadjuvant trial. The study would be coordinated out of the Brown University Oncology Group (BrUOG). Our aim would be to determine the feasibility of treating 30 volunteers within 2 years.

Cluster Term or PT	Talazoparib 1 mg/day Population[a] N = 502		
	All Grades	Grade 3	Grade 4
Fatigue[b]	289 (57.6%)	20 (4.0%)	0 (0.0%)
Nausea	224 (44.6%)	5 (1.0%)	na
Anemia[c]	254 (50.6%)	177 (35.3%)	3 (0.6%)
Thrombocytopenia[d]	150 (29.9%)	64 (12.7%)	21 (4.2%)
Diarrhoea	114 (22.7%)	3 (0.6%)	0 (0.0%)
Vomiting	114 (22.7%)	8 (1.6%)	0 (0.0%)
Neutropenia[e]	156 (31.1%)	80 (15.9%)	11 (2.2%)
Leukopenia[f]	82 (16.3%)	25 (5.0%)	2 (0.4%)
Lymphopenia[g]	32 (6.4%)	15 (3.0%)	0 (0.0%)
Alopecia	112 (22.3%)[h]	na	na
Abdominal pain[i]	109 (21.7%)	8 (1.6%)	na
Headache	135 (26.9%)	5 (1.0%)	na
Decreased appetite	102 (20.3%)	2 (0.4%)	0 (0.0%)
Dizziness	73 (14.5%)	1 (0.2%)	na
Dysgeusia	42 (8.4%)	na	na
Dyspepsia	44 (8.8%)	0 (0.0%)	na
Stomatitis	32 (6.4%)	0 (0.0%)	0 (0.0%)

Toxicity grades according to NCI CTCAE v4.03. No grade 5 ADRs were reported with the exception of one case of grade 5 fatigue, which was corrected after the data lock point, and included above as the corrected severity of grade 3.
ADR = adverse drug reaction; CTCAE = Common Toxicity Criteria for Adverse Events; na = not applicable; NCI = National Cancer Institute; PT = preferred term.
[a] Includes 502 patients treated with talazoparib 1 mg/day for solid tumors in Studies 673-301, 673-201, MDV3800-13, PRP-001, and MDV3800-14 as of 31 January 2018.
[b] Includes preferred terms of fatigue and asthenia.
[c] Includes preferred terms of anemia, hematocrit decreased and hemoglobin decreased.
[d] Includes preferred terms of thrombocytopenia and platelet count decreased.
[e] Includes preferred terms of neutropenia, and neutrophil count decreased.
[f] Includes preferred terms of leukopenia and white blood cell count decreased.
[g] Includes preferred terms of lymphopenia and lymphocyte count decreased
[h] Grade 1 for 20.7% and Grade 2 in 1.6%.
[i] Includes preferred terms of abdominal pain, abdominal pain upper, abdominal discomfort, and abdominal pain lower.

Table 2. ADRs Associated With 1 mg/day Talazoparib in Solid Tumors

Sinusitis	27 (5.4%)
Aspartate aminotransferase increased	25 (5.0%)
Dry skin	25 (5.0%)
Mucosal inflammation	25 (5.0%)

Data cutoff date for Studies 673-301, 673-201 and MDV3800-13 was 31 Jan 2018. Date of last patient discontinued for Studies PRP-001 was 30 Jan 2017, and MDV3800-14 was 22 Jun 2017.
Includes all patients who completed studies PRP-001, MDV3800-03, MDV3800-04 and MDV3800-14, and subsequently enrolled in the open-label extension study MDV3800-13 and initiated treatment with talazoparib at 1 mg/day in either the originating or extension study (Talazoparib 1 mg/day Population). Excludes the physician's choice treatment arm of Study 673-301.

4 VOLUNTEER SELECTION, ELIGIBILITY, AND INELIGIBILTY CRITERIA

4.1 Eligibility Criteria

A volunteer cannot be considered eligible for this study unless ALL of the following conditions are met.

1. Volunteers must have clinical and radiographic evidence of newly detected FIGO stage II, III or IV epithelial ovarian, primary peritoneal or fallopian tube cancer, deemed by a gynecologic oncologist as not amenable to an R0 resection at presentation.
2. Institutional confirmation of Müllerian epithelial adenocarcinoma
3. Histologic epithelial cell types: high grade serous carcinoma, high grade endometrioid carcinoma, or a combination of these.

4. Documented mutation in BRCA1 or BRCA2 by genetic or commercial somatic testing. Reports will require submission at the time of enrollment.
5. Measurable disease as defined by RECIST 1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by CT, MRI or caliper measurement by clinical exam; or ≥ 20 mm when measured by chest x-ray. Lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI.[14]
6. Age ≥ 18
7. Adequate hematologic function determined within 28 days of consent as follows:
    - ANC greater than or equal to 1,500/mcl. NOTE: ANC cannot have been induced by granulocyte colony stimulating factors.
    - Platelets greater than or equal to 100,000/mcl
    - Hemoglobin greater than 10 mg/dl (NOTE: While transfusions are permitted to achieve baseline hemoglobin level, **patients must not have transfusion within 14 days prior to obtaining baseline screening labs**)
8. Creatinine Clearance > 15 mL/min. (NOTE: Please see Section 6.2.1 for dosing requirements for patients with renal insufficiency)

    CrCl = (140- age in years) x weight in kg x 0.85/ 72 x serum creatinine in mg/ dL

9. Adequate hepatic function within 14 days prior to registration defined as follows:
    - Bilirubin ≤ 1.5 x ULN
    - ALT and AST < 2.5 x ULN
    - Alkaline phosphatase ≤ 2.5 x ULN
10. Neurologic function: Neuropathy (sensory and motor) less than or equal to CTCAE v5.0 Grade 1.
11. Ability to swallow and retain oral medication. Adequate gastrointestinal absorption with no use of parenteral nutrition within two weeks of trial enrollment and no evidence of bowel obstruction.
12. The volunteer must provide study-specific informed consent prior to study entry.

4.2 Ineligibility Criteria

Volunteers with any of the following conditions are NOT eligible for this study.

1. Suspected non-gynecologic malignancy, evidenced by tumor markers and/or histologic evaluation.
2. Prior history of other invasive malignancies, with the exception of nonmelanoma skin cancer and other specific malignancies as noted in Section 4.2.4 and Section 4.2.5 are excluded if there is any evidence of other malignancy being present within the last three years (2 years for breast cancer, see Section 4.2.4). Volunteers are also excluded if their previous cancer treatment contraindicates this protocol therapy.

3. Prior chemotherapy for any abdominal or pelvic tumor within the last three years is excluded. Volunteers may have received prior adjuvant chemotherapy and radiotherapy for localized breast cancer, provided that it was completed more than 2 years prior to registration, the volunteer remains free of recurrent or metastatic disease and hormonal therapy has been discontinued.
4. Prior radiotherapy to any portion of the abdominal cavity or pelvis or thoracic cavity within the last three years are excluded. Prior radiation for localized cancer of the head and neck or skin is permitted, provided that it was completed more than three years prior to registration, and the volunteer remains free of recurrent or metastatic disease.
5. Synchronous primary endometrial cancer, or a past history of primary endometrial cancer, unless all of the following conditions are met: Stage not greater than I-A, grade 1 or 2, no more than superficial myometrial invasion, without vascular or lymphatic invasion; no poorly differentiated subtypes, including serous, clear cell or other FIGO grade 3 lesions.
6. Severe, active co-morbidity defined as follows:
    - Chronic or current active infectious disease requiring systemic antibiotics, antifungal or antiviral treatment
    - Known brain or central nervous system metastases or history of uncontrolled seizures
    - Clinically significant cardiac disease including unstable angina, acute myocardial infarction within 6 months from enrollment, New York Heart Association Class III or IV congestive heart failure, and serious arrhythmia requiring medication (this does not include asymptomatic atrial fibrillation with controlled ventricular rate).
    - Partial or complete gastrointestinal obstruction
7. Volunteers who are not candidates for major abdominal surgery due to known medical comorbidities.
8. Volunteers with any condition that in the judgment of the investigator would jeopardize safety or volunteer compliance with the protocol.
9. Concurrent anticancer therapy (e.g. chemotherapy, radiation therapy, biologic therapy, immunotherapy, hormonal therapy, investigational therapy).
10. Receipt of an investigational study drug for any indication within 30 days or 5 half-lives (whichever is longer) prior to Day 1 of protocol therapy.
11. Prior exposure to a PARP inhibitor.
12. People of child-bearing potential (WOCB). This includes:
    - Any volunteer who has experienced menarche and who has not undergone surgical sterilization (hysterectomy and/or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12-month amenorrhea in a woman over 45 in the absence of other biological or physiological causes.
    - Volunteers who are pregnant or nursing. Volunteers 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 7 months after completing therapy.

People with an intact uterus and ovaries must have a screening negative serum or urine pregnancy test within 14 days of registration. A second pregnancy test must be done within 24 hours prior to the start of the first cycle of study treatment

13. Potent P-gp inhibitors that result in ≥ 2-fold increase in the exposure of an in vivo probe P-gp substrate, including: amiodarone, carvedilol, clarithromycin, cobicistat, dronedarone, erythromycin, glecaprevir/pibrentasvir, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, sofosbuvir/velpatasvir/voxilaprevir, telaprevir, tipranavir, valspodar and verapamil. More instruction available at: https://www.druginteractionsolutions.org/ and https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-2.

4.3 Inclusion of Gender, Racial, and Sexual Minorities

All volunteers born with ovaries are eligible for this trial.

5 REGISTRATION PROCEDURES

All volunteers will be registered through the Brown University Oncology Research Group Central Office. Eligibility Checklist with supporting documentation, On Study Form and the signed Volunteer Consent Form must be emailed to the BrUOG Central Office, BrUOG@brown.edu, at the time of registration and prior to volunteer treatment.

Details of patient's study participation should be documented in clinic/file notes. This project will leverage the Lifespan REDCap instance for making electronic health data accessible for research purposes. REDCap was developed by Vanderbilt University with collaboration from a consortium of institutional partners as a software toolset and workflow methodology for electronic collection and management of research and clinical trial data.[15] The REDCap platform is a secure, web-based application flexible enough to be used for a variety of types of research, provides an intuitive interface for users to enter data, and enforces real time validation rules (with automated data type and range checks) at the time of entry. This platform provides an intuitive data manipulation interface, custom reporting capabilities, audit trail functionality, and real-time data monitoring/querying of participant records. REDCap has multiple data export options to common statistical packages (SPSS, SAS, Stata, R/S-Plus). The investigator will electronically sign the REDCap case reports prior to DSMB review and at the end of follow-up to indicate that, to his/her knowledge, they are complete and accurate.

Sites are to be sure that elements to support all inclusion and exclusion criteria are submitted and that all assessments from the schedule of evaluations (Section 9) are submitted for registration.

This protocol will allow for enrollment of patients remotely. All patients will require a signed informed consent and that visit will be conducted by a member of the Research Team remotely via telehealth according to institutional procedures. For patients undergoing protocol treatment and not able to travel to the Investigator's institution, data will be collected by the Research Team using locally obtained data.

6 TREATMENT PLAN

6.1 Summary of the treatment plan

Following consent and registration, volunteers will take talazoparib monotherapy as 1 mg capsule orally on a daily basis for three cycles, defined as a **21-day period**, prior to surgery. Please see Section 6.2.1 dosing for patients with baseline moderate to severe renal impairment and those taking a p-gp inhibitor. Volunteers will continue treatment to complete three cycles, unless disease progression or unacceptable toxicity occurs.

Volunteers who complete neoadjuvant treatment with talazoparib should undergo surgical cytoreduction within three weeks of their last dose of talazoparib. The procedure for cytoreduction will be left to the discretion of a specialist-trained gynecologic oncologist. Specifically, Heated Intraperitoneal Chemotherapy (HIPEC) or the placement of an intraperitoneal (IP) port will be allowed as per Institutional standards of care in the management of newly diagnosed ovarian cancer. All volunteers should then undergo standard of care adjuvant therapy using carboplatin and paclitaxel. While not mandated per protocol, we suggest carboplatin and paclitaxel every 3 weeks for six cycles. The exact regimen will be left to the treating investigator. In the case of a volunteer who has no evidence of residual disease at surgery (i.e., achieves a pathologic complete remission), the option to forego chemotherapy and continue on single agent talazoparib must be discussed with the PI and coincide with BrUOG's procedures.

For volunteers, who agree to continue talazoparib as maintenance therapy, treatment should begin three weeks (+/- 2 weeks) from the end of adjuvant chemotherapy or after cytoreductive surgery alone (based on the above paragraph), but not before hematologic recovery has occurred and maintenance initiation criteria are met. Each maintenance talazoparib cycle will be 21 days for two years. Follow-up during the maintenance phase will be required on D1 of each cycle for the first six months. Patients who are otherwise tolerating treatment will then be seen every third cycle thereafter.

6.2 Talazoparib

6.2.1. Dosing

Talazoparib will be provided by Pfizer as capsules to be taken daily (24 hours apart) with or without food. Talazoparib capsules must be swallowed whole and not dissolved or opened. The starting dose will be 1mg taken orally daily (see below for

starting doses for patients with renal impairment and those taking a p-gp inhibitor).

6.2.2. Modifications for renal insufficiency

For patients with renal insufficiency, the starting dose of Talazoparib will be reduced as follows:

Creatinine Clearance (mL/min)	Starting dose (mg)
30-59 mL/min	0.75
15-29	0.50

6.2.3. Drug Product, Safety and Handling

Talazoparib is supplied by Pfizer as capsules in strengths of 0.25 mg, and 1.0 mg. The drug product is stored at room temperature (15°C–30°C; 59°F–86°F) or per approved local label. Capsules are provided as 0.25 mg, opaque white, size 4; and 1 mg, opaque flesh (light pink), size 4 capsules in high-density polyethylene (HDPE) bottles, with heat induction-sealed closures, containing 30 drug product capsules of a single strength.

Talazoparib is considered a cytotoxic and clastogenic agent; precautions regarding appropriate secure storage and handling must be used by healthcare professionals, including personal protective clothing, disposable gloves, and equipment. Volunteers should be advised that oral anticancer agents are toxic substances and that caregivers (other than the volunteer) should always use gloves when handling the capsules.

6.2.4. Missing dose

If the volunteer misses or skips a dose for any reason, it should be taken provided it is within 2 hours of the planned dose. Any missing or skipped dose not taken within this window should not be taken and the next prescribed dose should be taken at the usual time.

6.2.5. Dose modifications

The following tables will be utilized for dose modifications due to toxicities. For patients with renal dysfunction and starting at a lower dose level at baseline, dose reduction is allowable up to 0.25mg daily.

Dose Level	Dose
Starting	1 mg (1 capsule) daily
DL-1	0.75 mg (3 0.25 mg capsules) daily
DL-2	0.50 mg (2 0.25 mg capsules) daily
DL-3	0.25 mg (1 0.25 mg capsule) daily
DL-4	None. Discontinue protocol treatment

Toxicity

Parameter	Hold Talazoparib until:	Resume dose level
Hemoglobin	≥9 mg/dL	Resume at reduced dose level
Platelet	≥75,000/μL	
ANC	≥1,000/μL	
Clinically Significant G3 or G4 Non-hematologic toxicity	≤G1	Resume at reduced dose level

NOTES:

1. No dose modifications are indicated based on: volunteer's age, race, body weight.
2. No dose adjustment is required for volunteers with mild hepatic impairment (total bilirubin ≤1 × ULN and AST >ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST).
3. No dose adjustment is required for volunteers with mild renal impairment (60 mL/min ≤CrCl < 90 mL/min). HOWEVER:
    a. For moderate renal impairment (30 mL/min ≤CrCl < 60 mL/min), the recommended dose of talazoparib is 0.75 mg QD.
    b. For severe renal impairment (15 mL/min ≤ CrCL < 30 mL/min), the recommended dose of talazoparib is 0.5 mg once daily.
4. The maximal delay of treatment is six weeks. Volunteers who hold study drug beyond six weeks will stop protocol treatment.

6.2.6. Contraindications

Talazoparib is contraindicated in volunteers with known hypersensitivity to talazoparib or any of the excipients.

6.2.7. Special warnings and precautions for use

6.2.7.1. Myelosuppression

Myelosuppression consisting of anemia, leukopenia/neutropenia, and/or thrombocytopenia, has been reported in volunteers treated with talazoparib. Talazoparib maintenance should not be initiated until volunteers have recovered from hematological toxicity caused by previous therapy (≤ Grade 1). Volunteers will be routinely monitored for hematology parameters and signs and symptoms associated with anemia, leukopenia/neutropenia, and/or thrombocytopenia. If any of these events occur, dose modifications will be instituted as discussed in Section 6.2.4. Supportive care with or without blood and/or platelet transfusions may be used as appropriate.

6.2.7.2. Myelodysplastic syndrome/Acute Myeloid Leukemia

MDS/AML have been reported in volunteers who received PARP inhibitors. Overall, MDS/AML has been reported in < 1% solid tumor volunteers treated with talazoparib in clinical studies. Potential contributing factors for the development of MDS/AML include previous platinum-containing chemotherapy, other DNA damaging agents or radiotherapy. Complete blood counts should be obtained at baseline and monitored monthly for signs of hematologic toxicity during treatment. If MDS/AML is confirmed, talazoparib should be discontinued.

6.2.7.3. Embryo-Fetal Toxicity

Studies in animals have shown embryo-fetal toxicity and talazoparib was clastogenic in in vitro and in in vivo assays. Talazoparib should not be given to pregnant volunteers or those who plan to become pregnant during treatment. People of childbearing potential should be advised to avoid becoming pregnant while receiving talazoparib. Talazoparib may cause fetal harm when administered to a pregnant volunteer. A highly effective method of contraception is required for volunteers during treatment with talazoparib, and for at least 7 months after completing therapy.

6.2.7.4. Drug-Drug interactions

Agents that may affect talazoparib plasma concentrations

Effect of P-gp inhibitors (see Exclusion criteria for list - https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-2.)

Data from a drug-drug interaction study in volunteers with advanced solid tumors indicated that coadministration of multiple daily doses of a P-gp inhibitor, itraconazole 100 mg twice daily with a single 0.5 mg talazoparib dose increased talazoparib total exposure (AUC_{inf}) and peak concentration (C_{max}) by approximately 56% and 40%, respectively, relative to a single 0.5 mg talazoparib dose administered alone.

Population PK analysis has shown that concomitant use of potent P-gp inhibitors (known to increase AUC of in vivo P-gp probe substrates by ≥2 fold) with talazoparib increased talazoparib exposure by 44.7%, relative to talazoparib given alone.

Volunteers taking any of these agents should consider discontinuation of agents prior to start of therapy. If not an option, volunteers will begin on a dose of 0.75 mg/daily.

Effect of P-gp inducers

Data from a drug-drug interaction study in volunteers with advanced solid tumors indicated that co-administration of a P-gp inducer (rifampin 600 mg once daily) with a single 1 mg talazoparib dose increased talazoparib C_{max} by 37% with no effect on talazoparib exposure.

Effect of BCRP inhibitors

Examples of agents: These include, but are not limited to: curcumin, cyclosporine, and elacridar [GF120918]).

The effect of BCRP inhibitors on PK of talazoparib has not been studied. Concomitant use of strong BCRP inhibitors should be avoided. If co-administration of strong BCRP inhibitors cannot be avoided, volunteer should be monitored for potential increased adverse reactions.

Effect of acid-reducing agents

Population PK analysis indicates that co-administration of acid-reducing agents including proton pump inhibitors (PPI), histamine receptor 2 antagonists (H2RA), or other acid-reducing agents had no significant impact on the absorption of talazoparib. [13]

6.2.7.5. Fertility

There is no information on fertility in volunteers. Based on non-clinical findings in testes and ovary, male and female fertility may be compromised by treatment with talazoparib.

6.2.7.6. People of Childbearing Potential/ Pregnancy

There are no data from the use of talazoparib in pregnant volunteers. Studies in animals have shown embryo-fetal toxicity. Talazoparib may cause fetal harm when administered to a pregnant volunteer. Talazoparib is not recommended during pregnancy or for people of childbearing potential not using contraception. [13]

People of childbearing potential should not become pregnant while receiving talazoparib and should not be pregnant at the beginning of treatment. A pregnancy test should be performed on all people of child bearing potential prior to treatment.

A highly effective method of contraception is required for volunteers during treatment with talazoparib, and for at least 7 months after completing therapy.

6.2.7.7. Lactation

It is unknown whether talazoparib is excreted in human breast milk. A risk to newborns/infants cannot be excluded and therefore breastfeeding is not recommended during treatment with talazoparib and for at least 1 month after the final dose.

6.3 Pre-treatment criteria for Talazoparib

6.3.1. Day one of Cycle 1 (Neoadjuvant treatment only)

If screening labs are performed greater than 14 days prior to Cycle 1 Day 1, labs must be repeated on Cycle 1 Day 1. The volunteer may not start on study treatment until Cycle 1 Day 1 labs meet eligibility criteria. If screening labs are performed within 14 days prior to Cycle 1 Day 1, and meet eligibility criteria, labs do not need to be repeated on Cycle 1 Day 1 unless the investigator believes they are likely to have changed significantly.

6.3.2. Subsequent cycles (Neoadjuvant talazoparib and maintenance therapy)

All treatment related toxicities- heme or non-heme- must resolve to ≤grade 1 or to baseline prior to a volunteer initiating a new cycle. Exceptions to this will be for weight loss/gain and alopecia and labs deemed not to be clinically significant by the investigator.

6.4 Criteria for discontinuation of protocol treatment

Whether to continue talazoparib (either in the neoadjuvant setting OR during the optional maintenance setting) will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment will continue unless one of the following criteria applies:

- Disease progression.
- Intercurrent illness that prevents further administration of treatment.
- Unacceptable adverse event(s).
- Volunteer demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements.
- Volunteer decides to withdraw from the protocol therapy.
- General or specific changes in the volunteer's condition renders her unacceptable for further treatment in the judgment of the treating investigator
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events:
    - Grade 4 neutropenia ≤ 7 days
    - Grade 4 lymphopenia or leukopenia
    - isolated Grade 4 lab abnormalities, including hepatic function, renal function, and/or electrolyte imbalances not associated with clinical sequelae and are corrected with supplementation/appropriate management.
- Any treatment delay resulting in no dosing for > 6 weeks
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the volunteer with continued dosing.

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was

removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, treating investigators must immediately notify BrUOG.

6.5 General concomitant medication and supportive care guidelines

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented source documents as concomitant medication.

6.5.1. Permitted supportive/ancillary care and concomitant medications

- Analgesics
- Antibiotics
- Anticonvulsants
- Antiemetics
- Anticoagulants
- Antihistamines
- Corticosteroids +/- mineralocorticoid component
- Hydration
- Nutritional supplementation

6.5.2. Prohibited therapies

None

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 Serious Adverse Events Reported from Clinical Trials

The safety profile of Talazoparib is reviewed in Section 3.3.7. The Reference Safety Information (RSI) will be used for the assessment of expectedness of serious ADRs reported on this trial and is noted below. The RSI includes only the AEs that have been previously reported more than once as serious and treatment related (ie, serious adverse reactions [SARs]) in talazoparib clinical trials and where, after a thorough assessment by the sponsor, reasonable evidence of a causal relationship between the event and the investigational medicinal product exists. [13]

Fatal and life-threatening SARs are considered unexpected. Frequency categories are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

System Organ Class PT[a] Frequency	All SARs n (%)
Blood and lymphatic system disorders	
Common	
Anaemia	26 (4.3)
Thrombocytopenia	7 (1.2)
Uncommon	
Neutropenia	3 (0.5)
Investigations	
Common	
Platelet count decreased	6 (1.0)

PT = preferred term.
[a] PTs are listed according to MedDRA v22.1.

7.1.1. Adverse event characteristics

This study will utilize the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for grading all adverse events. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

An Adverse Event (AE) is defined as any untoward medical occurrence in a volunteer or clinical investigation volunteer administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of Talazoparib whether or not considered related to Talazoparib. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

During clinical trials, adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a volunteer. (In order to prevent reporting bias, volunteers should not be questioned regarding the specific occurrence of one or more adverse events.)

Adverse events (AEs) will be recorded in the case report form for the duration of the trial, regardless of whether or not the event(s) are considered related to trial medication. All AEs considered related to trial medication will be followed until resolution even if this occurs post-trial.

7.1.2. Definitions

An adverse event is any new, undesirable medical experience or change of an existing condition that occurs during or after treatment, whether or not considered product-related.

7.1.2.1. Attribution of the AE

The following will be used to define attribution to study drug:

- 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.

Suspected adverse reaction: BrUOG, for the sponsor-investigator, is required to report in an IND safety report any suspected reaction to the study treatment that is both serious and unexpected.

As per 21 CFR 312.32 (a), the FDA has defined a suspected adverse reaction as any adverse event where there is reasonable possibility that the drug may have caused the adverse event. A reasonable possibility means there is evidence suggesting a causal relationship between the drug and the adverse event.

A suspected adverse reaction outlines the possibility of the causal relationship between the event and the drug, whereas an adverse reaction means the drug caused the event.

7.1.2.2. Serious adverse event

An adverse event occurring at any dose that results in any of the following outcomes (CFR 312.32):

- death
- is life-threatening
- involunteer hospitalization or prolongation of existing hospitalization excluding those for study drug administration, transfusional support, disease staging/re-staging procedures, concomitant radiotherapy, thoracentesis / paracentesis, or placement of an indwelling catheter, unless associated with other serious events.
- persistent or significant disability or incapacity,
- congenital anomaly / birth defect.

The definition of serious adverse event (experience) also includes important medical event. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the volunteer or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. A new diagnosis of cancer during the course of treatment should be considered an important medical event.

Unexpected adverse event

An adverse event that is not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the investigator's brochure or package insert.

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

NOTE: The following hospitalizations are **not considered SAEs**:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)
- elective surgery, planned prior to signing consent and which would have been documented to BrUOG at time of registration (otherwise it will be a SAE) admissions as per protocol for a planned medical/surgical procedure per study
- routine health assessment requiring admission for baseline/trending of health status (ie, routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases and which would have been documented to BrUOG at time of registration

- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (ie, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative)

7.2 Monitoring of Adverse Events and Period of Observation

Adverse events, both serious and non-serious, and deaths that occur during the volunteer's study participation will be recorded in the source documents.

7.3 BrUOG Adverse Event Reporting Requirements

Investigators are required by Federal Regulation to report adverse drug reactions. Questions regarding drugs as used in this study should be directed to the Brown University Oncology Research Group (BrUOG) Central Office, Phone: (401) 863-3000 Fax (401) 863-3820, which will in turn notify the Principal Investigator.

All adverse events and special reporting situations, whether serious or non-serious, related or unrelated, will be reported from the time a signed and dated ICF is obtained until 30 days after the last treatment (whether that be during neoadjuvant, on standard chemotherapy, or during maintenance), or until the volunteer withdraws consent from

study participation (declines participation) or at the time volunteer does not meet eligibility criteria, whichever occurs first.

7.3.1. Pregnancies

Pregnancies occurring while the volunteer is on study drug or within 30 days (+1 week) after the volunteer's last dose of study drug are considered expedited reportable events. If the volunteer is on study drug, it is to be discontinued immediately. The pregnancy must be reported to the Brown University Oncology Research Group, by the site, immediately (within 24 hours of the site being made aware), via a 3500A MedWatch form (site to submit to BrUOG), and BrUOG will in turn report to Pfizer immediately (within 1 working day and once in receipt of the site submitted SAE form). Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a volunteer occurring while they are on study drug or within 30 days (+1 week) of the volunteer's last dose of talazoparib are considered immediately reportable events. Study drug treatment is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Pfizer immediately by facsimile, email, or other appropriate method.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects to be related to the in-utero exposure to the study drug should also be reported. In the case of a live "normal" birth, Pfizer should be advised as soon as the information is available (BrUOG will advise Pfizer once information is submitted to BrUOG).

7.4 Serious Adverse Event Reporting Procedures

The principal investigator (or his designee) has the obligation to report all serious adverse events to the Brown University Oncology Research Group's (BrUOG) office who in return will report to the FDA, Pfizer, and all sites participating in the trial. All SAE reports will be forwarded to Pfizer by BrUOG. All events must be reported by the investigator utilizing the Form FDA 3500A (MedWatch Form). Sites must alert BrUOG to SAEs within 24 hours of being made aware of the event via phone or email, and the site will have 5 business days (from when site was made aware of the event) to submit formal signed report via the 3500A. BrUOG will then alert Pfizer within 1 business day of being in receipt of the signed MedWatch report.

BrUOG will submit a SAE memo and MedWatch 3500A to the FDA within the reporting time frames.

The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse

event or laboratory values received after the report) must be documented on a follow-up report.

A final report to document discharge from hospital (or end of important medical event) is required.

All deaths during treatment or within 30 days following completion of active protocol treatment must be formally reported to BrUOG within 5 business days of being made aware of the event or as soon as the investigator is made aware of the event. If the death is thought to be related to the study drug, deaths must be reported to BrUOG within 24 hours of the investigator being made aware of the event.

All adverse events and special reporting situations, whether serious or non-serious, related or unrelated, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of talazoparib, or until the volunteer withdraws consent from study participation (declines participation) or at the time volunteer does not meet eligibility criteria, whichever occurs first.

Serious adverse events occurring more than 30 days (+1 week) after study discontinuation need only be reported if a relationship to talazoparib is suspected.

7.4.1. Types of report and guidelines:

Telephone report: For SAE's contact the BrUOG office within 24 hours of learning of a SAE. For SAE notification: (initial and follow-up) contact BrUOG Central Office (401) 863-3000 or via email, BrUOG@brown.edu with a 24- hour notice prior to submitting a SAE report.

Written report: Send the signed MedWatch 3500A form within 5 business days of being made aware of the event to the BrUOG Central Office by email. For Follow-up reports, please submit the signed MedWatch 3500A when new information has become available and the event can be closed out.

Brown University Oncology Research Group
Phone: (401) 863-3000, Fax: (401) 863-3820
Emails: BrUOG@brown.edu

All deaths during treatment or within 30 days following completion of active protocol treatment must be reported within 5 business days (from when site was made aware of the event) or as soon as the investigator is made aware of the event. If the death is thought to be related to talazoparib, **deaths must be reported to BrUOG within 24 hours of the investigator being made aware of the event. SAEs post 30 days since last dose of drug (+1 week) that are thought to be possibly related to talazoparib must be reported to BrUOG within the 5-business day time frame noted above.**

MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- **Description of event, severity, treatment, and outcome, if known**
- **Action taken with talazoparib as a result of the SAE and expectedness (based on the IB and consent)**
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to talazoparib
- Site to be clear to outline which events are being reports as serious
- Must be typed
- **A final report to document discharge from hospital (or resolution of important medical event) is required.**

Follow-up information:

For any follow-up SAE report, submit a new MedWatch 3500A report; do not resubmit the initial report with any additions. The follow-up report must be submitted to BrUOG with subject identifiers (subject number, initials, and date of birth), protocol description, suspect drug, a brief summary of previously reported SAE information, and any new information, including modification of prior events, causality, new serious events, discharge date, etc.

A final report documenting discharge date from the hospital is required.

The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

7.5 BrUOG Responsibility regarding reporting

The sponsor-investigator by way of BrUOG, the sponsor representative and central coordinating office, is required to promptly review all information relevant to the safety of the drug (21 CFR 312.32(b)).

Safety Reporting for IND Holders
In accordance with 21 CFR 212.32, Sponsor-Investigator of the study conducted under an IND must comply with following safety-reporting requirements:

The BrUOG Central Office will notify all drug reaction reports to the FDA, the Principal Investigator, and the participating sites (who will in turn notify their local IRBs) as soon as possible but no later than 15 calendar days after initial receipt of the signed information, submitted to BrUOG by the site, as per regulatory requirements.

BrUOG, for the sponsor-investigator, is required to report in an IND safety report any suspected reaction to the study treatment that is both serious and unexpected (21 CFR 312.32 (c)(1)(i)). It is required that events that are suspected, serious and unexpected, be reported to the FDA via an IND safety report.

BrUOG will fax reports to the FDA for IND Safety Reports: to the CDER DOP1 fax number at: (301)-796-9845 SAEs will be reported as an amendment to the IND (if applicable) within 15 days of sponsor notification. The FDA will all receive a simultaneous copy via facsimile of all adverse events filed with the FDA (which will be sent to the division fax). A copy of the form will be kept by the BrUOG Central Office.

- "IND safety report" for 15-day reports
- "Follow-up IND safety report" for follow-up information
- "7-day IND safety report" for unexpected fatal or life-threatening adverse reaction reports

Fax: For this IND study a SAE will be sent to Center Drug Evaluation Division fax line that has responsibility for review of IND): CDER DOP1: (301)-796-9845

Mail: For IND studies BrUOG will send the SAE as an amendment to the IND as well.

All SAEs that are serious and reasonably or probably related to the use of talazoparib will also be sent to Pfizer within 1 business day of being in receipt of the complete signed site submitted documentation.

7.6 IND Annual Reports (if IND study only)

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report will be filed in the study's Regulatory Binder, and a copy provided to Pfizer as a supporter of this study.

7.7 Adverse event updates/IND safety reports

Pfizer shall notify the Brown University Oncology Research Group (BrUOG) via an IND Safety Report of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

BrUOG will then notify the sites who shall notify their IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

8 ORDERING TALAZOPARIB

8.1 Initial orders

The drug supply request form in Global Medical Grants System (GMGS) will be used to for drug ordering. Once the site has been activated by BrUOG and once Pfizer has received all initial approval documentation, the drug supply request form will be completed in GMGS. Pfizer's grant administrator receives an automated message regarding the drug request.

8.2 Resupply

Resupply of drug will be requested via the GMGS. Please allow for 2-3 weeks for the shipment of drug.

8.3 Drug excursions

Temperature excursions should be emailed to GCSTempExcursionSupport@pfizer.com and cc BrUOG@brown.edu

Storage excursion:
Include the following in the body of the email for temperature excursions:
Study number (BrUOG 390)
Site
Temperature recorder data of monitoring log showing the date and duration of excursion (data should include previous acceptable reading and reading showing return to acceptable conditions)

Shipment excursion:
Include the following in the body of the email:
Study number (BrUOG 390)
Site
Shipment number
Temperature recorder data of monitoring log showing the date and duration of excursion (data should include previous acceptable reading and reading showing return to acceptable conditions)

8.4 Questions on drug expiration, delayed shipment, etc.

Questions regarding drug expiration or delayed shipment may be directed to Ying at ying.zhangying@pfizer.com, waqas.ahmed@pfizer.com, and cc BrUOG@brown.edu.

8.5 Accountability

The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form.

For patients undergoing protocol treatment who are unable to travel to Providence, drug accountability will be documented during a telehealth visit. If patients discontinue study treatment, all remaining drug will be shipped back to the PI's Institution for accounting.

8.6 Destruction and return

All opened Talazoparib (full, partially used, and empty) may be destroyed at the site by the appropriate site personnel (e.g. Pharmacist; Study Nurse/Coordinator) following local environmental requirements and institutional policies.

All destruction of unused drug must be fully documented at the time of destruction on the drug accountability log at the time of destruction.

All unused, unopened and rejected supplies will need to be approved by Pfizer for destruction prior to any drug being destroyed. BrUOG will obtain Pfizer approval to destroy. Documentation of all destruction is required on the drug accountability log.

9 STUDY CALENDAR

9.1 Pre-Treatment assessments

The day an assessment (PE, Lab, scan etc.) is performed is considered day 0 for counting.

	Required for Registration	Prior to Cycle 1
Informed consent	≤28 days	
Tissue confirmation	X	
mBRCA confirmation	X	
Concurrent meds	≤28 days	≤14 days
History and Physical exam	≤28 days	≤28 days
Blood pressure, Pulse	≤28 days	≤28 days
Weight and Height (Height only at baseline)	≤28 days	≤28 days
Performance status	≤28 days	≤28 days
CBC w/diff	≤28 days	≤14 days
Serum chemistry*	≤28 days	≤14 days
CA125	≤28 days	≤7 days
HCG**	≤14 days	Within 24 hours
Adverse event evaluation	≤14 days	≤14 days
CT Chest, Abdomen, and Pelvis	≤28 days	

*Electrolytes including BUN, Crea, Ca, and Mg; LFTs including Bilirubin, ALT, AST, Alk Phos, and albumin.
** Urine or serum in applicable volunteers, per eligibility criteria.

9.2 On-treatment assessments

9.2.1. During neoadjuvant treatment. The following table applies to all volunteers receiving talazoparib prior to surgery. Volunteers who discontinue talazoparib during this period (nine weeks) will be discontinued from the protocol. For patients undergoing protocol treatment and not able to travel to the Investigator's institution, data will be collected by the Research Team using locally obtained data.

	D1 of each cycle[1] (Cycles 1-3)	Weekly	End of treatment[2]
History and Physical (includes weight, blood pressure, heart rate, and ECOG performance status)	X		X
CBC with differential	X	X	X
Chemistries (liver function, renal function)[3]	X		X
CA125	X		
Urine pregnancy test[4]	X		
Pill counts	X[5]		X
Concurrent meds	X		
Adverse event evaluation	X	X	X
Tumor measurements[6]			X

1. One cycle = 21 days. Assessment can be performed within 72 hours of D1.
2. End of treatment evaluation should occur within 14 days (+/- 7) of C3D21
3. Electrolytes including BUN, Crea, Ca, and Mg; LFTs including Bilirubin, ALT, AST, Alk Phos, and albumin.
4. In women of childbearing potential.
5. Reviewed on D1 of C2 and C3
6. CT Chest, Abdomen, and Pelvis is required at the end of treatment. Volunteers who discontinue neoadjuvant treatment early for whatever reason are encouraged to undergo imaging within 14 days (+/- 7 days) of treatment.

9.2.2. Surgery and adjuvant treatment

Volunteers who complete neoadjuvant treatment with talazoparib should undergo surgical cytoreduction within three weeks of their last dose of talazoparib. The procedure for cytoreduction will be left to the discretion of a board certified gynecologic oncologist. Specifically, Heated Intraperitoneal Chemotherapy (HIPEC) or the placement of an intraperitoneal (IP) port will be allowed as per Institutional standards of care in the management of newly diagnosed ovarian cancer.

The following data will be collected:

- Description of disease burden
- Cytoreduction status (R0, optimal with microscopic residual, suboptimal, and CR Score – Reference 5)
- Clinical FIGO stage
- Final pathology (with pathologic stage)

Following surgery, all volunteers should undergo carboplatin and paclitaxel adjuvant therapy. However, patients with an optimal cytoreduction and who according to the treating physician has had a good response to Talazoparib, and who wish to forego adjuvant chemotherapy, may be allowed to do after consultation with the Principal Investigator or his designate. The regimen and duration will be determined by the local provider. We will plan to collect the following data:

- Regimen prescribed (including whether HIPEC was performed)
- Cycles planned
- Cycles administered
- Start and stop dates
- Adverse events

NOTE: While we will not mandate a specific adjuvant regimen, we will plan to collect toxicity data at 21-day intervals.

9.2.3. Maintenance therapy

The following data will be collected during maintenance:

	D1 of each cycle[1] (Cycles 1-8)	D1 of every 3rd cycle (Cycles 9 to 24)	Weekly[2]	Every 3 months	End of treatment[3]
History and Physical (includes weight, blood pressure, heart rate, and ECOG performance status)	X	X			X
CBC with differential	X	X	X		X
Chemistries (liver function, renal function)[4]	X	X			X
CA125	X	X			
Urine pregnancy test[5]	X	X			
Pill counts	X[6]	X[6]			X
Concurrent meds	X	X			
Adverse event evaluation	X	X	X		X
Tumor measurements[7]				X	X

1. One cycle = 21 days. Treatment will be administered daily. Assessment can be performed within 72 hours of D1.
2. Weekly labs will be collected during the first two cycles after which volunteers will not be required to do labs weekly, unless recommended by their local investigator.
3. End of treatment evaluation should occur within 14 days (+/- 7)
4. Electrolytes including BUN, Crea, Ca, and Mg; LFTs including Bilirubin, ALT, AST, Alk Phos, and albumin.
5. In women of childbearing potential.
6. Reviewed on D1 starting with Cycle 2.
7. CT Chest, Abdomen, and Pelvis are required every three months (+/- 2 weeks) during maintenance and at the end of treatment. Volunteers who discontinue talazoparib maintenance treatment early for whatever reason are encouraged to undergo imaging within 14 days (+/- 7 days) of treatment.

Volunteers who decide not to proceed with maintenance talazoparib will be withdrawn from the study and will be followed according to the follow-up schedule in Section 10.

9.2.4. <u>For patients undergoing protocol treatment and not able to travel to the Investigator's institution, data will be collected by the Research Team using locally obtained data.</u>

10 ASSESSMENTS IN FOLLOW-UP

Following completion of treatment, all volunteers enrolled will be followed for five years from date of registration. The following will be collected:

	Schedule

History and Physical Exam (includes weight, performance status, blood pressure)	X[1]
Serum Ca-125	X[1]
Toxicity Assessment[2]	X[1]
CT Chest, Abdomen, and Pelvis	Every 3 months[3]
Disease Status	X[1]

1. Every 3 months (+/- 7 days) for the first 2 years; then every 6 months (+/- 7 days) for the next 3 years until disease progression or volunteer initiates a subsequent cancer therapy.
2. Volunteers who discontinue treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.
3. Imaging should be performed every 3 months (+/- 3 weeks) in the first three years, and then every 6 months to the fifth year. However, they can be repeated any other time if clinically indicated based on symptoms, physical signs or rising CA-125 levels suggestive of new or progressive disease.

11 MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, during neoadjuvant therapy, a baseline and end-of-treatment (pre-surgery) CT Chest, Abdomen, and Pelvis will be performed. During maintenance therapy, CT Chest, Abdomen, and Pelvis will be performed every three months (+/- 2 weeks) and at the end of treatment, and in follow-up, CT Chest, Abdomen, and Pelvis will be performed every three months (+/- 3 weeks) for the first three years and then every 6 months until the fifth year.

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

11.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

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

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥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.

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, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered 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 participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as

reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. For purposes of this trial, all patients are to undergo imaging using CT of the chest, abdomen, and pelvis for disease assessment and only CTs will be used for disease evaluation.

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.

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

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in 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.

MRI. The use of MRI cannot be used for disease assessment on the trial.

PET/CT: Not allowed for measurement of disease.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not permitted.

Tumor markers. Tumor markers alone will not be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. The Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

11.1.4 Response Criteria RECIST 1.1

11.1.4.1 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.

11.1.4.2 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).

11.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.4.4 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 Participants 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: Participants 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.

11.1.4.5 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, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: 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, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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.

Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

12 STATISTICAL CONSIDERATIONS

12.1 Primary objectives

The primary objective for this feasibility trial will be to determine if we can enroll 30 volunteers in to this neoadjuvant PARP inhibitor trial. Given that mBRCA carriers

represent less than 15% of all people with newly diagnosed ovarian cancer, it will be challenging not only to find this population but to see if they are also comfortable with a non-chemotherapy regimen as neoadjuvant treatment. It is also based on the experience of Litton and colleagues who sought to enroll a similar cohort with newly diagnosed breast cancer.[7]

In addition to enrolling these volunteers, we aim to define the proportion of volunteers completing the planned 9 weeks of treatment without disease progression. For women receiving neoadjuvant carboplatin and paclitaxel, the estimated rate of progression on treatment is 15%.[16] For purposes of this trial, we will adopt a more stringent criterion for progression at 10%. As such, if 3 or more volunteers progress during treatment, we will declare it non-feasible.

12.2 Secondary objectives

Preliminary effectiveness: We will determine the clinical response of volunteers on this trial, determined by standard of care measurements (e.g., CA125 and CT scan). For those undergoing surgery, we will also report the rate of optimal cytoreduction and of resection to no residual disease (R0).

Safety of neoadjuvant treatment: This will be defined by the aggregate toxicity rate in the first seven enrolled volunteers. If 2 or more volunteers experience either a grade 4 toxicity attributable to the treatment or require a delay in treatment for greater than 4 weeks due to toxicity, the study will be discontinued. Treatment-related toxicities will be summarized by maximum grade and by term using CTCAE v5.0 and reported with 90% binomial exact confidence intervals.

12.3 Exploratory objectives

For those who undergo interval cytoreduction, we will also determine the effect of treatment by CRS. While this was developed for the use of carboplatin and paclitaxel treatment for high-grade serous carcinoma, we will report this as well to determine if this is a useful measure in this setting.

All volunteers enrolled on this trial will be offered talazoparib maintenance treatment following completion of adjuvant chemotherapy. We will measure progression-free survival, measured from the start of maintenance therapy. This will be modeled after the SOLO-1 trial, where maintenance olaparib significantly extended 3yPFS compared to placebo with a Hazard Ratio of 0.3. Based on this HR, using 80% power with an alpha of 0.05, we estimate that 22 patients would be needed to meet this exploratory objective. By enrolling 30 women, we anticipate we will be able to treat 22 to achieve this objective.

13 REGULATORY CONSIDERATIONS

13.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and in the US Code of Federal Regulations. The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

13.2 Patient Confidentiality

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from Pfizer or its designees and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

13.3 Protocol Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Pfizer and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority (ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to Pfizer and the regulatory authority (ies) in accordance with the governing regulations. Any departures from the protocol must be fully documented in the source documents.

13.4 On-site Audits

Regulatory authorities, the IRB and/or Pfizer clinical quality assurance group may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

13.5 Drug Accountability

Accountability for the drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site

(if applicable), inventory at the site (if applicable), use by each patient, and return to Pfizer for disposal of the drug (if applicable and if approved by Pfizer) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

All material containing Talazoparib will be treated and disposed of as hazardous waste in accordance with governing regulations.

13.6 Premature Closure of the Study

This study may be prematurely terminated, if in the opinion of the investigator or Pfizer, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Pfizer by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug
- Should the study be closed prematurely, all study materials must be returned to Pfizer

13.7 Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). The Brown University Oncology Research Group, as coordinator of this study, is responsible for ensuring proper conduct of the study with regard to protocol adherence and the validity of the data recorded on the case report forms. The Principal Investigator (Don Dizon, M.D.) and Brown University Oncology Research Group Director of Operations (Roxanne Wood) will monitor this study. The case report forms will be monitored against the submitted documents for accuracy, completeness, adherence to the protocol and regulatory compliance.

U.S. FDA regulations (21CFR312.62[c] require all records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consents forms, laboratory test results and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the FDA and the applicable local health authorities are notified. Pfizer will notify the Principal Investigator if an application is filed.

14 DATA SAFETY AND MONITORING BOARDS

All trials initiated by the Brown University Oncology Research Group (BrUOG) are

subject to oversight by the Data Safety Monitoring Board (DSMB). This board meets two times per year with any additional meetings scheduled when needed. The responsibilities are as follows:

- Familiarize themselves with the research protocol (s)
- The DSMB reviews trial performance information such as accrual information.
- Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.
- The DSMB also determines whether and to whom outcome results should be released prior to the reporting of study results.
- All adverse events are reviewed by the committee, with assurances that these have been in fact sent for review to all pertinent IRBs.
- Review of reports of related studies to determine whether the monitored study needs to be changed or terminated.
- Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).
- Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial.

The study leadership will provide information on cumulative toxicities and relevant recommendations to the local principal investigators to be shared with their IRB's.

15 PUBLICATION PLAN

The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. It is anticipated that a report will be presented in a national or international meeting within 24 months of last patient entered on study. This abstract will meet the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes will be made public no later than three (3) years after the end of the study.

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Appendix A. Pill Calendar

Please see attached CRF – Patient Drug Diary

Appendix B. Informed Consent

Agreement to Participate in a Research Study And Authorization for Use and Disclosure of Information

BrUOG 390: Neoadjuvant treatment with Talazoparib for women with newly diagnosed, advanced ovarian cancer associated with a mutation in BRCA1 or BRCA2 (mBRCA): A Feasibility Trial

You are being asked to take part in a research study. All research studies at <INSERT HOSPITAL NAME> follow the rules of the state of <INSERT STATE>, the United States government and <INSERT HOSPITAL NAME>. Before you decide whether to be in the study, you and the researcher will engage in the "informed consent" process. During this process, the researcher will explain the purpose of the study, how it will be carried out, and what you will be expected to do if you participate. The researcher will also explain the possible risks and benefits of being in the study, and will provide other information. You should feel free to ask any questions you might have. The purpose of these discussions is for you to decide whether participating in the study is the best decision for you.

If you decide to be in the study, you will be asked to sign and date this form in front of the person who explained the study to you. This form summarizes the information you discussed. You will be given a copy of this form to keep.

Nature and Purpose of the Study

Your doctors are participating in this research study with the Principal Investigator, Dr. Don S. Dizon in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study.

You are being asked to take part in this study because you have recently been diagnosed with advanced ovarian cancer which is associated with a mutation in either BRCA1 or BRCA2.

The purpose of this study is to learn whether it is safe to use this oral drug prior to your surgery. Talazoparib is a type of drug called a PARP inhibitor. Prior studies have shown PARP inhibitors help keep cancer cells from reproducing, especially in women who have BRCA1 and BRCA2 cancers. If you do benefit from treatment, you will be given the option to continue it for another two years as maintenance treatment.

This study is financially supported by Pfizer, the maker of Talazoparib.

How Many People will take part in the Study?

We hope to enroll approximately 30 women into this study. Only women with either BRCA1 or BRCA2 mutated advanced ovarian cancer will be eligible to participate in this study.

Explanation of Procedures

What will happen if I take part in this research study?

If you take part in this study, you will have exams, tests and procedures to show that you can be in the study, and you choose to take part, then you will need the following tests and procedures, while on the study. They are part of regular cancer care.

Screening and prior to participation in this study:

- Review and sign this informed consent form
- Confirmation of your diagnosis and BRCA1 or BRCA2 status
- Your doctor will review your medical history, review your medications, perform a physical exam, and see if you have any side effects
- Vital signs to include height and weight
- Evaluate how you perform everyday activities – this is called a performance status
- Obtain blood samples, approximately 6 tablespoons of blood, for the following:
    - A complete blood count (CBC with differential)
    - Blood chemistries (which will test your liver, kidney and electrolyte function)
    - A CA-125, which is a tumor marker for ovarian cancer
    - A blood test called an HCG if your ovaries were not removed at the time of your surgery.
- Obtain a CT Scan of the chest, abdomen, and pelvis

During treatment before your surgery/Prior to each cycle of therapy:

- Your doctor will review your medical history, review your medications, perform a physical exam and see if you have any side effects
- Vital signs to include weight
- Evaluate how you perform everyday activities – this is called a performance status
- Obtain blood samples, approximately 6 tablespoons of blood, for the following:
    - A complete blood count (CBC with differential)
    - Blood chemistries (which will test your liver, kidney and electrolyte function)
    - A CA-125, which is a tumor marker for ovarian cancer
    - A blood test called an HCG if your ovaries were not removed at the time of your surgery
- Obtain a CT scan of the chest, abdomen, and pelvis at the end of your treatment and before your surgery
- Review the amount and if you took all the study drug, talazoparib

At the time of your surgery:

- The type of surgery and the report from the analysis of your tissue will be obtained

After your surgery:

- Information on the type and amount of therapy will be obtained
- Any side effects from the therapy you receive will be obtained

Maintenance Therapy (for patients who continue to receive the study drug talazoparib after surgery)

- Your doctor will review your medical history, review your medications, perform a physical exam and see if you have any side effects
- Vital signs to include weight
- Evaluate how you perform everyday activities – this is called a performance status
- Obtain blood samples, approximately 6 tablespoons of blood, for the following:
    - A complete blood count (CBC with differential)
    - Blood chemistries (which will test your liver, kidney and electrolyte function)
    - A CA-125, which is a tumor marker for ovarian cancer
    - A blood or urine test called a HCG if you are a women of child-bearing potential
- Obtain a CT scan of the chest, abdomen, and pelvis approximately every three months
- Review the amount and if you took all the study drug, talazoparib

Off study/Follow-up:

- Your doctor will review your medical history, review your medications, perform a physical exam and see if you have any side effects
- Vital signs to include weight
- Evaluate how you perform everyday activities – this is called a performance status
- A blood test, CA-125, which is a tumor marker for ovarian cancer
- Obtain a CT scan of the chest, abdomen, and pelvis every 3 months for the first three years and then every 6 months for years four and five unless you have more disease.

  Your doctor will speak to you if more or less frequent testing is appropriate.

A CT scan is a radiological test that uses special x-ray equipment to make detailed pictures of body tissues and organs. For the CT scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). The contrast material may be given orally or through one of your veins. Oral contrast material is given to you to drink and is used to help outline the stomach and intestines. Intravenous (IV) contrast material is given to you by injecting the contrast material into a line which is attached to a needle in your arm, and is used to get clearer pictures of your body cavity. After you have been given the contrast material

(either by mouth, by vein), you will lie flat on a table that will move you into the CT scan machine. You will be asked to lie still and may be asked to hold your breath for a few seconds. Each CT scan will take about 15 minutes to a half hour.

If you decide to participate in this study, you will receive the study drug Talazoparib once a day for three cycles before your surgery unless you have side effects or your doctor believes it is best for you to stop. Each cycle will be 21 days long.

After your surgery, your doctor may recommend standard of care therapy for your cancer. Once the standard of care therapy is complete, you may be eligible to take the study drug Talazoparib for up to an additional 24 months.

How long will I be in the study?

You will continue to be in the study until you finish protocol therapy or experience disease progression, discontinue treatment due to side effects, your doctor believes it is in your best interest or you withdraw informed consent.

Follow up for this study is expected to be for a total of five years.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the discontinuation of treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

Costs for participating in this study

Pfizer, the maker of the study drug Talazoparib, is providing the drug at no cost.

The study procedures done during this research study are considered "routine clinical services" that you would have received even if you were not in the research study. Examples are blood tests, doctor visits, diagnostic imaging tests such as CT scans. These services will be billed to your health insurance company, but you will be responsible for paying any deductibles, co-payments, or co-insurance that are a normal part of your

health insurance plan. If you do not have health insurance, you will be responsible for those costs.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call **1-800-4-CANCER (1-800-422-6237)** and ask them to send you a free copy.

Will I be paid for taking part in this study?

You will not be paid for taking part in this study.

Contact Information: If you have any questions regarding this study, you may contact your site
Principal Investigator, <INSERT CONTACT NAME> at <INSERT PHONE NUMBER>.

Discomforts and Risks
You may have side effects while on this study. We will monitor everyone in the study for any side effects. Contact your study doctor if you experience a side effect or have any questions about possible side effects.

Side effects may be mild or serious. We may give you medicines to help lessen side effects. Some side effects will go away as soon as you stop taking the drug. In some cases, side effects can be serious, long-lasting, or can cause death. In some cases, side effects can be serious, long-lasting, or may never go away.

Taking part in this study may lead to time away from work.

Risks related to Talazoparib:

You may have side effects while you are in the study, but you will be carefully checked by the study doctor for any problems. There may be risks or side effects of the study drug that are unknown at this time. You should tell the study doctor/staff about anything that is bothering you or any side effects you have, even if you do not think they are related to the study drug.

The following is a list of the most medically significant or most common side effects reported in completed studies considered to be related to Talazoparib. In some cases, side effects can be serious, long-lasting, or can cause death. Some side effects go away soon after you stop the study drug/therapy and some may never go away. The study doctor may alter the dosage regimen of Talazoparib (if allowed by the study) or give you

medicines to help lessen the side effects. This is not a complete list of all side effects that may occur. For more information about risks and side effects, please ask the study doctor.

Very Common (occurs in 1 in 10 subjects or more (10% or more chance that this will happen):

- Fatigue (feeling tired)
- Nausea, vomiting and diarrhea
- Anemia (decreased hemoglobin, which is a protein in red blood cells that carries oxygen through the body). This can lead to feeling tired and pale skin
- Leukopenia (decreased number of a type of white blood cell count, leukocytes, which can make you at increased risk for infection)
- Neutropenia (decreased number of white blood cells called neutrophils, which can make you at increased risk for infection)
- Thrombocytopenia (decreased number of a component of blood called platelets that help with the formation of blood clots)
- Lymphopenia (decreased number of a type of blood cells called lymphocytes, which have important functions in the immune system)

Common (between a 1% to less than 10% chance that this will happen):

- Hair loss (alopecia)
- Abdominal pain
- Headache
- Decreased appetite
- Dizziness
- Dysgeusia (altered taste)
- Dyspepsia (heartburn)
- Stomatitis (sores inside of your mouth)
- Sinusitis (sinus infection)
- Dry skin
- Mucosal inflammation (inflammation of the lining of the stomach)
- Aspartate aminotransferase increased (elevation in your blood that can show signs of liver damage)

Uncommon (between a 0.1 to less than 1% chance that this will happen):

- Death

Risk of Secondary Cancers:

Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML)

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been reported in a very small number of patients treated with Talazoparib. MDS is a pre-cancerous condition where the bone marrow is not as good at producing blood cells (red and/or white blood cells and/or platelets) as it was before. People with MDS need transfusions (red blood cells and/or platelets) and/or other treatments. In some cases, MDS will progress to AML, which is a cancer of the bone marrow where more abnormal and immature white blood cells (also called blasts) are made than normal white blood cells. People with AML need treatment with chemotherapy and/or a transplant. Patients may develop AML without first being diagnosed with MDS.

Cases of MDS and AML have also been reported with PARP inhibitors similar to rucaparib. At this time, it is not known whether rucaparib or other PARP inhibitors cause MDS or AML, or if these developed as a result of previous chemotherapy these patients received. Your study doctor will closely monitor your blood cell levels during treatment. If your study doctor has any concerns about your blood counts you may be asked to have a biopsy of your bone marrow.

Reproductive Risks

Because the drugs in this study can affect an unborn baby, you should not become pregnant while on this study. Ask your study doctor for more information regarding preventing pregnancy during the study treatments. If you have a newborn, you should not nurse your baby while on this study. If you are premenopausal, your periods are likely to stop temporarily and may stop permanently due to the study treatments, which may lead to symptoms of menopause, such as hot flashes, and the inability to become pregnant, which may be permanent. If you are concerned about this, ask your study doctor about options for preserving your reproductive choices, which may include referral to a specialist in this field.

By signing this document, you are acknowledging that you understand and agree to the information presented in this Reproductive Risk section.

Antiemetics (anti-nausea medications): Various medications used to prevent nausea and vomiting may cause drowsiness, dry mouth, diarrhea, constipation, headache, restlessness, agitation, anxiety, dizziness, involuntary tremors, skin rash, and possible allergic reaction. Your doctor may prescribe such medications for you prior to starting, or else, it will be made available to you if you have symptoms.

There may be other side effects that have not been reported. If you have any unusual symptoms, you should report them immediately to your doctor or nurse.

Benefits

Taking part in this study may or may not make your health better. Your condition may even get worse during the study. We do know that the information from this study will help doctors learn more about the study drug Talazoparib with your type of cancer. This information could help future cancer patients. However, there is no guarantee that this will happen.

Alternative Therapies

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

Talk to your doctor about your choices before you decide if you will take part in this study.

Refusal/Withdrawal

It is up to you whether you want to be in the study. You are not required to enroll or participate. If you decide to participate, you can always change your mind and quit at any time. If you decide not to be in the study, or if you quit later, you will still be able to get the standard of care health care services you normally get. If you join, but later on the researcher or your doctor feels being in the study is no longer good for you, they may choose to take you out of the study before it is over. If new information becomes available that might change your mind about whether you want to stay in the study the researcher will share this information with you as soon as possible.

It is important to tell the study doctor if you are thinking about stopping so any risks from the discontinuation of treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

If you make the decision to withdraw from this study (stop taking study medication) for any reason, tell your doctor immediately. You will be asked to sign a form indicating whether you give your permission for your doctor and the research staff to continue to collect and submit follow-up information on your health status from your physicians and medical record. After signing the form, you still have the right to change your mind, at any time, regarding follow-up after withdrawal.

Medical Treatment/Payment in Case of Injury

A research injury is any physical or mental injury or illness caused by being in the study. If you are injured by a medical treatment or procedure you would have received even if

you were not in the study that is not a research injury. To help avoid research injury and added medical expenses, it is very important to follow all study directions carefully. If you do experience a research injury, <INSERT HOSPITAL NAME> or the study doctor can arrange medical treatment for you. Such treatment will be paid for as described below.

Medical treatment will be available if you suffer a research related injury; however, you and/or your health insurance company will be charged for this treatment. The study will not pay for this medical treatment. Neither Dr. Don Dizon nor the sponsor of the study, BrUOG, the coordinating center, have money set aside to reimburse you for medical bills from treatment of a research related injury or otherwise compensate you in the event of a study-related injury.

If you have insurance and have a research injury that is not covered by the study, it is possible that some or all of the cost of treating you could be billed to your insurer. If your health insurance will not cover such costs, it is possible you would have to pay out of pocket. In some cases, <INSERT HOSPITAL NAME> might be able to help you pay if you qualify for free care under <INSERT HOSPITAL NAME> policy. However, <INSERT HOSPITAL NAME> has no policy to cover payment for such things as lost wages, expenses other than medical care, or pain and suffering.

Rights and Complaints

Signing this form does not take away any of your lawful rights. If you have any complaints about this study, or would like more facts about the rules for research studies, or the rights of people who take part in research studies you may contact <ENTER CONTACT INFORMATION IRB>, in the <ENTER NAME OF IRB>, at <ENTER CONTACT INFORMATION>.

Confidentiality

Your research records will be treated as private health care records and will be protected according to <INSERT HOSPITAL NAME> privacy practices and policies that are based on state and federal law. In particular, federal law requires us to get your permission to use or disclose (release your information to someone outside of<INSERT HOSPITAL NAME>) your health information for research purposes. If you sign this form you agree to be in this research study and you permit the use and disclosure of your health information for the purpose of conducting the research, providing treatment, collecting payment and running the business of the hospital. This permission has no expiration date. You may withdraw from the study at any time. However, if you do not want the researchers to use or disclose any further information in this study you must cancel permission in writing and may do so at any time. If you cancel your permission, you will stop taking part in the study and no new information will be collected about you. However, if you cancel your permission, it will not apply to actions already taken or information already collected about you by the hospital or the researchers before you canceled your permission.

Generally, the entire research record and any medical records held by the hospital may be used and released for research purposes. The following people or businesses/companies might use, release, or receive such information:

□ The researcher and their support staff;

□ The study sponsor, PI, Don Dizon, MD, BrUOG, The Brown University Oncology Research Group and their representatives and Pfizer, (Financial study supporter);

□ Doctors, nurses, laboratories and others who provide services to you in connection with this study;

□ The Company or section of the U.S. government that is paying for the study and others they hire to oversee, administer, or conduct the research;

□ The United States Food and Drug Administration, the Department of Health and Human Services, the Office of Inspector General, and the Office of Civil Rights;

□ People who volunteer to be patient advocates or research volunteer protectors;

□ Members of the hospital's administrative staff responsible for reviewing, approving and administering clinical trials and other healthcare or research activities.

There are times when the law might require or permit <INSERT HOSPITAL NAME>to release your health information without your permission. For example, <ENTER STATE> law requires researchers and health care workers to report abuse or neglect of children to the Department of Children, Youth and Families (DCYF) and to report abuse or neglect of people age 60 and older to the Department of Elderly Affairs.

All researchers and health care providers are required to protect the privacy of your health care information. Other people and businesses/organizations that are not health care providers are not required by law to do that so it is possible they might re-release your information.

You have the right to refuse to sign this form and not participate in the research. Your refusal would have no effect on your treatment, charges billed to you, or benefits at any <INSERT HOSPITAL NAME> health care site. If you do not sign, you will not be able to enroll in the research study and will not receive treatment as a study participant.

If you decide to quit the study after signing this form (as described in Section 6) no new information will be collected about you unless you gave us permission to do so. However, the hospital or the researchers may continue to use information that was collected before you quit the study to complete analysis and reports of this research.

You will not be allowed to see or copy the information described in this form as long as the research study is open. You may see and copy the information when the study is completed.

Additionally, 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.

For more detail about your privacy rights see the <INSERT HOSPITAL NAME>Joint Privacy Notice which has or will be given to you.

SIGNATURE

I have read this informed consent and authorization form. ALL OF MY QUESTIONS HAVE BEEN ANSWERED, AND I WANT TO TAKE PART IN THIS RESEARCH STUDY.

By signing below, I give my permission to participate in this research study and for the described uses and releases of information. *I also confirm that I have been now or previously given a copy of the* <INSERT HOSPITAL NAME> *Privacy Notice*

This informed consent document expires on _____.
DO NOT sign this document after this expiration date

The Researcher is required to provide a copy of this consent to you.

_____ _____ _____
Signature of study volunteer/authorized representative* Date and Time when signed

I was present during the consent PROCESS AND signing of this agreement by the study volunteer or authorized representative

_____ _____
Signature of witness (required if consent is presented orally or at the request of the IRB) Date

_____ _____
Signature of Translator Date

_____ _____ _____
Signature of researcher or designate Date Time when signed

* If signed by agent other than study volunteer, please explain below.

_____

_____

Appendix C BrUOG checklist for patient registration

BrUOG 390: Neoadjuvant treatment with Talazoparib for women with newly diagnosed, advanced ovarian cancer associated with a mutation in BRCA1 or BRCA2 (mBRCA): A Feasibility Trial

Patient initials: _____
Hospital where pt will receive treatment: _____
Day 1 of treatment: _____
Treating MD:_____
Your name:_____
☐ Site: please include this table in a note or email and have treating MD confirm. Please submit this checklist via email or upload into REDCap.

Inclusion criteria ☒indicates patient meets inclusion	**Site-comment/source to verify**	**BrUOG verified (Y/N)*internal use**
☐ 4.1.1Volunteers must have clinical and radiographic evidence of newly detected FIGO stage II, III or IV epithelial ovarian, primary peritoneal or fallopian tube cancer, deemed by a gynecologic oncologist as not amenable to an R0 resection at presentation.		
☐ 4.1.2 Institutional confirmation of Müllerian epithelial adenocarcinoma.		
☐ 4.1.3 Histologic epithelial cell types: high grade serous carcinoma, high grade endometrioid carcinoma, or a combination of these.		
☐ 4.1.4 Documented mutation in BRCA1 or BRCA2 by genetic or commercial somatic testing. Reports will require submission at the time of enrollment.		
☐ 4.1.5 Measurable disease as defined by RECIST 1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by CT, MRI or caliper measurement by clinical exam; or ≥ 20 mm when measured by chest x-ray. Lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI.		

☐ 4.1.6 Age ≥ 18		
☐ 4.1.7 Adequate hematologic function determined within 28 days of consent as follows: • ☐ ANC greater than or equal to 1,500/mcl. NOTE: ANC cannot have been induced by granulocyte colony stimulating factors. • ☐ Platelets greater than or equal to 100,000/mcl • ☐ Hemoglobin greater than 10 mg/dl (NOTE: While transfusions are permitted to achieve baseline hemoglobin level, patients must not have transfusion within 14 days prior to obtaining baseline screening labs) • ☐ Creatinine clearance > 15ml/min. (NOTE: Please see Section 6.2.1 for dosing requirements for patients with renal insufficiency)		
☐ 4.1.8 CrCl = (140- age in years) x weight in kg x 0.85/ 72 x serum creatinine in mg/dL		
☐ 4.1.9 Adequate hepatic function within 14 days prior to registration defined as follows: • ☐ Bilirubin ≤ 1.5 x ULN • ☐ ALT and AST ≤ 2.5 x ULN • ☐ Alkaline phosphatase ≤ 2.5 x ULN		
☐ 4.1.10 Neurologic function: Neuropathy (sensory and motor) less than or equal to CTCAE v.5.0 Grade 1.		
☐ 4.1.11 Ability to swallow and retain oral medication. Adequate gastrointestinal absorption with no use of parenteral nutrition within two weeks of trial enrollment and no evidence of bowel obstruction.		
☐ 4.1.12 The volunteer must provide study-specific informed consent prior to study entry.		
Ineligibility criteria- ☒indicates patient **does not** meet criteria		
☐ 4.2.1Suspected non-gynecologic malignancy, evidence by tumor markers and/or histologic evaluation.		

☐ 4.2.2 Prior history of other invasive malignancies, with the exception of nonmelanoma skin cancer and other specific malignancies as noted in Section 4.2.4 and Section 4.2.5 are excluded if there is any evidence of other malignancy being present within the last three years (2 years for breast cancer, see Section 4.2.4). Volunteers are also excluded if their previous cancer treatment contraindicates this protocol therapy.		
☐ 4.2.3 Prior chemotherapy for any abdominal or pelvic tumor within the last three years are excluded. Volunteers may have received prior adjuvant chemotherapy and radiotherapy for localized breast cancer, provided that it was completed more than 2 years prior to registration, the volunteer remains free of recurrent or metastatic disease and hormonal therapy has been discontinued.		
☐ 4.2.4 Prior radiotherapy to any portion of the abdominal cavity or pelvis or thoracic cavity within the last three years are excluded. Prior radiation for localized cancer of the head and neck or skin is permitted, provided that it was completed more than three years prior to registration, and the volunteer remains free of recurrent or metastatic disease.		
☐ 4.2.5 Synchronous primary endometrial cancer, or a past history of primary endometrial cancer, unless all of the following conditions are met: Stage not greater than I-A, grade 1 or 2, no more than superficial myometrial invasion, without vascular or lymphatic invasion; no poorly differentiated subtypes, including serous, clear cell or other FIGO grade 3 lesions.		
☐ 4.2.6 Severe, active co-morbidity defined as follows: • ☐ Chronic or current active infectious disease requiring systemic antibiotics, antifungal or antiviral treatment • ☐ Known brain or central nervous system metastases or history of uncontrolled seizures • ☐ Clinically significant cardiac disease including unstable angina, acute myocardial infarction within 6 months from enrollment,		

New York Heart Association Class III or IV congestive heart failure, and serious arrhythmia requiring medication (this does not include asymptomatic atrial fibrillation with controlled ventricular rate). • ☐ Partial or complete gastrointestinal obstruction		
☐ 4.2.7 Volunteers who are not candidates for major abdominal surgery due to known medical comorbidities.		
☐ 4.2.8 Volunteers with any condition that in the judgment of the investigator would jeopardize safety or volunteer compliance with the protocol.		
☐ 4.2.9 Concurrent anticancer therapy (e.g. chemotherapy, radiation therapy, biologic therapy, immunotherapy, hormonal therapy, investigational therapy).		
☐ 4.2.10 Receipt of an investigational study drug for any indication within 30 days or 5 half-lives (whichever is longer) prior to Day 1 of protocol therapy.		
☐ 4.2.11 Prior exposure to a PARP inhibitor		
☐ 4.2.12 People of child-bearing potential are excluded. Criteria are as follows: • ☐ Any volunteer who has experienced menarche and who has not undergone surgical sterilization (hysterectomy and/or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12-month amenorrhea in a woman over 45 in the absence of other biological or physiological causes. • ☐ Volunteers who are pregnant or nursing. Volunteers 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 7 months after completing therapy. • ☐ People with an intact uterus and ovaries must have must have a screening negative serum or urine pregnancy test within 14 days of registration. A second pregnancy test		

must be done within 24 hours prior to the start of the first cycle of study treatment.		
☐ 4.2.13 Potent P-gp inhibitors that result in ≥ 2-fold increase in the exposure of an in vivo probe P-gp substrate, including: amiodarone, carvedilol, clarithromycin, cobicistat, dronedarone, erythromycin, glecaprevir/pibrentasvir, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, sofosbuvir/velpatasvir/voxilaprevir, telaprevir, tipranavir, valspodar and verapamil. More instruction available at: https://www.druginteractionsolutions.org/.		

The pre-treatment assessment support documentation, per the requirements under the study parameters section of this study, as well as the consent form must be uploaded into REDCap the time of registration.

Pre-Treatment assessments **The day an assessment (PE, Lab, scan etc.) is performed is considered day 0 for counting.**	**Date completed**	**Required for Registration**	**Upload to REDCap (site to indicate Y/N)**	**BrUOG verified (Y/N)*internal use**
Informed consent		☐ ≤28 days		
Tissue confirmation		☐ X		
mBRCA confirmation		☐ X		
Concurrent meds		☐ ≤28 days		
History and Physical exam		☐ ≤28 days		
Blood pressure, Pulse		☐ ≤28 days		
Weight and Height (Height only at baseline)		☐ ≤28 days		
Performance status		☐ ≤28 days		
CBC w/diff		☐ ≤28 days		
Serum chemistry*		☐ ≤28 days		
CA125		☐ ≤28 days		
HCG**		☐ ≤14 days		
Adverse event evaluation		☐ ≤14 days		

CT Chest, Abdomen, and Pelvis		☐ ≤28 days		

*Electrolytes including BUN, Crea, Ca, and Mg; LFTs including Bilirubin, ALT, AST, Alk Phos, and albumin.
** Urine or serum in applicable volunteers, per eligibility criteria.

BrUOG use:

CRC completing checklist	**Second reviewer:**
Initials:	**Initials:**
Date:	**Date:**

Appendix D. FDA MedWatch Reporting Checklist for site to submit with report

Patient #: _____ Initials: _____
☐ Initial SAE Report ☐ Follow-up #1 SAE Report ☐ Follow-up #2 SAE Report
☐ Report must be typed

☐ **Section A** Include protocol # (and patient number, if assigned) (i.e. Br390 initials #)

Section B Description of event:
☐ Include description of event (i.e. this is an initial SAE report to document pt X presented to the hospital on XX-XX-XXXX for X, X, X)

☐ Include protocol description (i.e. pt X began treatment on BrUOG 390 on X)

☐ Include treatment regimen (dosing frequency, combination therapy) (i.e. patient received last dose of X on XX-XX-XX)

☐ Clearly outline which events are being reported as serious and non-serious (i.e. serious events are grade 3 fatigue and grade 3 nausea, non-serious events at time of hospitalization include grade 1 fever and grade 1 vomiting)

☐ Investigator's assessment of the relationship of the serious adverse event to talazoparib and suspect medication (i.e. fatigue is not related to talazoparib, related to disease)

☐ Include treatment of event (i.e. patient received IV antibiotics and fluids for treatment of serious event X)

☐ Outcome of event, if known (i.e. grade 3 serious fatigue resolved upon discharge or grade 3 serious fatigue downgraded to non-serious grade 2 upon discharge)

☐ Action taken with talazoparib as a result of the SAE and expectedness (based on the IB and consent) if it is unknown at the time of submission, please indicate "at this time, treating MD is uncertain when treatment with talazoparib will resume"

☐ Create unscheduled event in REDCap and upload all supportive documents

☐ A final report to document discharge from hospital (or resolution of important medical event) if patient still admitted at the time of report, this must be submitted as a follow-up

☐ **Section C Suspect Products(s)** site to complete if the initial reporter suspected the product was associated with the SAE. If the product was <u>not</u> suspected to be associated with the SAE, only C2 conmed section should be completed (lot # and expiration date must be included if applicable).