A Phase 2 clinical trial of the PARP inhibitor talazoparib in BRCA1 and BRCA2 wild-type patients with advanced triple-negative breast cancer and homologous recombination deficiency or advanced HER2-negative breast cancer or other solid tumors with a mutation in homologous recombination pathway genes

Coordinating Center
Stanford Cancer Institute
875 Blake Wilbur Drive
Stanford, CA 94305

Investigators

Melinda L Telli, MD
Assistant Professor of Medicine
Division of Oncology
Stanford University School of Medicine
875 Blake Wilbur Dr, Stanford, CA 94305
Telephone: [redacted]; Fax: [redacted]
Email: [redacted]

Joshua Gruber, MD, PhD
Post-Doctoral Fellow
Departments of Medicine and Genetics
Stanford University School of Medicine
3165 Porter Dr, Palo Alto, CA 94304
Telephone: [redacted]
Email: [redacted]

Biostatistician
Alex McMillan, PhD
Senior Research Scientist
Biomedical Data Science
Stanford University School of Medicine
HRP Redwood Building, Room T160A
259 Campus Dr, Stanford, CA 94305
Phone: [redacted]; Fax: [redacted]
Email: [redacted]

Study Coordinator
Wyatt Forrest Gross, BS
800 Welch Road, Room FC3C45
Stanford, CA 94304
Phone: [redacted]; Fax: [redacted]
Email: [redacted]

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TABLE: SUMMARY OF CHANGES

Revision Date	Changes
Prior amendments	• Title corrected on page 1 and throughout • Clarified SAE reporting guidance for Pfizer, the new study sponsor. Added SCI SAE reporting guidelines for investigator-initiated trials in Appendix B. • Clarified study calendar – changed study weeks to study cycles. • Clarified definition of child bearing potential on eligibility checklist and in eligibility criteria section in protocol • Clarified needed imaging at baseline on eligibility checklist • Added the following to eligibility checklist o Availability of archival tumor tissue from primary breast/tumor site o Adequate fresh or archival tumor tissue from metastatic biopsy site, if biopsy is technically feasible o Subjects of child bearing potential must be willing to have additional urine pregnancy tests during the study. o Clarified that leptomeningeal disease is excluded The above changes were previously reported to the IRB, but are retained for alignment with this version of the protocol, as submitted to the IND. • Eligibility Criteria harmonized with Eligibility Checklist, and presented as a single instance at Section 3.1. o Updated the reference to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 to version 5. .
2 September 2020	Inadvertently omitted text is restored

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PROTOCOL SYNOPSIS

Title of Study: A phase 2 clinical trial of the PARP inhibitor talazoparib in BRCA1 and BRCA2 wild-type patients with advanced triple-negative breast cancer and homologous recombination deficiency or advanced HER2-negative breast cancer or other solid tumors with a mutation in homologous recombination pathway genes

Concept and Rationale: In this phase 2 proof-of-concept clinical trial, we propose to test the efficacy of talazoparib, a potent, orally-bioavailable PARP inhibitor, with an established Phase 2 recommended dose, in the treatment of advanced BRCA wildtype (WT), HER2-negative breast cancer and other solid tumors with homologous recombination (HR) deficiency. The trial is composed of two patient cohorts. Cohort A consists of patients with advanced triple-negative breast cancer (TNBC) and a high homologous recombination deficiency (HRD) score as assessed by the Myriad HRD assay. Cohort B consists of patients with advanced HER2-negative breast cancer or other solid tumors with a germline or somatic mutation in a gene linked to the HR pathway. Patients already identified as harboring a deleterious or suspected deleterious germline or somatic mutation in the HR pathway will be immediately eligible for treatment in Cohort B.

The Myriad HRD assay is a tumor tissue-based assay that has been developed using an indirect approach that allows for the detection of HRD as assessed by quantifying levels of genomic instability. The Stanford Breast Cancer group has previously assessed this assay in a platinum-based neoadjuvant phase 2 trial and showed that a high HRD score significantly correlates with a favorable pathologic response in early-stage TNBC with and without a germline BRCA1/2 mutation. Likewise, Isakoff and colleagues recently reported the correlative endpoints of the TBCRC009 study, a single-arm phase 2 trial of platinum therapy in metastatic TNBC. While established biomarkers, including p63/p73 ratio and p53 and PIK3CA mutations failed to predict for platinum response, HRD assays did identify sporadic TNBC tumors that were more responsive to platinum therapy.

A separate approach to detecting HRD may be the use of multiplex gene panels that evaluate non-BRCA1/2 *germline* mutations implicated in homologous recombination. Mutations in genes linked to the HR pathway, such as ATM, PALB2 and RAD51 among others, are hypothesized to have similar chemosensitivity to DNA-damaging therapies as mutations in BRCA1 and BRCA2 given a similar synthetically lethal effect. Identification of *somatic* mutations in HR-related genes through commercially available next-generation DNA sequencing of tumor tissues also has potential to identify patients who may derive benefit from DNA repair defect-targeted therapy. However, no studies to-date have directly evaluated the role of DNA-damaging therapies in such patient populations.

Primary Objective(s):

To determine whether single agent talazoparib can result in a 30% or greater objective response in patients with advanced *sporadic* triple-negative breast cancer with homologous recombination deficiency as assessed by the HRD assay (Cohort A) or advanced HER2 negative (ie, TN or ER/PR positive) breast cancer or other solid tumors with a *germline* or *somatic* mutation in the HR pathway, excluding BRCA1/2 (Cohort B).

Secondary Objective(s):

1. To determine the clinical benefit rate (complete response, partial response or stable disease $\geq$ 24 weeks)
2. To determine progression-free survival
3. To evaluate the safety of talazoparib in this patient population

Correlative Objective(s):

1. To compare the rate of response in subjects with TNBC with or without an underlying

germline HR pathway mutation (Cohort A).

2. To compare the HRD scores in responders versus non-responders with underlying deleterious or suspected deleterious germline or somatic HR gene mutations (Cohort B).
3. To assess the concordance of the HRD scores in the primary tumor tissue with that in the metastatic tumor tissue.
4. To assess in metastatic tumor biopsy samples, the RAD51 status of the tumor at baseline (absent or present) as a functional readout of HR capacity and correlate this with HRD and mutational status

Primary Endpoint(s):

The objective response rate of talazoparib using RECIST 1.1 criteria

Secondary Endpoint(s):

1. Clinical benefit rate
2. Progression-free survival
3. Safety

Correlative Endpoint(s):

1. Objective response rate in subjects with TNBC with or without an underlying germline HR pathway mutation in Cohort A
2. Correlation of HRD scores with response in subjects with underlying germline or somatic HR gene mutations in Cohort B
3. Correlation of HRD scores in the primary tumor tissue and the metastatic tumor tissue.
4. Correlation of RAD51 status in the metastatic tumor with HRD and mutational status.

Study Design: A single-arm, phase 2 clinical trial consisting of 2 patient cohorts (parallel design), using an optimal two-stage design. The two patient cohorts are the following:

Cohort A: TNBC patients with HR deficiency as measured by the Myriad HRD assay

Cohort B: HER2-negative (ie, triple-negative or estrogen/progesterone receptor-positive) breast cancer or other solid tumor patients with a *germline* or *somatic* mutation in a HR pathway gene. Gene mutations of interest are: PTEN; PALB2; CHEK2; ATM; NBN; BARD1; BRIP1; RAD50; RAD51C; RAD51D; MRE11; ATR; Fanconi anemia complementation group of genes (FANCA; FANCC; FANCD2; FANCE; FANCF; FANCG; FANCL).

Number of Patients: We will accrue 10 patients, if we observe a response in at least 2 patients, then we will accrue 10 additional patients for a total of 20 patients in each cohort, and require a response in at least 3 patients out of 20 to declare statistical significance at a one sided significance level of 5%, in order to assure 80% power. It is expected that at least 10 HER2-negative breast cancer patients will be enrolled in Cohort B.

Summary of Eligibility:

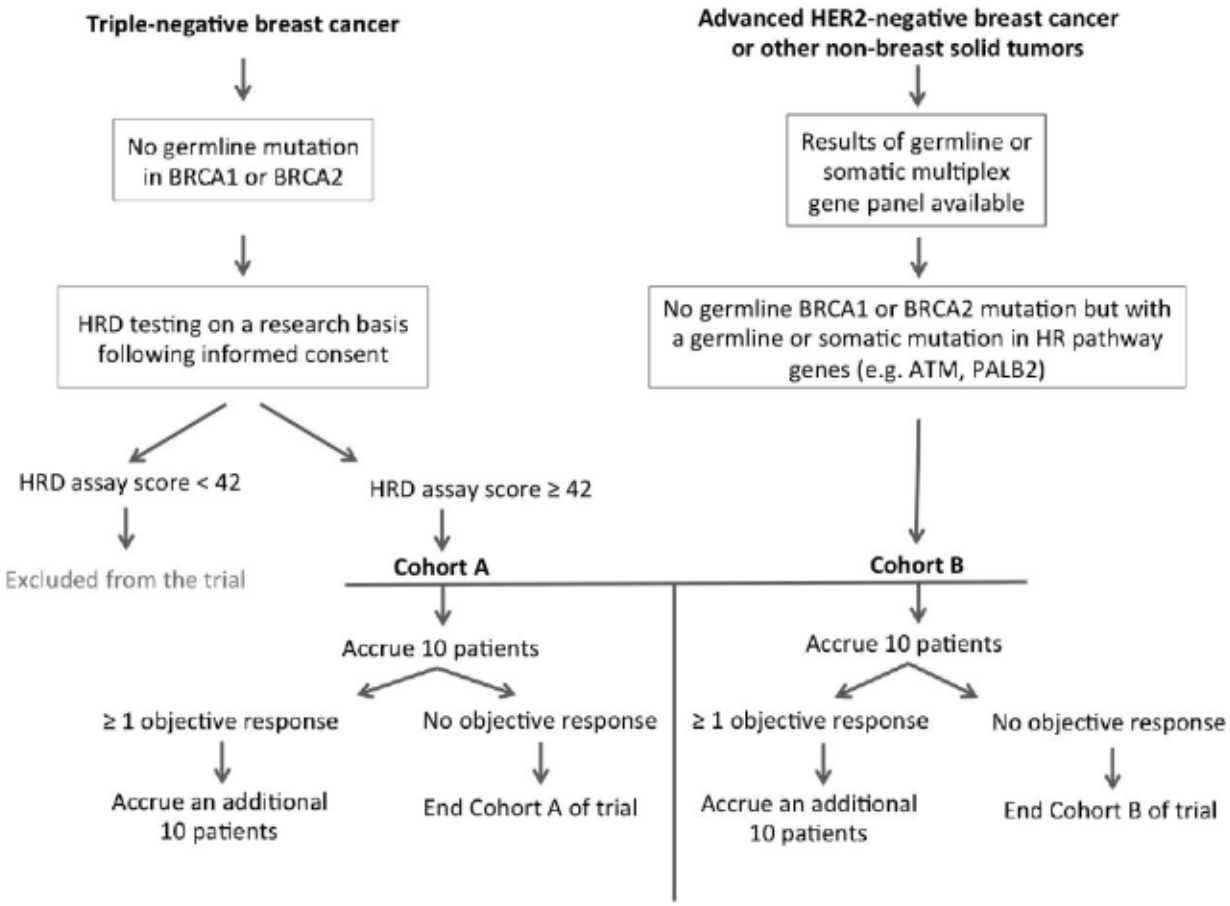
- Adults with a solid tumor measurable per RECIST v1.1, without suspected deleterious germline BRCA1 or BRCA2 gene mutation in the germline, and having received at least 1 prior systemic therapeutic regimen. Eligible subjects will have ECOG performance status of 0 to 2 and adequate organ function, with adequate birth control precautions. Please see complete Eligibility Criteria at Section 3.1.

Intervention and Mode of Delivery: Talazoparib, 1 mg PO daily (continuous dosing) on a 28-day cycle. Patients will be evaluated prior to each cycle. This will include a clinical evaluation, including safety assessment and physical exam, as well as laboratory assessment.

Duration of Intervention and Evaluation: The nominal duration of treatment is 36 cycles

(28 days per cycle), but CR, PR, or SD patients may continue therapy until evidence of progressive disease or unacceptable toxicity occurs. Protocol therapy will be discontinued for progressive disease at any time. Patients are free to halt therapy at their request. Treatment may be discontinued if intercurrent co-morbidities occur, which, in the opinion of the treating physician, would preclude safe administration of study drugs.
Funding, Regulatory, and Feasibility Issues: This investigator-initiated Phase 2 clinical trial will be funded by Pfizer Pharmaceutical, Inc. This pharmaceutical company has committed to providing the study drug, talazoparib.
Patient Acceptability/Ethics and Consent Issues: Given the lack of targeted therapy options for TNBC patients, we believe this trial will be a welcomed alternative compared to standard cytotoxic chemotherapy in this patient population. Of possible concern to the patient or advocate community may be that we will require tumor tissue of a metastatic site for trial participation. This biopsy is critical for the successful conduct of this study. Furthermore, as patients will require genetic testing, we will offer genetic counseling to all patients enrolled in this trial.

STUDY SCHEMA



LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BID	Twice daily
BSA	Body surface area
CBC	Complete blood count
CI	Confidence interval
CMAX	Maximum concentration of drug
CNS	Central nervous system
CRF	Case report/Record form
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
ER	Estrogen receptor
FDA	US food and drug administration
FFPE	Formalin-fixed paraffin embedded
GCP	Good clinical practice
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HNSTD	Highest non-severely toxic dose
HR	Homologous Recombination
HRD	Homologous Recombination Deficiency
IB	Investigator's brochure
IP	Investigational product
IRB	Institutional Review Board
IV	Intravenous
LFT	Liver function test
LOH	Loss of heterozygosity
MTD	Maximum tolerated dose
OS	Overall survival
PARP	Poly-ADP ribose polymerase
pCR	Pathologic complete response
PD	Progressive diseased or Pharmacodynamics
PFS	Progression-free survival
PK	Pharmacokinetic
Plt	Platelet count
PR	Partial response or Progesterone receptor
QD	Once daily
RECIST	Response evaluation criteria in solid tumors
RR	Response rate
SAE	Serious adverse event
SD	Stable disease
SRC	Scientific Review Committee
TN	Triple-negative
TK	Toxicokinetic
TNBC	Triple-negative breast cancer
ULN	Upper limit of normal
WBC	White blood cell

1. OBJECTIVES

1.1 Primary Objective

To determine whether single agent talazoparib produces better than expected responses in patients with advanced *sporadic* triple-negative breast cancer with homologous recombination deficiency as assessed by the HRD assay (Cohort A) and/or advanced HER2-negative (ie, TN- or ER/PR-positive) breast cancer or other non-breast solid tumors with a *germline* or *somatic* mutation in the HR pathway, excluding BRCA1 or BRCA2 (Cohort B).

1.2 Secondary Objectives

1.2.1 To determine clinical benefit rate (complete response, partial response or stable disease $\geq$ 24 weeks)

1.2.2 To determine progression-free survival in both cohorts

1.2.3 To evaluate the safety of talazoparib in both patient populations

1.3 Correlative Objectives

1.3.1 To compare the rate of response in subjects with TNBC with or without an underlying germline HR pathway mutation (Cohort A).

1.3.2 To compare the HRD scores in responders versus non-responders with underlying deleterious or suspected deleterious germline or somatic HR gene mutations (Cohort B).

1.3.3 To assess the concordance of the HRD scores in the primary tumor tissue with that in the metastatic tumor tissue.

1.3.4 To assess in metastatic tumor biopsy samples, the RAD51 status of the tumor at baseline (absent or present) as a functional readout of HR capacity and correlate this with HRD and mutational status

2. BACKGROUND

2.1 BRCA1/2-Mutation Associated Breast Cancer

Cancer is a genetic disease caused by an accumulation of changes in the DNA sequence over time, generally involving tumor suppressor genes or proto-oncogenes.[1] Cells continually acquire DNA damage and have robust and redundant DNA damage repair mechanisms that function to maintain genomic stability. Double-strand DNA breaks are extremely cytotoxic and their repair via non-homologous end joining and homologous recombination are critically important. Excision repair pathways, including base excision repair, nucleotide excision repair and mismatch repair, also play important roles in restoring the normal DNA sequence.

Breast cancers that arise in BRCA1 and BRCA2 mutation carriers are characterized by homologous recombination DNA repair deficiency due to loss of the functioning wild-type BRCA1 or BRCA2 allele. The BRCA1 and BRCA2 gene products are critical for DNA double-strand break repair via homologous recombination.[1] Poly (ADP-ribose) polymerase-1 (PARP1) and PARP2 are nuclear enzymes crucial for recruitment of a cell's base excision repair machinery to sites of DNA damage. It has been established that PARP1/2 inhibitors can cause selective cytotoxicity in cell lines mutant for BRCA1 or BRCA2, due to stalling of replication

forks induced by absence of PARP enzyme and subsequent shutting of the DNA damage to doublestrand breaks. With concurrent loss of homologous recombination-dependent DNA double-strand break repair, this leads to a synthetically lethal interaction.[2-7]

2.2 Sporadic Triple-Negative Breast Cancer

For some time, it has been appreciated that the majority of invasive breast cancers that develop in women with deleterious BRCA1 germline mutations are triple-negative,[8,9] defined pathologically as lacking expression of the estrogen and progesterone receptors (ER/PR) with no amplification of the HER2/neu oncogene,[10] and this has provided fascinating mechanistic clues to underlying tumor biology and possible therapeutic targets. Based on similarities between sporadic triple-negative breast cancer and BRCA1-deficient breast cancer and the known role of BRCA1 in DNA repair, the hypothesis has emerged that sporadic triple-negative breast tumors may possess similar DNA repair defects and demonstrate similar chemosensitivity as BRCA1 mutation-associated breast tumors. Pre-clinically, triple-negative breast cancer cell lines, like BRCA1-deficient cancer cell lines, demonstrate increased sensitivity to PARP inhibitors, cisplatin and gemcitabine.[11] Additionally, these cell lines are more sensitive to oxidative DNA damage compared to luminal breast tumor cells or normal breast epithelial cells and have been shown to be deficient in base excision repair.[12]

The activity of olaparib, a bona fide PARP inhibitor, was investigated in a small cohort of unselected sporadic triple-negative breast cancer patients, however, no objective responses were noted and further development was halted.[13] Unfortunately, this experience thwarted the clinical progress of PARP inhibitors in sporadic triple-negative breast cancer. The inability to select BRCA1/2 wild-type tumors with underlying DNA repair defects further compounded the problem. Due to these early challenges, the role of PARP inhibition in the treatment of sporadic triple-negative breast cancer has remained undefined.

2.3 Cancers with Germline or Somatic Deficiency in DNA Double-Strand Repair

In the past year, targeted gene panels have arisen that evaluate germline mutations in DNA repair pathways implicated in cancer development and progression. Mutations in genes linked to checkpoint control and regulation of the DNA-double strand break repair pathway, such as ATM, PALB2 and RAD51 are hypothesized to have similar chemosensitivity to DNA-damaging therapies, such as PARP inhibitors, as mutations in BRCA1 and BRCA2 given a similar synthetically lethal effect. However, no studies to date have directly evaluated the role of DNA-damaging therapies in such patient populations, in part due to a lack of commercially available multiplex gene panels using next generation DNA sequencing until recently as well as the low prevalence of such mutations in the general population.

In a French study published this year, next-generation-sequencing-based screening in 708 patients with either a personal history of breast or ovarian cancer at a young age, male breast cancer, or strong family history demonstrated an overall mutational rate of BRCA1 and BRCA2 of 10.8%. In addition, 10 inactivating mutations were found in PALB2 and RAD51C and 10 inactivating mutations found in CHEK2 and ATM, with a collective contribution estimated to be at least 3% (see figure).[14]

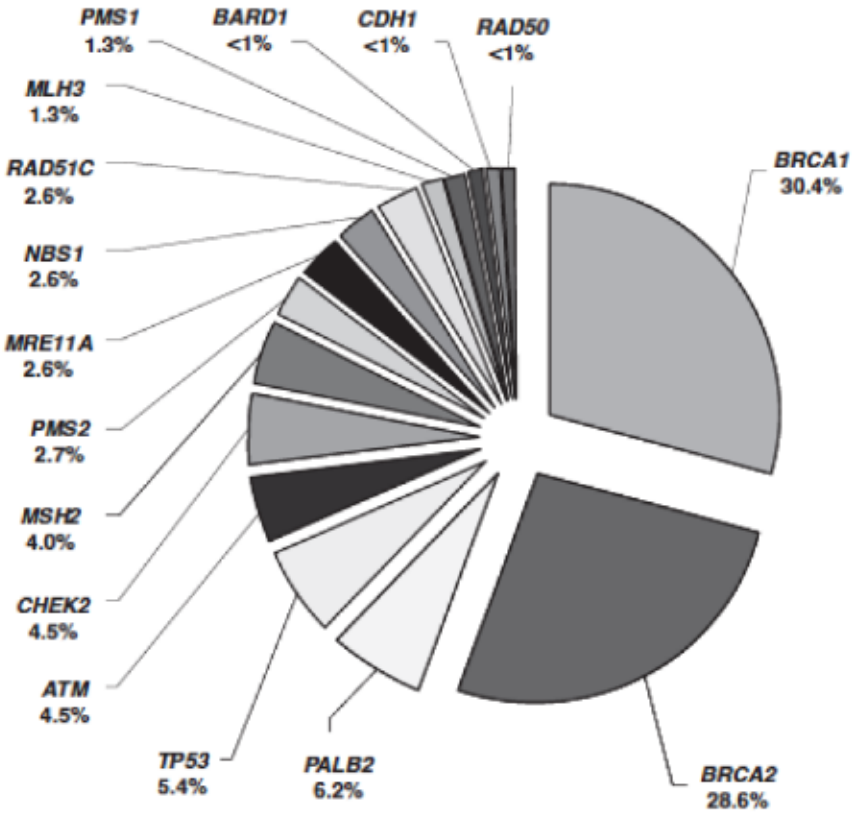


Figure 1. Castera L, *et al*. European Journal of Human Genetics, January 2014.

The myRisk gene panel developed by Myriad Genetics similarly evaluates a set of 25 cancer susceptibility genes implicated in hereditary breast and ovarian cancer by next generation sequencing. In an abstract presented at the 2013 San Antonio Breast Cancer Symposium, 1955 prospectively accrued patient cases (excluding patients of Ashkenazi Jewish heritage to determine relative prevalence in the general population) were tested, and demonstrated that 275 (14.07%) were mutation carriers in at least one of the 25 genes. Interestingly, 182 (9.3%) of patients had a mutation in BRCA1 or BRCA2, while 96 (4.91%) of patients had a mutation in other genes, including ATM, CHEK2, NBN, and PALB2. 1738 out of the 1955 patients in the study had a personal history of breast cancer, with 63% diagnosed prior to the age of 50, and 37% at or after the age 50. Notably 1902 (97.29%) patients had a variant of uncertain significance in at least one of the genes tested and an average of three variants was found per patient.[15]

In addition to breast cancer, homologous recombination pathway mutations have been implicated in multiple other solid tumors including ovarian, prostate, pancreas, and gastric cancers among others and are postulated to result in a 'BRCAness' phenotype. For example, a recent study has shown that germline mutations in DNA-repair genes can be detected in approximately 10% of patients with metastatic prostate cancer.[28] Of patients with identified mutations, *BRCA2* mutations comprised 44% of total mutations. Other mutations identified included *ATM* in 13%, *CHEK2* in 12%, *BRCA1* in 7%, *RAD51D* in 4%, and *PALB2* in 4%. These data provide strong

rationale for the use of PARP inhibitors in solid tumors with homologous repair deficiency outside of *BRCA1/2* mutations in tumors other than breast cancer.

Furthermore, identification of somatic mutations in HR-related genes through commercially available next generation sequencing of tumor tissues also has potential to identify patients with somatic DNA repair alteration who may derive potential benefit from DNA defect-targeted therapy, such as a PARP inhibitor. Studies to assess the efficacy of this approach are currently not available.

2.4 The Myriad Homologous Recombination Deficiency (HRD) Assay

The Myriad Homologous Recombination Deficiency (HRD) Assay is a novel assay that has been developed using an indirect approach that allows for the detection of HRD regardless of its etiology or mechanism as measured by levels of genomic instability. The assay is compatible with formalin-fixed paraffin-embedded (FFPE) tumor tissue and BRCA1 and BRCA2 tumor sequence data is simultaneously generated. Early in assay development, genomic regions of loss of heterozygosity (LOH) of intermediate length (> 15 Mb and < 1 chromosome) were shown to be highly associated with HR deficiency and the HRD-LOH score was derived as a count of LOH regions of this length across the tumor genome.[16]

Our group has previously assessed the HRD-LOH assay in PrECOG 0105, a neoadjuvant trial that explored a non-anthracycline, non-taxane, platinum-based regimen in patients with triple-negative or BRCA1/2 mutation-associated breast cancer. We showed that a high HRD score significantly correlates with favorable pathologic response to a platinum-based regimen in early-stage triple-negative and BRCA1 or BRCA2 mutation-associated breast cancer[17] In this study, patients received carboplatin AUC 2 and gemcitabine 1000 mg/m^2 on days 1 and 8 every 21 days in addition to iniparib on days 1, 4, 8, and 11.[18,19] The overall pCR rate in the intent-to-treat population was 36% (90% CI: 27-46%). Notably, BRCA1 and BRCA2 mutation status was comprehensively assessed and TNBC patients with a germline BRCA1 or BRCA2 mutation achieved a higher rate of pCR (56%) compared to patients who were BRCA1 and BRCA2 wild-type (33%).[18,19] A major aim of PrECOG 0105 was to evaluate biomarkers of response to this neoadjuvant therapy in patients with sporadic TNBC. The HRD assay score was assessed in a cohort of 77 tumors in PrECOG 0105 where pathologic response was assessed using the residual cancer burden (RCB) index.[17,20] The average HRD assay score for responders was 16.2 and the average score for non-responders 11.2 ($p = 0.0003$) using the HRD-LOH assay. Interestingly, no difference in median HRD scores was noted between BRCA1/2-deficient versus BRCA1/2-proficient responders. Furthermore, if BRCA1/2-deficient samples were excluded ($n = 58$), the association between response to treatment and HRD assay score remained significant ($p = 0.0006$). Overall, 70% of patients with an HRD assay score of ≥ 10 or a deleterious BRCA1/2 mutation responded compared with 12% of patients with an HRD assay score of < 10 and intact BRCA1/2 status ($p = 0.00002$).[17] These data suggest that tumor measures of LOH may be important biomarkers in the identification of germline BRCA1 and BRCA2 wild-type patients who may benefit from DNA defect-targeted therapy, such as platinum or a PARP inhibitor.

Additionally, the HRD-LOH assay has been validated in two prospective breast cancer cohorts. The Cisplatin-1 cohort included 28, mainly sporadic, triple-negative breast cancer patients treated with neoadjuvant cisplatin, 75 mg/m^2 every 21 days for 4 cycles. The Cisplatin-2 cohort included 51 triple-negative breast cancer patients treated with neoadjuvant cisplatin 75 mg/m^2

every 21 days for 4 cycles plus bevacizumab 15 mg/kg for 3 cycles. The pathologic response in these studies was assessed by the Miller-Payne (MP) score, with responders having a MP score of 4 or 5, and non-responders MP scores of 1 to 3. Analyses were also performed in patients achieving a pCR versus no pCR. The analysis of HRD score versus pathologic response was performed on the combined dataset. The mean HRD score among responders (MP 4-5) versus non-responders (MP 1-3) was 18.0 versus 12.9 with an odds ratio of 3.6 (3.2-4.0) and p-value of 0.013. Mean HRD scores among patients with a pCR versus non-pCR was 20.6 versus 13.4 with an odds ratio of 7.4 (6.3-8.6) and a p-value of 0.0048. Importantly, among patients with an HRD score < 10, no patients achieved a pCR while 24% of patients with an HRD ≥ 10 achieved a pCR resulting in 100% sensitivity and 100% negative predictive value for pCR. In this combined cohort, 72% of patients had an HRD score of 10 or greater.

Recently, the HRD assay has been further optimized and currently incorporates additional measures of genomic instability, including telomeric allelic imbalance (TAI; the number of regions with allelic imbalance that extend to the subtelomere, but do not cross the centromere) and large-scale state transitions (LST; the number of chromosomal breaks between adjacent genomic regions longer than 10 Mb after filtering out regions shorter than 3 Mb).[21,22] The HRD score is currently calculated by adding the LOH, TAI and LST scores and is reported as a continuous score from 0-100. An HRD score of < 41 (previously < 10) is defined as HR proficient and HRD score of ≥ 42 (previously ≥ 10) as HR-deficient. Using this cutoff, ~48% of TNBC patients are classified as HR-deficient.

2.5 Overview of the study agent talazoparib

2.5.1 Nonclinical Studies of talazoparib

Talazoparib is a highly potent and specific inhibitor of PARP1 and 2 with activity in tumor cell lines bearing DNA repair deficiencies.[23,24] talazoparib inhibits PARP *in vitro* at a lower concentration (IC50 = 0.57 nM) than ABT 888 (IC50 = 4.73 nM), AG14447 (IC50 = 1.98 nM), or olaparib (IC50 = 1.94 nM). Talazoparib also exerts single-agent synthetic lethality of BRCA 1 and 2 and PTEN deficient cell lines. In BRCA2 negative Capan 1-cells, talazoparib was more potent as single agent than ABT-888 (10,000 times), AG14447 (609 times) and olaparib (259 times) in inhibiting PARP activity. In animal models, potent anti-tumor activity was observed at oral daily doses < 1 mg/kg/day. Complete suppression of BRCA1-deficient tumor growth in the MX1 model was achieved in a 3-month study when dosed at 0.165 mg/kg BID.[24] Similarly, suppression of PTEN-deficient tumor growth was achieved in xenotransplant experiments with talazoparib dosed at 0.33 mg/kg once daily for 28 consecutive days.[24]

The oral bioavailability, calculated from the ratio of the area under the concentration-time curve (AUC) following oral administration relative to the AUC following intravenous (IV) administration (AUC_{oral}/AUC_{IV}), was > 42.7% in rats and > 50.5% in dogs based on single dose comparisons. The compound was metabolically stable. The terminal half-life of talazoparib at various doses in rats and dogs ranges from 28.5 to 32.0 hr and 69.7 to 91.2 hr, respectively, which allows for once daily dosing.

Pharmacokinetic studies have been performed in rats and dogs. Steady state concentrations were reached on Day 15 in rats and on Day 20 in dogs using daily administration of talazoparib. Comparing Day 15 and 28 with Day 1 for all dose levels in dogs, AUC and C_{max} increased from Day 1 to Day 15 to Day 28.

Five-day repeat dose toxicity and toxicokinetic (TK) studies with 28-day recovery were conducted in rats and dogs. In dogs (the most sensitive species), talazoparib was administered at dose levels of 0.003, 0.01, 0.03, 0.1 mg/kg/day over 5 consecutive days. Severe pancytopenia was observed in dogs treated with the two highest dose groups (0.03 and 0.1 mg/kg/day). At these doses, the mean (or median) reticulocyte nadir occurred on Day 6 and the platelet and WBC nadirs on Day 11. These changes were reversed in the group treated at 0.03 mg/kg/day on days 17 to 18 (ie, 12 to 13 days after the last dose of the drug). Mortalities occurred in animals given 0.1 mg/kg/day due to bacterial septicemia secondary to bone marrow hypocellularity and lymphoid organ depletion on Day 12 to 13. Coagulation parameters were unaffected. After repeat-dose administration of daily oral talazoparib in dogs for 5-days, the highest non-severely toxic dose (HNSTD) was 0.03 mg/kg/day. Twenty-eight day repeat dose toxicity and TK studies with 28-day recovery were also conducted in rats and dogs. In dogs, talazoparib was administered at dosage levels of 0.0005, 0.0015, 0.005, 0.01 mg/kg/day over 28 consecutive days. Talazoparib-related signs included hematology findings in males and females given 0.005 or 0.01 mg/kg/day such as mildly lower red cell mass, mildly to moderately lower platelet and absolute reticulocyte counts, and minimally to mildly lower white blood cell counts with a generalized decrease in all leukocytes. All of these signs reversed or were reversing by the end of the recovery phase. After repeat-dose administration of daily oral talazoparib in dog for 28 days, the HNSTD was 0.01 mg/kg/day.

In conclusion, the main nonclinical findings of early hematological changes, and subsequent bone marrow and lymphoid organ depletion as well as focal necrosis after repeat administration of talazoparib are in accordance with the mechanism of action and the exposure/distribution pattern. These findings were reversible and the decreased reticulocyte, platelet, red blood cell (RBC) and WBC counts were sensitive and early markers of target organ toxicity. Decreases in hematology parameters were used to clinically monitor safety. A starting clinical dose was estimated using the dog HNSTD as the dog was more sensitive to talazoparib-related primary toxicities than the rat. Based on a 6 times safety factor relative to the 28-day toxicity study in dog HNSTD, the estimated safe clinical starting dose is 1 µg/kg/day. The difference in relative bioavailability after administration of the capsule and oral gavage suspension of talazoparib was approximately two-fold. Taking into account the relative change in exposure with the capsule versus the oral gavage suspension, the estimated safe clinical starting dose was recalculated and is 0.5 µg/kg/day talazoparib. Therefore, the starting fixed clinical dose of 25 µg talazoparib in a capsule form corresponds to 0.42 µg/kg/day for a 60-kg adult.

2.5.2 Clinical Studies of Talazoparib

Three studies ongoing at the time of this update:

- PRP-001, initiated on January 3rd 2011, is a single-arm, open-label study to assess the safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of talazoparib in patients with advanced tumors with DNA-repair pathway abnormalities, particularly those associated with BRCA- and PTEN-dysfunction. The initial cohort of patients was treated with 25 µg talazoparib once daily. This two-stage phase 1 study was updated at the 2014 ASCO Annual Meeting. At this time expansion phase enrollment in small cell lung cancer, germline BRCA breast and ovarian cancer and Ewing's sarcoma is complete. The MTD and Recommended Phase 2 Dose (RP2D) was established at 1 mg/d in 39 pts (33F/6M) treated at doses ranging from 25 to 1100 µg/d. Dose-limiting thrombocytopenia occurred in 1/6 and 2/5 pts at 900 and 1100 µg/d, respectively[25].

- 673-301, initiated on October 30, 2013 is an open-label, randomized, parallel, 2-arm study of talazoparib versus protocol-specific physician's choice therapy in subjects with germline BRCA mutation with locally advanced and/or metastatic breast cancer.
- 673-201: 2-stage, 2-cohort phase 2 trial is to evaluate the safety and efficacy of talazoparib in subjects with locally advanced or metastatic breast cancer with a deleterious germline BRCA 1 or BRCA 2 mutation. Subjects will be assigned to either Cohort 1 or 2 based on prior chemotherapy for metastatic disease:
  - Cohort 1) Subjects who have previously responded to platinum-containing regimen for metastatic disease with disease progression > 8 weeks following the last dose of platinum; or
  - Cohort 2) Subjects who have received > 2 chemotherapy regimens and who have had no prior platinum therapy for metastatic disease

In addition, a food effect study (673-103) in 18 healthy volunteers has been completed. The food effect study showed that, while a high-fat, high-calorie meal delayed the absorption of orally administered talazoparib, it did not affect the overall extent of absorption. Single 500 µg doses were safe and well tolerated in healthy male volunteers.

Preliminary PK data from Part 1 of PRP-001, through Cycle 1, was available at the time of this report. Overall, plasma concentrations of talazoparib increased in a dose-dependent manner, with most patients obtaining steady-state plasma concentrations by the end of the second week of daily dosing (Day 22). As indicated by log-linear concentration-time profiles on Day 1 and Day 35, talazoparib elimination appeared to follow biphasic kinetics.

Cumulatively, there have been 111 SAEs reported in clinical studies with talazoparib as of November 30th 2013. The most common reasons for SAEs have been infectious (33 events), gastrointestinal disorders (16 events), blood and lymphatic disorders (13 events), and respiratory disorders (12 events). The most commonly reported SAEs by preferred term include febrile neutropenia (9 events), neutropenic sepsis (7 events), ascites (5 events), and bacteremia (5 events). All but 9 of these 111 SAEs were assessed by the investigators as not related to treatment with talazoparib.

Adverse events occurring in at least 10% of patients in the pooled study population of PRP-001, PRP-002, 673-103 and 673-301 have included: fatigue, nausea, anemia, constipation, diarrhea, vomiting, thrombocytopenia, cough, pyrexia, headache, neutropenia, alopecia, decreased appetite, abdominal pain, back pain, dyspnea, pain in extremities, hypokalemia, anxiety, arthralgia, and dizziness. Adverse reactions have not worsened with continued therapy at the same or reduced dose.

Based on its mechanism of action, preclinical activity and pharmacokinetic (PK) and toxicity profile, talazoparib was selected for clinical evaluation in tumors with demonstrated or potential defects in DNA repair pathways, such as BRCA mutations, PTEN dysfunction or abnormal RAD51 foci formation. Talazoparib has been shown to be highly selective and potent cytotoxic agent in human cancer cell lines and in animal models of tumors harboring mutations that compromise DNA repair pathways. Pharmacokinetic parameters demonstrated a high bioavailability with a distribution profile indicating extensive tissue distribution, and a duration of exposure sufficient to support once daily dosing. Changes in hematology parameters were early markers of toxicology findings. Anemia, thrombocytopenia, and neutropenia have all been

observed, including Grade 3-4 events. The events of fatigue, nausea, constipation, diarrhea, vomiting, cough, pyrexia, headache, alopecia, decreased appetite, abdominal pain, back pain, dyspnea, pain in the extremities, hypokalemia, anxiety, arthralgia, and dizziness have also been observed in subjects receiving talazoparib. All patients are being monitored for myelo-suppression in the ongoing studies.

The table below summarizes the safety data of talazoparib as assessed by the phase 1 trial in patients with advanced solid tumors.[25]

Table 1. Safety data for phase 1 dose escalation/expansion trial for patients with solid cancers[25]

SAFETY: DOSE ESCALATION AND EXPANSION Data as of 04/18/14

Drug Related Adverse Events	Number of patients = 105 (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Fatigue	20 (19.0)	12 (11.4)	2 (1.9)	0
Nausea	26 (24.8)	4 (3.8)	0	0
Alopecia	22 (21.0)	3 (2.9)	0	0
Diarrhea	8 (7.6)	1 (1.0)	0	0
Vomiting	6 (5.7)	1 (1.0)	0	0

SAFETY: HEMATOLOGIC TOXICITY Data as of 04/18/14

Hematologic Adverse Events	Number of patients = 105 (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	42 (40.0)	31 (29.5)	23 (21.9)	0
Thrombocytopenia	36 (34.3)	8 (7.6)	11 (10.5)	7 (6.7)
Neutropenia	17 (16.2)	29 (27.6)	11 (10.5)	1 (1.0)

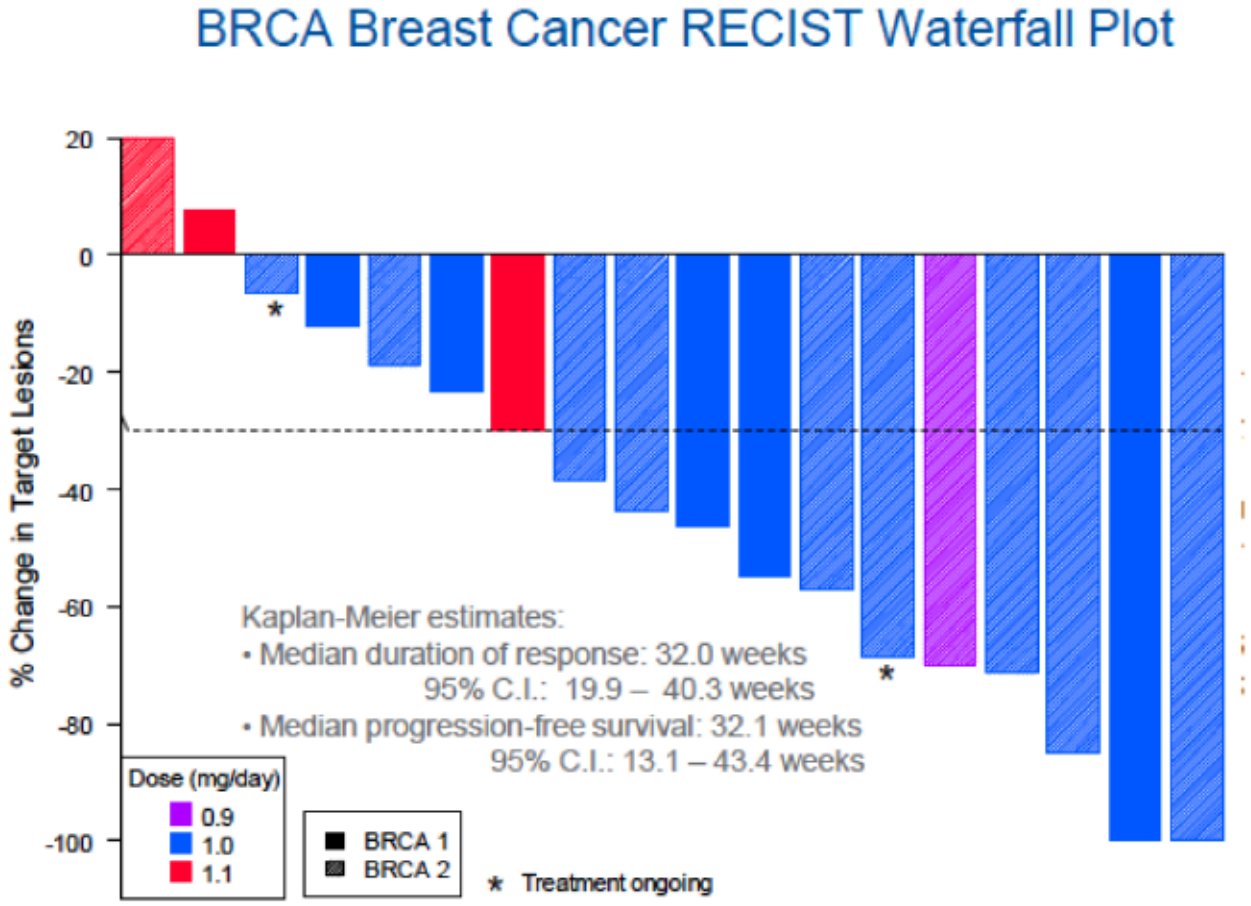


Figure 2. *BRCA1/BRCA2* breast cancer RECIST waterfall plot in phase 1 trial of talazoparib[25]

2.6 Rationale

Poly (ADP-ribose) polymerase-1 (PARP1) and PARP2 play important roles in DNA repair.[7] The clinical development of PARP1/2 inhibitors advanced when the principle of chemical synthetic lethality was established in BRCA1/2-deficient cells.[2] Synthetic lethality stems from the inability of BRCA-deficient cells to undergo homologous recombination-mediated double-strand DNA break repair, making them susceptible to DNA damage caused by a PARP inhibitor.[3,5,6] Two phase 2 proof-of-concept studies documented objective responses to single agent olaparib, an oral PARP inhibitor, in BRCA1/2 mutation carriers with advanced ovarian and breast cancer.[13,26] Given that sporadic triple-negative breast cancers share many pathological and molecular features with breast cancers arising in the setting of a hereditary BRCA mutation, it was suggested that these sporadic tumors might share similar DNA repair defects and show similar chemosensitivity to BRCA mutation-associated tumors. The activity of single-agent olaparib, a bona fide PARP inhibitor, was investigated in a small cohort of unselected sporadic triple-negative breast cancer patients, however, no objective responses were noted and further investigation was halted.[13] These experiences thwarted the clinical development of PARP inhibitors in sporadic triple-negative breast cancer. The inability to select BRCA1/2 wild-type tumors with underlying DNA repair defects further compounded the problem.

Due to these early challenges, the role of PARP inhibition in the treatment of sporadic triple-negative breast cancer has remained undefined. The challenge at hand is to appropriately select patients lacking a germline BRCA1/2 mutation for the next generation of clinical trials. Patient Cohort A of our proposed study with the PARP inhibitor talazoparib aims to address this important question by selecting a subpopulation of sporadic, triple-negative breast cancer patients enriched for homologous recombination deficiency (HRD) as assessed by a novel tissue-based assay developed by Myriad Genetics. The HRD assay has been developed using an indirect approach that allows for the detection of HRD regardless of its etiology or mechanism as assessed by levels of genomic instability.[16] Our group has previously evaluated the HRD assay in a neoadjuvant phase 2 trial of gemcitabine, carboplatin and iniparib and showed that a high HRD score significantly correlated with favorable pathologic response to this platinum-based regimen in early-stage triple-negative breast cancer patients with and without a germline BRCA1/2 mutation.[17,19]

Given our findings, we hypothesize that the HRD assay can be used to select triple-negative breast cancer patients most likely to derive benefit from a single-agent PARP inhibitor treatment strategy. Talazoparib is a novel oral PARP1/2 inhibitor shown in preclinical models to be more potent than other agents in its class and a recommended phase 2 dose has been determined.[24,25,27] As such, it is an ideal drug to evaluate in a proof-of-concept study of single-agent PARP inhibitor therapy in patients with advanced triple-negative breast cancer, who lack a germline BRCA1 or BRCA2 mutation, but are HR-deficient by the HRD assay.

Our second patient cohort (Cohort B) aims to evaluate the efficacy and safety of talazoparib in an emerging sub-group of breast cancer patients, or other non-breast metastatic solid tumors with high likelihood of HR deficiency stemming from germline or somatic mutations in genes other than BRCA1 and BRCA2 implicated in the double-stranded DNA break repair pathway. Based on the limited current data, the prevalence of such hereditary breast and ovarian cancer syndromes is estimated to be as high as 5% of the general breast cancer patient population.[14,15] Given the increased utilization of commercial multiplex germline gene panels as well as the increased availability of next generation tumor sequencing, we will likely capture more of these patients in community and academic oncology practices in coming years; however, due to the current lack of clinical trials assessing the utility of PARP inhibitors in this heterogeneous group of breast cancer patients, we do not yet know the efficacy of such a strategy. Thus, this proof-of-concept study will assess the role of PARP inhibition in advanced HER2-negative breast cancer and other non-breast solid tumors with presumed underlying HR-deficiency due to a germline or somatic mutation in the HR pathway.

2.7 Study Design

This is a single-arm, open-label treatment protocol designed to evaluate the efficacy and safety of talazoparib in 2 patient cohorts:

- **Cohort A:** Advanced sporadic, triple-negative breast cancer with homologous recombination deficiency based on a high HRD assay score (HRD score ≥ 42)

- **Cohort B:** Advanced HER2-negative (ie, ER and/or PR positive or TN) breast cancer or other non-breast metastatic cancer with a deleterious or suspected deleterious germline or somatic gene mutation in the homologous recombination pathway, excluding BRCA1 and BRCA2. Mutations of interest are:

    - PTEN; PALB2; CHEK2; ATM; NBN; BARD1; BRIP1; RAD50; RAD51C; RAD51D; MRE11; ATR; Fanconi anemia complementation group of genes (FANCA; FANCC; FANCD2; FANCE; FANCF; FANCG; FANCL); plus other HR-related genes at the discretion of the primary investigators.

This study will proceed with 2 phases: screening and treatment. During screening, all participants will be asked to provide a metastatic tumor biopsy sample to assess the HRD score based on the HRD assay. This result is required for eligibility determination in Cohort A. If the patient does not have an adequate tumor biopsy sample from a metastatic site, biopsy will be performed during screening. If this is not feasible, we will use the primary tumor for HRD score assessment. At this time, we will not be offering screening germline testing to assess the presence of a deleterious BRCA1 or BRCA2 mutation nor the other HR pathway genes of interest in this trial. Patients who have already been identified as harboring a deleterious or suspected deleterious germline mutation in the HR pathway on multiplex germline panels (MyRisk, Ambry, InVitae, BROCA, or other CLIA approved assay) or those patients who had an deleterious or suspected deleterious HR pathway somatic mutation identified through next generation sequencing of their tumor (Foundation One or other CLIA approved assay) will be eligible for treatment in Cohort B. All patients will be asked to provide a blood sample to run the myRisk hereditary 25-gene panel for research purposes only.

Patients who are eligible for treatment in **Cohort A** include those who are BRCA1 and BRCA2 wild-type, have advanced TNBC and a tumor HRD score of ≥ 42.

Patients who are eligible for treatment in **Cohort B** include those who are BRCA1 and BRCA2 wild-type with HER2-negative advanced breast cancer or other non-breast solid tumors and either a deleterious or suspected deleterious germline or somatic mutation in HR pathway-related genes beyond BRCA1 and BRCA2. These genes include:

> PTEN; PALB2; CHEK2; ATM; NBN; BARD1; BRIP1; RAD50; RAD51C; RAD51D; MRE11; ATR; Fanconi anemia complementation group of genes (FANCA; FANCC; FANCD2; FANCE; FANCF; FANCG; FANCL); plus other HR-related genes at the discretion of the primary investigators.

The nominal duration of treatment is 36 cycles (28 days per cycle), but CR, PR, or SD patients may continue therapy until evidence of progressive disease or unacceptable toxicity occurs. Protocol therapy will be discontinued for progressive disease at any time. Patients are free to halt therapy at their request. Treatment may be discontinued if intercurrent co-morbidities occur, which, in the opinion of the treating physician, would preclude safe administration of study drugs

Patients will be scheduled for follow-up genetic counseling if actionable mutations are found.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

3.1 Eligibility Criteria and Participant Eligibility Checklist

Inclusion and Exclusion Criteria are provided on the Eligibility Checklist following, which is to be extracted from this document for use in screening potential subjects. For each prospective study participant that is screened, this checklist will be printed, completed in its entirety and the results recorded, and the checklist will be filed in the respective subject binder or file. It is anticipated that not all prospective study participants that are screened will be enrolled.

Pursuant to Stanford Medicine SOP "Confirmation of Participant Eligibility in Clinical Trials," the treating Physician (investigator); the Study Coordinator; and an Independent Reviewer will verify that the subject's eligibility is accurate; complete; and legible in source records. A description of the eligibility verification process will be included in the EPIC or other Electronic Medical Record progress note.

Participant Eligibility Checklist

Protocol Title:	A Phase 2 clinical trial of talazoparib in BRCA1 and BRCA2 wild-type patients with advanced triple-negative breast cancer and homologous recombination deficiency or advanced HER2-negative breast cancer or other non-breast solid tumors with a mutation in homologous recombination pathway genes
Protocol Number:	**IRB-31913 / BRS0050**
Principal Investigator:	Melinda Telli, MD
Co-Investigator:	Joshua Gruber, MD, PhD

II. Subject Information:

Subject Name/ID:

III. Study Information:

SRC-approved ☐ IRB-approved ☐

IV. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Individuals (men and women) aged 18 years or older	☐	☐	
2. Solid tumor by cohort as follows. **Cohort A**: Tumor must be histologically-confirmed triple-negative breast cancer (estrogen receptor (ER) ≤ 5%; progesterone receptor (PR) ≤ 5%; AND HER2-negative via IHC or FISH per 2013 ASCO/CAP guidelines), with homologous recombination deficiency (HRD) score of ≥ 42 from a metastatic biopsy site. In the event that metastatic tumor biopsy is not feasible, the HRD score can be assessed from the primary breast biopsy. **Cohort B**: Must be histologically-confirmed metastatic or recurrent HER2-negative breast cancer (IHC or FISH per 2013 ASCO/CAP guidelines) or other histologically-confirmed metastatic solid tumor. **Cohort B**: Tumor must have a deleterious or suspected deleterious germline or somatic gene mutation implicated in the HR pathway (excluding BRCA1 or BRCA2), based on multiplex germline gene testing or direct tumor next generation DNA sequencing. The genes include: PTEN; PALB2; CHEK2; ATM; NBN; BARD1; BRIP1; RAD50; RAD51C; RAD51D; MRE11; ATR; Fanconi anemia complementation group of genes (FANCA; FANCC; FANCD2; FANCE; FANCF; FANCG; FANCL); plus other HR-related genes at the discretion of the primary investigators.	☐	☐	

Inclusion Criteria (From IRB approved protocol)	Yes	No	Supporting Documentation*
3. No deleterious or suspected deleterious BRCA1 or BRCA2 gene mutation in the germline, based on comprehensive testing including full sequencing and comprehensive rearrangement testing at an external reference laboratory. Patients with variants of unknown significance will be eligible.	☐	☐	
4. Patients must have measurable disease per RECIST v1.1 (CT CAP with contrast and bone scan or PET/CT with IV contrast needed within 28 days of Cycle 1 Day 1. If patients have a history of brain metastases, a MRI-brain or CT-head with contrast is required.).	☐	☐	
5. Must have progressed on at least 1 prior systemic therapy regimen for the treatment of advanced breast or other non-breast metastatic cancer. There is no upper limit on the number of prior therapies.	☐	☐	
6. No evidence of progression on a platinum agent (eg, carboplatin or cisplatin) or within 8 weeks of stopping platinum	☐	☐	
7. An ECOG performance status of 0 to 2	☐	☐	
8. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq$ 2.5 x upper limit of normal (ULN); if liver function abnormalities are due to hepatic metastasis, then AST and ALT $\leq$ 5 x ULN	☐	☐	
9. Total serum bilirubin $\leq$ 1.5 x ULN ($\leq$ 3 x ULN for Gilbert's syndrome)	☐	☐	
10. Calculated creatinine clearance $\geq$ 30 mL/min or serum creatinine $\leq$ 1.5 mg/dL	☐	☐	
11. Hemoglobin $\geq$ 9.0 g/dL with last transfusion at least 14 days before Day 1 of study drug	☐	☐	
12. Absolute neutrophil count (ANC) $\geq$ 1500/mm^3	☐	☐	
13. Platelet count $\geq$ 100,000/mm^3	☐	☐	
14. Able to take oral medications	☐	☐	
15. Willing and able to provide written, signed informed consent after the nature of the study has been explained, and prior to any research-related procedures	☐	☐	
16. Sexually-active patients of childbearing potential must be willing to use an acceptable method of contraception such as an intrauterine device or double barrier contraception during treatment and for 45 days after the last dose of study drug (hormonal contraception is not considered an acceptable method of contraception)	☐	☐	

Inclusion Criteria (From IRB approved protocol)	Yes	No	Supporting Documentation*
17. If pre-menopausal, females of childbearing potential must have a negative urine pregnancy test at screening and be willing to have additional urine pregnancy tests during the study. Females considered not of childbearing potential include those who have had no menstrual period for at least 2 years, or had tubal ligation at least 1 year prior to screening, or who have had total hysterectomy	☐	☐	
18. Willing and able to comply with all study procedures	☐	☐	
19. Availability of archival tumor tissue from primary breast cancer	☐	☐	
20. Adequate fresh or archival tumor tissue from metastatic biopsy site, if biopsy is technically feasible	☐	☐	

Exclusion Criteria (From IRB approved protocol)			
1. Prior progression on or within 8 weeks of the last dose of a platinum agent (ie, cisplatin or carboplatin) for recurrent or metastatic disease.	☐	☐	
2. Any patient with a deleterious or suspected deleterious BRCA1 or BRCA2 gene mutation	☐	☐	
3. Prior treatment with a PARP inhibitor	☐	☐	
4. Pregnant or lactating	☐	☐	
5. Any anti-cancer therapy within the 21 days before the first day of treatment	☐	☐	
6. Prior progression on or within 8 weeks of the last dose of a platinum agent (ie, cisplatin or carboplatin) for recurrent or metastatic disease	☐	☐	
7. Brain or CNS metastases OR leptomeningeal carcinomatosis. EXCEPTION: Adequately treated brain metastases documented by baseline CT or MRI scan that have not progressed since previous scans and do not require corticosteroids (prednisone ≤ 5 mg/day or equivalent allowed) for management of CNS symptoms. A repeated CT or MRI following the identification of CNS metastases (obtained at least 2 weeks after definitive therapy) must document adequately-treated brain metastases	☐	☐	
8. Other malignancy that is either active or for which patient has received treatment in the last 5 years excluding non-melanoma skin cancer and carcinoma in situ of the cervix	☐	☐	
9. Radiation therapy in the last 14 days	☐	☐	

Exclusion Criteria (From IRB approved protocol)			
10. Known to be human immunodeficiency virus (HIV)-positive	☐	☐	
11. Either known active hepatitis B or hepatitis C virus infection	☐	☐	
12. Use of any investigational product (IP) or investigational medical device within 28 days before Day 1 of study drug	☐	☐	
13. Major surgery requiring a prolonged hospitalization or recovery within 21 days before Day 1 of study drug	☐	☐	
14. Concurrent disease or condition that would interfere with study participation or safety, such as any of the following: o Active, clinically-significant infection either Grade > 2 by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5 or requiring the use of parenteral anti-microbial agents within 7 days before Day 1 of study drug o Clinically-significant bleeding diathesis or coagulopathy, including known platelet function disorders	☐	☐	
15. Known hypersensitivity to any of the components of talazoparib	☐	☐	

*All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

3.2 Informed Consent Process

All patients must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

3.3 Randomization Procedures

Patients will not be randomized in this study, as it is an open-label single arm trial consisting of 2 cohorts, both of which will receive the study drug. At least 10 HER2-negative breast cancer patients will be enrolled in Cohort B.

3.4 Study Timeline

Primary Completion: The study will reach primary completion 36 months from the time the study opens to accrual. This is the estimated time of accrual of the last patient (number 20) in each cohort.

Study Completion: The study will reach study completion 36 months from the time the study opens to accrual.

4. TREATMENT PLAN

4.1 Screening Procedures

Informed consent must be documented before any trial-specific procedures or treatments are conducted. This study will have a molecular pre-screen consent for Cohort A to assess the HRD score using FFPE tumor tissue evaluated by the Myriad HRD assay. All patients who meet eligibility criteria based on the pre-screen consent will be provided a written main study informed consent document. At this time we will not be offering screening for germline or somatic mutations in the HR pathways genes of interest. All patients enrolled in Cohort B of this trial will have a known deleterious or suspected deleterious germline or somatic mutation in a gene of interest prior to study enrollment.

The following screening procedures will be performed on subjects consenting for molecular pre-screening for Cohort A:

- Determination of HRD score based on formalin fixed paraffin embedded (FFPE) metastatic tumor site core biopsy. If the patient does not have an adequate tumor biopsy sample from a metastatic site, biopsy will be performed during screening. If this is not feasible, we will use the primary tumor for HRD score assessment.

The following screening procedures will be performed on consented and eligible subjects after the main study consent is signed within 28 days of initiating study treatment:

- Medical history
- Complete physical examination, including height and weight
- Vital sign assessment, including blood pressure and pulse
- Eastern Cooperative Oncology Group (ECOG) Performance Status assessment

- Laboratory evaluation, including CBC with differential, comprehensive metabolic panel, and urine pregnancy test
- Pathology review (including review of ER/PR/HER2 for breast cancers) of tumor from metastatic site or a biopsy of metastatic site, if not done previously.
- CT scan with IV contrast of chest, abdomen, and pelvis or PET/CT scan with IV contrast for complete disease evaluation. Continue to use the same evaluation method during the study as used for initial evaluation
- MRI brain or CT head, if prior history of brain metastases
- For patients eligible for Cohort B, determination of HRD score based on formalin fixed paraffin embedded (FFPE) metastatic tumor site core biopsy is required, but is not needed for eligibility and does not need to be reported prior to treatment initiation. If the patient does not have an adequate tumor biopsy sample from a metastatic site, biopsy will be performed during screening. If this is not feasible, we will use the primary tumor for HRD score assessment.
- Research germline blood collection
- Research MyRisk germline blood collection
- Research plasma collection
- Submission of archival tumor tissue from the primary breast tumor

4.2 Dosing and Administration Schedule

NOTE: 1 cycle = 28 days

Talazoparib will be administered at 1 milligram orally daily. Talazoparib should be taken at approximately the same time each day. Talazoparib will be taken orally and swallowed whole.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded. Medication labels will comply with US legal requirements and be printed in English. They will supply no information about the patient.

The IP is talazoparib, a white to off-white crystalline powder. The drug substance is a 4-methylbenzenesulfonate (tosylate) salt of talazoparib free base, the active moiety. The drug product consists of the drug substance formulated with a pharmaceutically-suitable excipient filled into hydroxymethylpropylcellulose capsules. Capsules will be provided to the site in 3 dose strengths of 0.10 mg, 0.25 mg, and 1.0 mg capsules. The dose strengths are based on the active moiety (talazoparib free base). The capsules are provided in dose-specific colors to provide a visual method of distinguishing dose strengths. Study drug should be stored at room temperature (15 to 30°C; 59 to 86°F). The capsules are supplied in 30-count induction-sealed high-density polyethylene (HDPE) bottles.

The investigator should promote compliance by instructing the patient to take the study drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed.

Capsules

The capsules should be swallowed whole with a glass of water and should not be chewed or crushed. If vomiting occurs, no attempt should be made to replace the vomited dose. Patients should be instructed that if they miss a dose on one day, they must not take any extra dose the next day, but instead to immediately contact the study center as soon as possible to ask for advice.

Patients may continue concomitant medications for other conditions and any additional appropriate supportive care medications or treatments.

4.3 Pre-Treatment Evaluations

Patients will be evaluated in clinic on Day 1 of each cycle. For the first cycle, we will also require a mid-cycle physician's visit. Furthermore, weekly CBC with diff will be required for the first cycle (q7 days +/- 3 days) and biweekly (q14 days +/- 3 days) CBC with diff will be required for the second cycle. Subsequent to this, we will only require a CBC with diff per cycle (q4 weeks +/- 3 days). Laboratory tests can be performed externally and faxed to the PI/research team. The following assessments will be performed at each physician's visit:

- Physical examination, including weight
- Vital signs, including blood pressure, pulse, and temperature
- ECOG Performance Status assessment
- Clinical laboratory tests: CBC with differential and comprehensive metabolic panel
- Urine pregnancy test (female subjects of childbearing potential)
- Assessment of concomitant medications
- Assessment of adverse events and dose modifications as necessary. Adverse events should be monitored continuously
- Tumor evaluation with imaging every 2 cycles (8 weeks +/- 1 week)

4.4 End of Treatment Procedures

If patients are no longer receiving treatment, the assessments should be completed within 30 days of the last dose of talazoparib.

- Physical examination, including weight
- Vital signs, including blood pressure, pulse, and temperature
- ECOG Performance Status assessment
- Clinical laboratory tests: CBC with differential, comprehensive metabolic panel
- Urine pregnancy test (female subjects of childbearing potential)
- Assessment of adverse events
- Study drug compliance (pill diary)

4.5 General Concomitant Medication and Supportive Care Guidelines

Concomitant treatment is permitted if the medication is not expected to interfere with the evaluation of safety or efficacy of the study drug. During the study, if the use of any concomitant treatment becomes necessary (eg, for treatment of an adverse event), the treatment must be documented, including the reason for treatment, generic name of the drug, dosage, route, and start and stop dates of administration.

All supportive measures consistent with optimal patient care will be given throughout the study.

The clinical tolerance of the patient, the overall tumor response, and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or discontinue treatment. If treatment is discontinued due to any toxicity, the patient must be followed to monitor duration of toxicity, response and time to progression or survival and initiation of any new systemic therapy.

4.6 Duration of Therapy and Follow-Up

The nominal duration of treatment is 36 cycles (28 days per cycle), but CR, PR, or SD patients will continue therapy until evidence of progressive disease or unacceptable toxicity occurs. Protocol therapy will be discontinued for progressive disease at any time. Patients are free to halt therapy at their request. Treatment may be discontinued if intercurrent co-morbidities occur, which, in the opinion of the treating physician, would preclude safe administration of study drugs.

4.7 Criteria for Removal from Study

Patients MUST be discontinued from study therapy AND be withdrawn from the study for the following reasons:

- Withdrawal of the patient's consent (patient's decision to withdraw for any reason)
- Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Inability to comply with protocol
- Discretion of the investigator
- Disease progression (patient continue to be followed for survival)
- Death

If a subject is withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form.

4.8 Alternatives

Alternatives to participation in this clinical trial include use of chemotherapeutic agents for the treatment of metastatic triple-negative breast cancer. Alternatives for metastatic ER and/or PR-positive, HER2-negative breast cancer include anti-estrogen therapy and chemotherapeutic agents.

4.9 Compensation

Patients may be eligible for travel and meal reimbursement if they live more than 50 miles from study site.

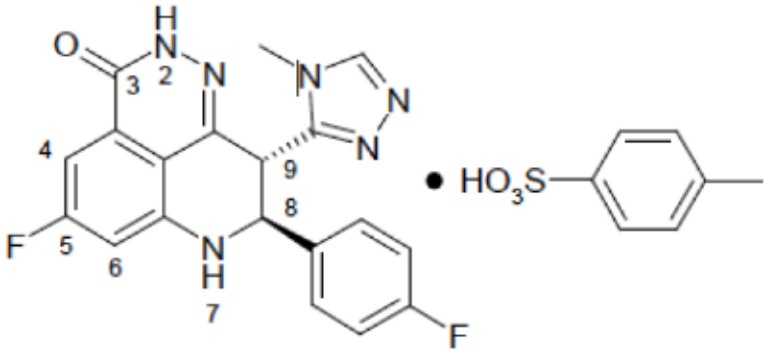
5. INVESTIGATIONAL AGENT/DEVICE/PROCEDURE INFORMATION

5.1 Investigational Agent

Please note that more complete information can be obtained from the Investigator's Brochure (IB).

Talazoparib is a novel poly(ADP-ribose) polymerase (PARP) inhibitor. The active ingredient is talazoparib; the chemical name is 3*H*-Pyrido[4,3,2-de]phthalazin-3-one, 5-fluoro-8-(4-fluorophenyl)-2,7,8,9-tetrahydro-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-, (8***S***,9***R***)-, 4-methylbenzenesulfonate (1:1).

Chemical structure of talazoparib:



BMN-673ts

Molecular Formula (talazoparib): C26H22F2N6O4S

Molecular Weight (talazoparib): 552.5624

Talazoparib is manufactured by chemical synthesis in accordance with current Good Manufacturing Practices (cGMP). The drug product is a capsule formulation comprised of a blend of talazoparib drug substance and silicified microcrystalline cellulose filled into a hypromellose capsule. The capsule is presented in four strengths – 25-µg; 50-µg; 250-µg; or 1-mg talazoparib free base equivalent – that are distinguished either by capsule color or size.

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

5.2 Pharmacodynamic Properties

Primary PD studies assessed talazoparib and related compounds for *in vitro* and *in vivo* pharmacological activities. Assessment of talazoparib effects in tumor cell incubations revealed selective and potent cytotoxicity in human cancer cell lines harboring mutations that compromise DNA repair pathways. Gene mutations that confer selective tumor cell cytotoxicity included

BRCA1 (MX-1 mammary tumor cells); BRCA2 (Capan-1 pancreatic tumor cells); PTEN (MDA-MB-468 mammary; LNCap and PC-3 prostate tumor cells); and MLH-1 mutations (HCT-116 colorectal tumor cells). The IC_{50} values of talazoparib in these tumor cell lines were in the single digit nanomolar or sub-nanomolar range. In contrast, the IC_{50} of talazoparib against normal human primary cell MRC-5 and several tumor cell lines that do not have reported DNA repair-related mutations are significantly greater (250 nM to > 1000 nM).

5.3 Pharmacokinetic Properties

The pharmacokinetic (PK) results for the dose escalation phase of PRP-001 have been assessed with preliminary concentration data from 25 µg/day through 1100 µg/day. In cycle 1, samples were collected for a week after the first single dose (Day 1) of a cohort, pre-dose samples were collected during daily dosing (troughs), and samples were collected for a week after the last dose in cycle 1 (Day 35). Following a single dose (Day 1), mean plasma C_{max} and $AUC_{0\text{-}24hr}$ ranged from 60.0 to 13,200 pg/mL and from 953 to 92,100 pg-hr/mL, respectively, over the 25 to 1100 µg dose range. Following multiple daily dosing (Day 35), mean plasma C_{max} and $AUC_{0\text{-}24hr}$ ranged from 300 to 23,400 pg/mL and from 3960 to 203,000 pg-hr/mL, respectively, over the 25 to 1100 µg/day dose range. At the defined maximum tolerated dose (MTD) of 1000 µg/day, mean (SD) C_{max} and $AUC_{0\text{-}24hr}$ were 21,000 (7,990) pg/mL and 203,000 (54,800) pg-hr/mL, respectively, on Day 35. The plasma profiles indicate enterohepatic cycling of talazoparib because of the additional concentration peaks beyond T_{max}. Elimination appears to be bi-exponential. Mean talazoparib $t_{1/2}$ ranged from 53.5 to 234 hours and from 40.4 to 115 hours on Day 1 and Day 35, respectively. At the upper end of the dose range evaluated (900 to 1100 µg), $t_{1/2}$ ranged from 53.5 to 66.1 hours and from 40.4 to 51.8 hours on Day 1 and Day 35, respectively. Steady state was apparent in most patients by two weeks with daily dosing. Accumulation based on $AUC_{0\text{-}24hr}$ was observed for all patients comparing Day 35 with Day 1 and mean values ranged from 2.42 to 9.92 and from 2.42 to 3.69 across the 25 to 1100 µg dose range and the 900 to 1100 µg dose range, respectively. Following single doses, talazoparib C_{max} and $AUC_{0\text{-}24hr}$ were linear between 400 and 1100 µg. Following multiple doses, talazoparib C_{max} and $AUC_{0\text{-}24hr}$ were linear between 25 and 1100 µg/day.

A food effect study (673-103) in 18 healthy volunteers has been completed. This study showed that while a high-fat, high calorie meal delayed the absorption of orally administered talazoparib, it did not affect the overall extent of the absorption. Based on these findings, talazoparib can be administered without regard to food.

5.4 Supplier

The investigational agent, talazoparib, will be provided by Pfizer Pharmaceutical, Inc.

5.5 Dosage Form

Talazoparib will be supplied as capsules for oral administration.

5.6 Agent Ordering and Packaging

Requests for shipments of the investigational agent will be coordinated by the study coordinator directly with Pfizer Pharmaceutical, Inc. Bottles will contain a sufficient number of capsules for one cycle of dosing.

5.7 Storage and shelf life

Stability data obtained for both prototype and clinical drug product batches currently support retest dating of 36 months for drug product. Both drug product and drug substance exhibit excellent stability trends. The drug product is stored at room temperature (15 to 30 deg C; 59 to 86 deg F) and should be protected from light.

5.8 Nature and Contents of Container

The capsules are packaged in perforated unit-dose blister cards composed of cold form aluminum foil and push through aluminum lidding. The 4 capsule strengths are packaged into the same blister card design. Additionally, 250-µg capsules (opaque white, size 4) are packaged in 30-count HDPE bottles with an induction seal and child-resistant cap.

5.9 Special Precautions for Disposal and Other Handling

Any unused product or waste material is to be disposed of in accordance with local requirements.

6. DOSE MODIFICATIONS

Daily dosing of talazoparib can be interrupted for recovery from toxicity for up to 28 days. Thereafter, treatment at the same or a reduced dose can be considered based on the discretion of the primary investigator if the subject has not developed progressive disease. Dose modifications should be made based on observed toxicity as follows:

- Grade 1 or 2 toxicity: No requirement for dose interruption or dose reduction. If the toxicity persists at Grade 2, a dose reduction to the next lower dose level (eg, from 1.0 mg/day to 0.75 mg/day) may be implemented at the discretion of the Investigator
- Grade 3 toxicity: Daily dosing should be stopped. Talazoparib dosing may resume at the next lower dose level (eg, from 1.0 mg/day to 0.75 mg/day; 0.75 mg/day to 0.5 mg/day; 0.25 mg/day to 0.10 mg/day) when toxicity resolves to Grade 1 or returns to baseline
- Grade 4 toxicity: Daily dosing should be stopped. Talazoparib may resume at a lower dose level (1 to 2 dose level decrease) with the approval of the PI when toxicity resolves to Grade 1 or returns to baseline

Table 3. Dose modifications for toxicities

	Dose Level
Initial dose level	1.0 mg/day
First dose level reduction	0.75 mg/day
Second dose level reduction	0.5 mg/day
Third dose level reduction	0.25 mg/day
Fourth dose level reduction	0.10 mg/day

Talazoparib will be permanently discontinued for individual subjects as a result of any unresolved Grade 3 or Grade 4 toxicity or based on a decision by the subject or Investigator that continued talazoparib treatment is not in the subject's best interest.

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Potential Adverse Events

According to the ICH definition, an adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, and that does not necessarily 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 a medicinal (investigational) product, whether or not considered related to the investigational product.

This definition includes intercurrent illnesses or injuries that represent an exacerbation (increase in frequency, severity, or specificity) of pre-existing conditions. Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of terms relating to a diagnosis. Adverse event information will be collected in an ongoing fashion through patient reporting AEs to their physician or health care provider. Seriousness and relatedness will be assessed by the treating physician, with appropriate reporting.

A designated primary contact person based at the treatment center will be responsible for the collection and reporting of AEs for patients participating in the program.

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 4)
- Its duration (start and end dates or if continuing at the Safety Follow-up Visit)
- Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, hospitalized, unknown, not applicable)
- Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- Outcome (not recovered/not resolved; recovered/resolved; recovering/resolving; recovered/resolved with sequalae; fatal; unknown)
- Whether it is serious, where a serious adverse event (SAE) is defined as in Section 7.1.2

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigators' Brochure. This information should be included in the patient informed consent and should be discussed with the patient during the study as needed. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Given other drugs in this class have been associated with hematologic malignancies, such as myelodysplastic syndrome (MDS) and acute leukemias, any prolonged cytopenias, defined as greater than 6 weeks, will be thoroughly evaluated including referral to hematology clinic, where routine procedures including bone marrow biopsy, if deemed appropriate, will be conducted.

7.1.1 Laboratory test abnormalities

Laboratory abnormalities that constitute an Adverse Event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (eg, anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol and is still, by definition, an adverse event.

7.1.2 Serious Adverse Events (SAE)

A serious adverse event is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug

- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, ie, defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

7.1.3 Pregnancy

If a patient becomes pregnant during the study, study drug administration must be discontinued and the pregnancy must be reported immediately (within 24 hours of becoming aware of the pregnancy) to Pfizer Safety portal system by using the FDA 3500A (MedWatch Form). Every effort should be made to follow the patient through resolution of the pregnancy (termination or delivery) and report the resolution of the FDA 3500A (MedWatch Form) to Pfizer Safety portal system ([redacted]).

7.2 Adverse Event and Pregnancy Reporting

Adverse events will be graded according to CTCAE v5. Both Serious and Non-Serious Adverse Events will be clearly noted in source documentation and listed on study specific Case Report Forms (CRFs). The Protocol Director (PD) or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Informed Consent, Protocol Document, or Investigator's Brochure, and related to the investigation. All Serious Adverse Events (SAEs) will be tracked until resolution, or until 30 days after the last dose of the study treatment.

SAEs CTCAE Grade 3 and above, and all subsequent follow-up reports will be reported to the Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) using the study specific CRF within 24 hours of notification of event regardless of the event's relatedness to the investigation. Please follow steps in Appendix B: Stanford Cancer Institute SAE reporting guidelines for investigator-initiated trials.

In investigator IND studies, talazoparib serious, related, unlabeled, (unexpected) adverse events will be reported to the FDA as required by 21 CFR§312.32 by the Investigator within 24 hours of notification of the event. The MedWatch Form (Form 3500A Mandatory Reporting) and FDA Form 1571 must be completed and sent to the FDA.

All SAEs (expected or unexpected, causally related or not) and pregnancy reports must also be reported to Pfizer Safety portal system, [redacted], and faxed to Pfizer [redacted] within 24 hours of the Investigator's awareness. Pfizer will review the AE data as documented in the site's final study report.

For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer.

The period during which all non-serious AEs and SAEs will be reported begins after informed consent is obtained and will continue through 30 days after the last study visit or 30 days after the last dose of study medication, whichever comes first.

7.3 Product Complaints Reporting

A product complaint ("Complaint") is any direct, written, electronic, or oral communication of dissatisfaction that alleges deficiencies related to the identity, quality, durability, labeling, purity, stability, appearance, effectiveness, safety, and/or design of a drug product after it is released for distribution.

Complaints that simultaneously fall under Adverse Event definitions under this Protocol need only be reported via the Adverse Event reporting procedure set forth in this Protocol.

Investigator or designee (Reporter) shall capture the following Complaint information as relates to talazoparib (BMRN 673) used under this Protocol:

- Date complaint received
- Product Name and Lot Number
- Indicate if the product is available for return to Pfizer for investigation
- Quantity Affected
- Detailed Description of complaint
- Study Protocol Number
- Investigator Name
- Site Contact
- Site Number
- Subject Number
- Name and contact information of the person who is reporting the complaint as well as name and contact information of the complainant. The reporter will be contacted by Pfizer Product Complaint Quality Assurance Department.

Investigator or designee (Reporter) will use his or her best efforts to report Complaints to Pfizer within five days of learning of the Complaint. Investigator or designee will submit the complaint information by email.

8. CORRELATIVE STUDIES

This study is designed to assess hereditary and somatic defects in genes that support homologous recombination double-strand break repair defects beyond BRCA and their implication in tumorigenesis. The goal is to use such identifiable defects as biomarkers to tailor drug therapy utilizing the principle of synthetic lethality; in this case with talazoparib, a potent PARP inhibitor. Correlative studies will be conducted to assess underlying germline mutations, genomic instability as assessed by the tumor HRD score, and response to drug. All participants will be asked to provide a blood sample to run the myRisk hereditary 25-gene panel on a research basis. The myRisk hereditary 25-gene panel evaluates a broad number of hereditary cancer syndromes including several genes implicated in HR double-stranded DNA repair. A separate research germline blood sample and plasma sample will also be collected. Furthermore, all participants will be asked to provide an adequate metastatic tumor biopsy to assess the HRD score based on the HRD assay and RAD51 status. Only in cases where a metastatic biopsy is not technically feasible will the HRD score or RAD51 status be assessed on the primary tumor. All subjects will be asked to submit an archival sample of their primary breast tumor. The RAD51

status of the tumor will be assessed using immunohistochemistry at baseline (absent or present) as a functional readout of HR capacity and this will be correlated with HRD status.

All correlative endpoints will be measured using univariate and multivariate logistic regression models, recognizing that these are exploratory analyses and thus may be insufficiently powered for statistical purposes. For specific correlative endpoints and the statistical methods used for evaluation, please refer to Section 12.3.

Tissue biopsies, whole blood and plasma will be sampled in this study. They will be stored and may be used for future research purposes provided the patient has given his/her consent. All such samples will be labeled with a unique numeric identifier that will be coded for patient privacy. Only authorized study personnel will have access to these tissues. If the patient declines this option, remaining tissue and blood will be discarded after specified correlative study procedures have been performed.

9. STUDY CALENDAR

	Pre-Study Screening	Cycle 1 (1 cycle = 28 days) +/- 3 days				Cycle 2 (1 cycle = 28 days) +/- 3 days		Cycle 3 to 36 (1 cycle = 28 days) +/- 3 days	End of Study [b]
	Days -28 to 0	D1	D8	D15	D22	D1	D15	D1	
Informed consent	X								
Demographics	X								
Medical history	X								
Family history	X								
Concurrent meds	X								
Talazoparib dispensing and daily dosing for 28 days starting cycle Day 1		X				X		X	
Physical exam	X	X		X		X		X	X
Vital signs	X	X		X		X		X	X
Height	X								
Weight	X	X		X		X		X	X
Performance status	X	X		X		X		X	X
CBC w/diff (+/- 3 days)	X	X	X	X	X	X	X	X	X
Serum chemistry [a] (+/- 3 days)	X	X		X		X		X	X
Adverse event evaluation		X		X		X		X	X
Urine pregnancy (women of childbearing potential)	X	X				X		X	X
Assessment of HRD score using HRD assay from core biopsy of metastatic site. If an adequate metastatic biopsy is not available, a fresh biopsy will be performed. Results are required prior to treatment initiation for Cohort A only.	X								
Submission of archival tumor sample of primary tumor	X								
Myriad MyRisk blood collection	X								
Whole blood collection	X								
Plasma collection	X								X
Tumor measurements	X	Tumor measurements are repeated every 8 weeks through cycle 8 (option to repeat every 12 weeks after cycle 8). Documentation must be provided for patients removed from study for progressive disease.							X
Radiologic evaluation (CT with IV contrast and bone scan or PET CT with IV contrast, plus MRI brain or CT head if history of brain metastases).	X	Radiologic measurements should be performed every 8 weeks ± 1 weeks. There is the option to decrease radiologic evaluation to every 12 weeks after cycle 8.							X

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

b. To be collected at first clinic visit after evidence of disease progression (± 7 days).

10. MEASUREMENTS

10.1 Primary Endpoint

The objective response rate of talazoparib defined as complete response or partial response per RECIST v1.1

Objective response rate is defined as complete response or partial response and determined by RECIST v1.1 criteria. All study participants will have measurable disease at study initiation.

Objective responses are defined using RECIST v.1.1 criteria:

- 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 diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of 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 progression)

Confirmation of a response requires a repeat observation at least 4 weeks apart.

For the purposes of this study, patients should be evaluated for response at 8 weeks +/- 1 week, then re-evaluated for response every 8 weeks +/- 1 week, or sooner if there is a clinical or laboratory finding that is concerning for disease progression. The type of imaging modality is dependent on sites of metastases but will mainly consist of CT chest, abdomen and pelvis with contrast and bone scan or PET CT with IV contrast. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before initiation.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). [29] Changes in the largest diameter (uni-dimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria. The Eisenhauer 2009 European Journal of Cancer manuscript details the complete description of RECIST v1.1 criteria for response assessment and will be followed for this study.

10.2 Secondary Endpoints

10.2.1 Clinical benefit rate ≥ 24 weeks

This is defined as complete response, partial response or stable disease as assessed after at least 24 weeks on the investigational drug. Response and progression will be evaluated using RECIST guideline v1.1. Imaging will be performed every 8 weeks.

10.2.2 Progression-free survival

Progression-free survival is defined as the time from randomization to documented disease progression or death. Patients without progression at the end of the study will be censored at the date of their last radiographic evaluation.

10.2.3 Safety of talazoparib in this study population

All adverse events will be graded according to CTCAE v5.

10.3 Correlative Endpoints

10.3.1 Objective response rate in subjects with TNBC with or without an underlying germline HR pathway mutation in Cohort A

The 25-gene MyRisk germline mutation panel will be performed on all subjects on a research basis in Cohort A. Objective response rates by RECIST v1.1 will be compared in subjects with and without an identified HR pathway gene mutation of interest.

10.3.2 Correlation of HRD scores with response in subjects with underlying deleterious or suspected deleterious germline or somatic HR gene mutations in Cohort B

The HRD score is a continuous measurement (0 to 100) that will be assessed from metastatic FFPE tumor tissue using the Myriad HRD assay on a research basis in subjects enrolled on Cohort B. Based on prior studies, an HRD cutoff score of 42 or higher will be used to define HR-deficient breast cancer. We will correlate the mean HRD scores and dichotomous HRD scores (HRD deficient versus HRD intact) with therapy response.

10.3.3 Correlation of HRD scores in the primary tumor tissue and the metastatic tumor tissue.

All subjects will have both metastatic and archival primary breast tumor samples assessed for HRD. We will assess the correlation of scores (mean and dichotomous scores) for these two tumor sample types within each patient. Patients in whom a metastatic biopsy was deemed not feasible will be excluded.

10.3.4 Correlation of RAD51 status in the metastatic tumor with HRD and mutational status.

RAD51 by immunohistochemistry as a functional readout of HR capacity will be assessed in baseline FFPE metastatic tumor biopsy samples. RAD51 status, absent or present, will be correlated with HRD and mutational status.

11. REGULATORY CONSIDERATIONS

11.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (eg, advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

11.2 Data and Safety Monitoring Plan

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms,

eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

11.3 Data Management Plan

Electronic Case Report Forms (CRFs) will be used to record all protocol-related information on each trial participant. CRFs will summarize the clinical findings and observations necessary to ensure safety of participants on the study, and to document the study outcomes.

RedCap Electronic Case Report Forms (eCRF) will be used to record all protocol-related information on each trial participant. A CRF will be completed for each enrolled study participant. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the participant's CRF. Source documentation supporting the CRF data should indicate the patient's participation in the study and should document the date and details of study procedures, AEs, other observations and patient status.

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. The study data for each enrolled participant will be entered into a CRF by site personnel using a secure, validated, web-based electronic data capture application. Any changes to study data will be made to the CRF and documented in an audit trail that will be maintained within the clinical database.

12. STATISTICAL CONSIDERATIONS

12.1 Analytic Plan for Study Objectives

12.1.1 Primary Objective

To determine the objective response rate, defined as complete response or partial response per RECIST 1.1, the objective response rate and 95% confidence interval will be calculated using the exact binomial model.

12.1.2 Secondary Objectives

To determine the clinical benefit rate, defined as complete response, partial response or stable disease $\geq$ 24 weeks per RECIST v1.1, the clinical benefit rate and 95% confidence interval will be calculated using the exact binomial model.

To determine progression-free survival, Kaplan-Meier curves will be calculated, along with a 95% confidence interval for PFS at one year, calculated using Greenwood's formula.

To assess safety of talazoparib in this study population, adverse events will be graded using CTCAE v5 and summarized descriptively as described in Section 7.1.

12.1.3 Correlative Objectives

In correlating HRD score (ranging over 0 to 100) with a binary variable such objective response status, RAD51 status and so on, we will calculate the mean and standard deviation of HRD score in the two subsets and evaluate the strength of the association using the Wilcoxon rank sum statistic.

In evaluating the concordance of HRD score in the primary tumor and HRD in the metastatic tumor, the Wilcoxon signed rank test will be used.

All remaining comparison involve correlating two binary variables, which will be done by presenting proportions with 95% exact confidence intervals. The significance of the correlation will be assessed using Fisher's exact test. A two-sided P value of 5% or less will be considered statistically significance.

The proportion of specific mutations with its 95% confidence interval will be calculated using the exact binomial model.

12.2 Analysis population

Safety analysis will be conducted on all patients who received at least one dose of trial therapy. Efficacy analysis will be performed on all patients who receive at least 1 cycle of therapy unless the reason for completing less than 1 cycle of therapy was attributable to disease progression. Patients who come off trial before completing 1 cycle of therapy for reasons other than disease progression will be considered non-evaluable for response and will be replaced.

12.3 Sample Size Calculations

This phase 2 proof-of-concept trial is an open-label study in patients with advanced, HER2-negative breast cancer or non-breast metastatic cancer. A two-stage design will be used for enrollment of study participants separately in Cohort A and in Cohort B with a set null hypothesis of $\leq 5\%$ objective response rate and alternative response rate of $\geq 30\%$ based on standard RECIST v1.1 criteria.

Interim analysis will be performed, separately in each cohort, after accrual of 10 patients and have had at least one response assessment in that cohort. Patients will be observed for responses every 8 weeks +/- 1 week. If at least two out of the 10 patients responds, then we will accrue 10 additional patients for a total of 20 patients in each cohort (total number of patients for the trial = 40). Based on our statistical constraints, at least 3 patients out of the 20 respond in each cohort to declare statistical significance at a one-sided 5% level with 80% power or better

12.4 Accrual Estimates and Feasibility

We see > 75 new patients with advanced, triple-negative breast cancer at the Stanford Women's Cancer Center each year and from 2009 to 2013 have consistently enrolled > 25 patients per year to triple-negative specific clinical trials. Based on our previous neoadjuvant study utilizing the HRD assay, approximately half of sporadic, triple-negative breast cancer patients have an HRD score that is greater than or equal to 42. As such we are confident that we can accrue our patients in the projected timeline provided.

Given that the utilization of multiplex gene panels to assess germline mutations in the HR repair pathway has recently emerged and because the use of tumor NGS is just recently on the rise, we have no historical measures to help estimate the number of patients we will be accrue in Cohort B within our single institution. That being said, we are encountering an increasing number of these patients through our Cancer Genomics Program. We will work closely with the hereditary cancer non-profit organization FORCE to publicize this trial. Should accrual be limited, we will consider adding additional study sites to complete this cohort accrual.

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APPENDICES

APPENDIX A: SAE Reporting Guidelines; SCI SOP 10-16-2014

HOW TO REPORT SERIOUS ADVERSE EVENTS (SAEs)

IN INVESTIGATOR-INITIATED TRIALS

☐ 1. Determine if the event meets criteria for SAE in Study protocol and Stanford SOP (all SAEs Grade 3 and above, must be submitted to CCTO/Stanford).

☐ 2. Complete ALL fields of CCTO SAE Case Report Form (CRF) and verify with investigator.

☐ 3. Confirm with investigator SAE grade, Expected or Unexpected and Attribution.

☐ 4. Obtain investigator signature on the form after filling out all the information.

☐ 5. Send signed CCTO SAE form to [redacted] via SECURE email within 24 hours of notification of the event. CCTO Safety will enter it into OnCore.

☐ 6. Verify with investigator if the SAE is Unanticipated Problem (UP: unexpected, related to research and harmful) and report it to IRB, within 24 hours of notification of the event.

- Click on report in eProtocol.
- Upload the complete SAE report.
- Fill out eProtocol report form.
- Click on "Submit protocol" button on the left.

☐ 7. If SAE is not UP, then report during next IRB renewal.

For Investigator-initiated study with an IND and If SAE is Unanticipated Problem (UP) then report to FDA within 24 hours of notification of the event

☐ 8. Complete MedWatch Form (Form 3500A). The form MUST be typed! For assistance contact [redacted]. Actual link for the form:

https://www.pdffiller.com/en/project/150700520.htm?f_hash=7a4e5d&reload=true

☐ 9. With assistance from the regulatory facilitator, send the completed MedWatch form and FDA Form 1571 to the FDA following the website instructions.

☐ 10. If required, notify manufacturer. De-identify applicable source documents: MD notes (admission, progress note, discharge note, and date of death if available), laboratory reports, radiology reports, medical administration records.

☐ 11. Send signed CCTO SAE form and de-identified source documents.

☐ 12. File SAE report in patient research chart.

☐ 13. Follow SAE and submit updated reports to Stanford and/or Sponsor until:

- Resolution of event.
- Resolution of event with sequelae.
- Death of patient.

Unless otherwise specified by sponsor