# A Pilot Study of Talazoparib as a Neoadjuvant Study in Patients with a Diagnosis of Invasive Breast Cancer and a Deleterious BRCA Mutation

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**List of Abbreviations**

| | |
|---|---|
| AE | Adverse Event |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| b.i.d. | bis in diem/twice a day |
| Chem-12 | Comprehensive metabolic panel |
| CRF | Case Report/Record Form |
| CS&E | Clinical Safety and Epidemiology |
| CR | Clinical Research |
| CRO | Contract Research Organization |
| DFS | Disease-free survival |
| ECG | Electrocardiogram |
| IEC | Independent Ethics Committee |
| i.v. | intravenous(ly) |
| IRB | Institutional Review Board |
| LFT | Liver Function Test |
| o.d. | omnia die/once a day |
| OS | overall survival |
| pCR | pathologic complete response |
| p.o. | per os/by mouth/orally |
| PST | preoperative systemic therapy |
| RCB | residual cancer burden |
| REB | Research Ethics Board |
| SAE | Serious Adverse Event |
| SOP | Standard Operating Procedure |
| TNBC | Triple negative breast cancer |
| WHO | World Health Organization |

## 1.0 OBJECTIVES AND RESEARCH HYPOTHESIS

### 1.1 Primary Objectives

**1.1.1** To evaluate the feasibility of using talazoparib prior to initiating standard neoadjuvant therapies

**1.1.2** To evaluate the toxicity profile in women taking talazoparib in the neoadjuvant setting

**1.1.3** In an expansion cohort, to estimate the pathologic complete response to talazoparib in 4 and up to 6 months of therapy prior to definitive surgery.

### 1.2 Secondary Objectives

**1.2.1** To provide first estimate of clinical response to talazoparib in the neoadjuvant setting in a pilot trial setting.

**1.2.2** To evaluate biomarkers of therapy efficacy as well as initiate patient derived xenograft (PDX) models:

- Targeted or whole exome sequencing for BRCA pathway mutations and other somatic and germline alterations
- RNA sequencing
- Evaluation of changes in immune response
- Transcriptional profile to assess TNBC subtype, BRCA-ness signature and putative PARP sensitivity predictors
- Functional proteomics with reverse phase protein array (RPPA)
- Generate PDX models and mammosphere cultures from patient derived tumors
- PTEN, gamma-H2A.X, Ki-67 and cleaved caspase 3 by IHC

### 1.3 Research Hypothesis

Sequential administration of Talazoparib followed by an anthracycline and taxane regimen in patients with a known BRCA deleterious mutation will be well tolerated and show response to single agent therapy.

A biomarker-defined population can be identified in which a higher pCR rate is observed in subjects treated with Talazoparib followed by anthracycline and taxane systemic therapy.

PDX models will provide models to understand sensitivity and resistance mechanisms.

## 2.0 BACKGROUND

### 2.1 Breast Cancer

Invasive breast cancer is the most common malignancy in women worldwide. In the United States, breast cancer is the most common female cancer, the second most common cause of death in women (after lung cancer), and is the main cause of death in women between the ages of 45 and 55. [1] However, over the last decade the mortality rate has declined in the United States and United Kingdom largely because of widespread use of mammography, breast cancer screening programs, advances in evaluation technique, and more effective adjuvant treatments. [2]

Studies that compared preoperative (neoadjuvant or primary systemic therapy) and adjuvant chemotherapy in patients with early stage breast cancer have shown no difference in overall survival or disease free survival. [3] Primary systemic therapy (PST) is increasingly being used in the management of patients with early breast cancer. Neoadjuvant chemotherapy allows for monitoring of response to chemotherapy and enhances chances of breast conservation surgery and/or a better cosmetic outcome following mastectomy in patients with locally advanced breast cancer. [4, 5] Additionally, the neoadjuvant setting is ideal for correlative studies to identify breast cancer patients likely to best respond to therapy. The provision of a surgical specimen, at the end of therapy, allows for a more rapid assessment of response (pathological responses) than adjuvant trials. Pathological complete response (pCR) is widely accepted as a valuable prognostic indicator of long-term outcome after neoadjuvant therapy. [6]

### 2.2 Primary Systemic Therapy: Historical Perspective

The rationale for considering the evaluation of primary systemic therapy (PST) in patients with operable breast cancer began to evolve as clinical observations demonstrated the utility of this approach in patients with locally advanced breast cancer (LABC), [7-9] and inflammatory breast cancer (IBC). In addition, preclinical observations, [10, 11] and mathematical models of tumor growth, dissemination, and development of resistance to chemotherapy support the use of PST rather than adjuvant therapy. These could lead to achieve longer disease-free survival (DFS) and overall survival (OS), presumably through early treatment of systemic micrometastatic disease. Since its initial use in the early 1970s, PST has become the standard of care for management of LABC and IBC, and increasingly been used for treatment of large operable and more recently for early-stage breast cancer.

Chemo-, hormone-, and anti-HER2 therapies are potential PST options for the different sub- types of breast cancer. PST provides several advantages, including down-staging allowing surgery for non-operable breast cancer, and increasing breast-conservative surgery rate in patients with large operable breast cancer. It also provides an early surrogate factor, pCR, for long-term outcome and in-vivo model to assess clinical benefit and finally a research tool for understanding breast cancer biology and treatment mechanisms of action(s). pCR has also been recently added as an appropriate endpoint for FDA approval pathways in breast cancer.

## 2.3 Pathological Assessment

A variety of endpoints can be used to measure outcomes of PST for breast cancer other than directly measuring survival (DFS, and OS), which requires a large number of patients and long term follow-up. These endpoints included clinical response, radiologic response, rate of breast conservative surgery (BCS), and pathologic response. The results of several studies have been shown that pCR is predictive of long-term survival. [12-15] At present, the achievement of pCR has emerged as the primary end point of most interest in the clinical research literature. Attainment of pCR is associated with a favorable prognosis; such patients have a far lower risk of subsequent recurrence than do patients with residual invasive tumor at the time of surgery, and also seem to have improved overall survival. Despite the strong evidence of predictive value of pCR in this context, there is no consensus on the measurement of this important endpoint. Clinical and pathological responses are both frequently used as objective measurements of effectiveness of PST. Three of the most commonly used criteria in the literature are those by Sataloff et al [15], Feldman et al, [12] and most recently Symmans and collaborators from the University of Texas, MD Anderson Cancer Center. The first 2 sets of criteria have some overlap but, for the most part, differ from each other.

In general, 60% to 90% of patients with invasive breast cancer show clinical response, however, only 3% to 30% of patients achieve pCR. Two large studies using PST, NSABP B-18 and B-27 defined pCR as no residual invasive cancer in the breast after PST and at the time of surgery, whereas other studies also take node status and noninvasive cancer into account. An International Expert Panel recently recommended that pCR be defined as no invasive or noninvasive tumors in the breast and axillary tissues removed at the time of surgery. [7]

Symmans et al [16] showed a continuous index combining pathologic measurements of the primary tumor (size and cellularity) and nodal metastases (number and size) and tested as an independent predictor of distant relapse-free survival. Patients with minimal residual disease (RD) (RCB-I) carried the same prognosis as pCR (RCB-0). On the other hand, patients with extensive RD (RCB-III) had poor prognosis. RCB was independently prognostic in a multivariate model that included age, pretreatment clinical stage, hormone receptor status, hormone therapy, and pathologic response (pathologic complete response [pCR] vs. RD; hazard ratio = 2.50; 95% CI 1.70 to 3.69; P < .001). Seventeen per cent of patients had minimal RD (RCB-I). These patients carried the same prognosis as pCR (RCB-0). Extensive RD (RCB-III) was seen in 13% of patients. It was associated with poor prognosis, regardless of hormone receptor status, adjuvant hormone therapy, or pathologic American Joint Committee on Cancer stage of residual disease. The calculation formula and detailed description can be found at a dedicated Web site: http://www.mdanderson.org/breastcenter_RCB.

## 2.4 Phase II and III Randomized PST Breast Cancer Trials

Several large Phase III trials investigated the efficacy of chemotherapy when administered as PST compared with adjuvant systemic treatment.

In 1998 the National Surgical Adjuvant Breast and Bowel Project (NSABP) conducted a large phase III study (NSABP P-18) to compare PST and post-operative chemotherapy. [6, 17, 18]

A total of 1,523 patients with T1-3 N0-1 M0 breast cancer were randomized to receive four cycles of doxorubicin and cyclophosphamide (AC) either as PST or adjuvant therapy. Breast tumor size was reduced in 79% of patient after PST, and 36% had a clinical complete response (cCR) rate, 43% clinical partial response (cPR), and a 13% pCR. Clinical nodal response was observed in 89% of patients with node-positive disease; 73% had nodal cCR, and 44% of these patients had pCR. At 9 years, the authors reported no difference in DFS (67% for both groups) or OS (69% PST vs. 70% adjuvant groups; P = .80). However, there was a favor trend in favor of PST in women less than 50 years old (HR 0.85, P = .053). The investigators reported that the use of PST improved BCS from 60% to 67% (P < .01). Even with improved rates of BCS, there was no statistically significant difference in the rate of local recurrence between treatment groups (P = .12). A marginal increase in the rate of local recurrence for patients who were converted from proposed mastectomy to segmental mastectomy (15.9%) was seen when compared with patients who were eligible to undergo segmental mastectomy as per initial plan (9.9%) (P = .04). This difference loses statistical significance after controlling for age and initial clinical tumor size.

NSABP B-27, a large prospective randomized trial, [14, 19] was designed to evaluate whether the addition of docetaxel to AC PST would prolong DFS and OS and improve clinical and pathologic tumor response rates. Women with operable breast cancer (n = 2,411) were randomly assigned to receive either 4 cycles of PST AC followed by surgery (Group 1), 4 cycles of AC followed by 4 cycles of docetaxel, followed by surgery (Group 2), or 4 cycles of AC followed by surgery and then 4 cycles of docetaxel (Group 3). The addition of docetaxel to AC increased pCR rate (26.1% vs 13.7%; P < .001). pCR was a significant predictor of OS (HR 0.33, P < .0001). The pathologic nodal status after chemotherapy was also a significant prognostic factor for OS (P < .0001). However, this study did not prospectively assess the role of docetaxel in patients with residual disease after PST AC. There was no stratification after AC. The patients with all eight cycles of PST administered up front had a trend toward improvement in RFS. [14] One caveat with this study is that at the time it was conducted, all patients received tamoxifen, which was initiated concurrently with chemotherapy, regardless of hormone-receptor status. The simultaneous administration of tamoxifen and chemotherapy may have decreased the benefit from chemotherapy.

The European Organization for Research and Treatment of Cancer (EORTC) Trial 10902 randomized 698 patients with stage I to IIIB breast cancer to receive four cycles of PST or adjuvant FEC-100. [20] The primary objective of this study was to determine the impact of timing of therapy on DFS and OS. After a follow-up of 4-years the OS was 82% for PST group compared to 84% for those treated in the adjuvant setting (P = .38). For patient who received PST, the overall response rate (ORR) (cCR + cPR) was 49% and cCR 7%. Thirteen of 350 patients (4%) in the PST group had a pCR. For this study, response was determined by both clinical examination and changes with the mammogram, possibly explaining the low overall clinical CR. PST was associated with an increased rate of 35% BCS compared to 22% for the control group. The rate of locoregional recurrence was equivalent between treatment groups.

The European Cooperative Trial in Operable (ECTO) Breast Cancer randomly tested the efficacy of postoperative chemotherapy doxorubicin followed by cyclophosphamide, methotrexate, and

5-fluorouracil (CMF) or doxorubicin and paclitaxel (AP) followed by CMF versus PST consisting in AP followed by CMF. [21, 22] A total of 1,355 patients entered the study. Overall, PST induced a clinical response in 78% of the patients and pCR 23%. There was no significance in RFS when AP/CMF was given before surgery compared with the same regimen given after surgery (HR, 1.21; P = .18) However, the rate of breast-conserving surgery was significantly higher with preoperative chemotherapy (63% vs. 34%; P < .001)

The wide variety of PST clinical trials recently completed or ongoing in early breast cancer reflects the pressing need to identify the most effective agents and regiments to optimize both surgical and long-term outcomes for these patients.

Lastly, Buzdar el al [23] compared two taxane schedules (weekly paclitaxel [WP] x 12 versus 3-week docetaxel plus capecitabine (DC) x 4 cycles, followed by: FEC-100 x 4 cycles. Patients were randomized 1:1 and stratified by the timing of therapy (PST vs. adjuvant). A total of 216 patients were treated with PST and 107 were randomized to WP arm and 109 to DC arm. The pCR rates were 18.7% and 17.4% on each arm, respectively (P = .81). The DC arm had higher incidence of hand foot syndrome, and myelosuppression, and WP treatment higher neurotoxicity. The primary endpoint was DFS, and the secondary endpoint pCR. The study was designated to include 930 patients to have 80% power. After interim analysis in June 2008 by the data monitoring committee the study was closed due to futility. The authors concluded that WP and DC in the PST setting had same efficacy and WP was associated with better tolerance and less toxicity.

## 2.5 Current Primary Systemic Chemotherapy Regimens

Pathological complete response rates are generally higher with anthracycline-based combinations than with regimens not containing anthracyclines (doxorubicin or Epirubicin). Consequently, most PST regimens for breast cancer are anthracycline-based combination: AC (doxorubicin/Cyclophosphamide); FAC (fluorouracil/doxorubicin/cyclophosphamide); CE (cyclophosphamide/epirubicin); and FEC (fluorouracil/epirubicin/cyclophosphamide). However, other non-anthracycline based drug combinations, such as CMF (cyclophosphamide/methotrexate/fluorouracil) with or without a taxane, are also in common use. Increased duration of chemotherapy administration from 12 to 18 weeks or longer improves pCR rates. [5] The addition of paclitaxel or docetaxel to anthracyclines based regimes has resulted in pCR of up to 28.2%. [24] The Aberdeen study showed that tumors that did not respond to an anthracycline-based regimen may respond to docetaxel. Additionally sequential and non-concomitant addition of taxane to anthracycline-based chemotherapy results in higher pCR rates. [25]

Additionally, from data presented at the San Antonio Breast Cancer Symposium in 2013 by Sikov, et al [26] evaluated the addition of both carboplatin and bevacizumab in a 2 x 2 trial design to neoadjuvant weekly paclitaxel and AC. There was a 13% absolute difference in pCR. However, given toxicity profile, this combination has been administered but as of the date of this protocol, not added to the Institutional or NCCN guidelines. Therefore given that this trial is being written while there is a shifting landscape of neoadjuvant regimens in the neoadjuvant setting, we will refer to the physician's treatment of choice that includes a taxane, anthracycline and may or may not include carboplatin.

Table 1 shows multiple studies in the literature reporting pCR rates

Table 1: Pathological Response Rates in the Literature

| Trial/Reference | No. of Patients | Agent(s) | No. of Cycles | pCR (%) |
|---|---|---|---|---|
| Fisher [6] | 15 | AC | X | 9 |
| Buzdar [27] | 87 | Paclitaxel | X | 9 |
| Amat [28] | 80 | Docetaxel | X | 20 |
| NSABP B27 [19] | 15<br>02 | AC | X<br>4 | 13 |
| Aberdeen [29] | 47 | CVAP-Docetaxel | X4 and x4 | 34 |
| Green [24] | 25<br>8 | T-FAC | 12 w and x 4 | 15.7 (q3w Pac)<br>28.1 (qw Pac) |
| SWOG0012 [30] | 26 | AC-Pac | X 4 and 12 w | 17% |
| CALGB 40603 (Alliance)[26] | 45<br>4<br>TNBC only | Paclitaxel +/- carbo-AC second comparison was with bevacizumab | X12w and x 4 | 54 vs 41% for addition of carbo |

AC = doxorubicin and cyclophosphamide; CVAP = cyclophosphamide, vincristine, doxorubicin and prednisone; FAC = Fluorouracil, doxorubicin, and cyclophosphamide; T = Paclitaxel.

## 2.6 Primary Systemic Therapy in Operable Breast Cancer

The Breast Medical Oncology Department at MD Anderson has been one of the pioneers in the use of neoadjuvant chemotherapy for the treatment of breast cancer. The sequential or concurrent administration of taxane and anthracycline constitute the backbone of early breast cancer treatment.

PST has several potential advantages compared with the traditional strategy of surgery followed by adjuvant chemotherapy. PST reduces the size of the primary tumor and lymph node metastasis in greater than 80% of cases, increasing the probability that breast-conserving surgery can be performed. [12-15] A second advantage of this sequencing schedule is that it permits the assessment of response of the primary tumor to the particular chemotherapy regimen. This assessment allows the opportunity to "cross-over" to a different regimen for an individual patient if

there is minimal or no response to the first regimen. These and other theoretic advantages for PST must be balanced carefully with other aspects of individual patient management.

One of the first considerations for studying PST for breast carcinoma was to investigate whether earlier delivery of chemotherapy offered the possibility of improved survival in patients with locally advanced breast carcinoma. To test these concepts, the National Surgical Adjuvant Breast and Bowel Project (NSABP) began the B-18 trial to test whether sequencing chemotherapy before surgery would improve outcomes. [12-14] The trial enrolled 1523 patients with early- stage, operable breast carcinoma and randomized them to receive four cycles of doxorubicin/Cyclophosphamide (AC) either before or after surgical treatment. The primary end points of this trial were disease-free survival (DFS) and overall survival (OS). With respect to these end points, the trial was a negative study. After 9 years, the OS and DFS were nearly identical between the two groups (P = .80, P =0.5, respectively). A second large randomized prospective trial that directly compared the sequencing of chemotherapy and surgery was performed by the European Organization of Research and Treatment of Cancer (EORTC). [15] This trial randomized 698 patients to preoperative or postoperative chemotherapy comprised of four cycles of FEC (5-Fluorouracil, Epirubicin, and Cyclophosphamide). Like the NSABP B-18 trial, the EORTC study demonstrated equivalent survival and rates of distant metastases between the two treatment arms.

Gianni el al, [16] randomized 1,355 patients with breast cancer > 2 cm to three groups: adjuvant doxorubicin (A) followed by cyclophosphamide, methotrexate, and 5-FU (CMF) (Sx→A→CMF); adjuvant doxorubicin and paclitaxel (AT) followed by CMF (Sx→AT→CMF); and neoadjuvant AT followed by CMF (AT→CMF→Sx). pCR rates in the neoadjuvant arm were 23% in breast only and 20% in breast plus axilla patients. The breast conservative treatment rate was also better in this arm (65% vs. 34%; P <.001). At 5 years of follow up, adjuvant chemotherapy was similar to PST in terms of freedom for progression (P =.24) and OS (P = .81)

A recent meta-analysis addressed directly the question of neoadjuvant versus adjuvant chemotherapy. [17] Nine randomized clinical trials involving 3,946 patients were included. pCR rates were highly variables among these trials. Six trials had a higher rate of BCT after PST. No difference was observed between the two arms for death, disease progression, or distant recurrence. Surprisingly, PST was associated with a higher locoregional recurrence (risk ratio, [RR] 1.22; P = .15). This greater risk was largely attributed to those trials in which radiation alone without surgery was used in patients who achieved a clinical complete response to PST. (RR, 1.53; P =.009).

## 2.7 Role of the Pathological Complete Response in Breast Cancer

A pathological complete response (pCR) implies the absence of residual invasive disease following PST. Pathological complete response is associated with long-term survival, and has been adopted as the primary end point for neoadjuvant trials. While it is generally held that a definition of pCR should include patients without residual invasive carcinoma in the breast (pT0), the presence of nodal metastasis, minimal residual cellularity, and residual in situ carcinoma are not consistently defined as pCR or residual disease (RD). When there is no residual invasive cancer in the breast, the number of involved axillary lymph nodes is inversely related to survival. [18] Conversely, patients who convert to node-negative status after treatment have excellent survival, even if there is RD in the breast. [19] Symmans and collaborators, [31] recently introduced a residual breast cancer burden (RCB) index as a novel independent new risk factor that improves the prediction of distant relapse after PST compared with currently used risk factors. RBC can be divided in four categories: patients with minimal residual disease (RBC-I) have the same 5-year prognosis as those with pCR

(RBC-0), irrespective of the type of neoadjuvant chemotherapy administered, adjuvant hormonal therapy, or the pathologic stage of RD. Extensive RD (RBC-III) was associated with poor prognosis, irrespective of the type of neoadjuvant chemotherapy administered, adjuvant hormonal therapy or the pathologic stage of RB.

### 2.8 BRCA mutations

The BRCA genes were first described in families with breast and ovarian cancers through the use of genetic linkage analysis.[32-34] Since that time, over 5000 different mutations in these genes have been identified including both private and founder mutations.[35] Overall these mutations are estimated at 0.1% in the general population. [36-38]

A recent meta-analysis of ten studies estimated the lifetime risk of breast cancer in BRCA1 mutation-carriers to be 47-66% and 40-57% in BRCA2 mutation-carriers. The ovarian cancer risk was estimated at 35-46% in BRCA1 mutation-carriers and 13-23% in BRCA2 mutation carriers.[39] Other studies have estimated these risks to be even higher.[40] Given this increasing risk of cancers, women with cancers in the family at young age, or multiple cases of breast and/or ovarian cancer have sought genetic testing, not only to further manage their own cancer risk, but also to share with their family members.

In an analysis by Arun, et al. women with a known BRCA mutation who received neoadjuvant therapy at The University of Texas MD Anderson Cancer Center were evaluated.[41] Of the BRCA1 carriers, 26/57 (46%) achieved a pCR. In the multivariate model, both BRCA1 and triple receptor negative breast cancer (TNBC) were independent predictors of pCR. In this cohort >80% of the patients received an anthracycline and taxane based therapy. Other studies have shown a significant increase in response to platinum-based therapy in a similar cohort. Silver, et al. evaluated 28 women with TNBC who received 4 cycles of cisplatin at 75 mg/m2 every 21 days with 22% achieving a pCR.[42] Both of the BRCA1 mutation carriers had a pCR in this small cohort. Therefore neoadjuvant chemotherapy in BRCA mutation carriers will be important to further identify responders and non-responders.

Interestingly, some studies suggest that BRCA mutation carriers are less sensitive to taxane chemotherapy in the metastatic setting.[43] Therefore BRCA mutation status as well as optimizing PST will be ever more important in the early breast cancer setting and may have implications as to the systemic regimes evaluated in clinical trials and ultimately chosen for patient care in the future.

At our institution, women and men are referred to the Clinical Cancer Genetics service where they are seen and counseled by a genetic counselor as well as a physician. This service is staffed in the Breast Center by Dr. Jennifer Litton and Dr. Banu Arun and there are 4 dedicated breast genetic counselors as well as 2 additional counselors in the Gynecologic Oncology Clinic. In 2012 there was a total of 1708 genetics consultations through Clinical Cancer Genetics with 818 being in the Breast Center and 216 in Gynecologic Oncology. Additionally, since the inception of this service, we have identified over 1000 patients at our institution with a BRCA mutation with that number expected to increase given the increase in awareness and through outreach through the Women's Moonshot Program.

Once a consultation is done, blood is obtained with a usual turn-around time of 2 weeks. Patients eligible for this protocol and who meet National Testing Guidelines [44] will have a genetics consultation expedited so as not to delay start of preoperative systemic therapy.

## 2.9 PARP inhibitors

Poly-(adenosine diphosphate [ADP]-ribose) polymerase (PARP) is a family of enzymes responsible for multiple cellular processes, including DNA repair through the base excision repair (BER) process as well as maintains genetic stability.[45]During DNA repair, when a cell is BRCA deficient, the DNA is unable to be repaired through homologous recombination (HR) and therefore depends on BER. PARP inhibitors (PARPi) work by also blocking BER. Therefore when both HR and BER DNA repair pathways are impaired, DNA repair is thwarted causing "synthetic lethality."[46] Although PARPi have been tested in TNBC, solid tumors, most activity has been seen to date as single agents concentrated in patients with known BRCA mutations.

Several trials have evaluated PARPi in both triple receptor negative breast cancer (TNBC) as well as in BRCA mutation carriers. Due to overlapping toxicities of cytopenias, it has been difficult to give in combination with other systemic chemotherapies such as the taxanes or platinum compounds. [47, 48]

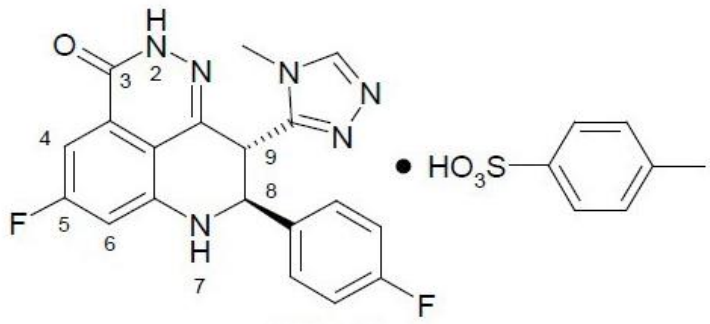
Below is a brief overview of selected studies that have reported to date. Of note, Iniparib is not included as it was not shown to have superior efficacy when added to gemcitabine and carboplatin and later was not found to inhibit PARP. [49]

| Study | Phase | N | Intervention | Outcome | Toxicity | MTD |
|---|---|---|---|---|---|---|
| Fong et al. 2009[50] | I | 60, 23 BRCA + | Olaparib 600 vs. 400 vs. 200 mg BID | Of evaluable BRCA+ pts: PR or and 12/19 with CBR | Grade 4 thrombocytopenia | |
| Dent, et al. 2013[47] | I | 19, all TNBC | Olaparib 200 mg BID + weekly paclitaxel at 90mg/m2 | 37% with a PR and one with a durable response remains on single agent olaparib | Neutropenia (n=7/9 in first cohort, 5 of which were grade 3 or higher) Nausea and diarrhea | Neutropenia required opening of second cohort to be given with G-CSF |
| Lee et al. ASCO Annual Meeting 2013 | I | 45, 37 ovarian and 8 breast | Escalating Olaparib and carboplatin- AUC 3 day 8 and q 21 days | | Thrombocytopenia, neutropenia, anemia | |
| Kummar, et al. Clin 2012[51] | I | 35, solid tumor and lympho ma patients | Escalating doses of velaparib 20-60 mg x 7 days and metronomic cyclo-phosphamide 50 mg daily | Partial response in 7 breast cancer patients, 6 of whom were BRCA mutation carriers | Thrombocytopenia, neutropenia, anemia | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Rajan et al. 2012[48] | I | 21 patients with solid tumors | Olaparib 100 mg daily on days 1-4, de-escalated to day one only, +gemcitabine and cisplatin | PARP levels less effectively inhibited given in shorter duration. Only 2 patients had a partial response | | Thrombo-cytopenia, febrile neutropenia |
| Somlo et al. ASCO Annual Meeting 2013 | I | 12 BRCA 1, 15 BRCA 2 and 1 had both | Escalating Velaparib BID and carboplatin AUC 6 | CBR 74% median PFS 7.8 months | Thrombocytopenia (requiring de-escalation of carboplatin) | MTD carboplatin AUC 5 and velaparib150 BID |
| Bell-McGuinn et al. ASCO Annual Meeting | I | 59 advanced solid tumors 39 ovarian | Escalating velaparib and carboplatin AUC 4 day 1, gemcitabine 800 mg/m2 | | Neutropenia, leukopenia, Thrombocytopenia and anemia | |
| Tutt et al. 2010[52] | II | 54, 27 at 400 mg bid, then 27 at 100 mg BID | Olaparib | ORR 41% at 400 mg BID<br>ORR 22%<br>at 100 mg | Nausea, vomiting, fatigue, anemia | |
| Gelmon et al. 2011[53] | II open label | 91, 65 with ovarian cancer and 26 with breast cancer | Olaparib 400 mg po BID | No objective responses in breast cancer cohort | | |
| Malireddy et al. ASCO Annual Meeting TIP 2013 | Phase II in progress for residual disease | | Rucaparib IV + cisplatin 75 mg/m2 IV q 3 weeks x 4 | | | |

## 2.10 Talazoparib

Talazoparib is an oral PARP inhibitor manufactured by Pfizer. For complete product information please refer to the Appendix for the Investigator's Brochure.



BMN-673ts

Talazoparib has been shown to have effective synthetic lethality in BRCA and PTEN deficient cell lines and xenograft models and was additionally been found to be orally more potent than other available PARP inhibitors currently being tested.

Poly adenosine diphosphate (ADP)-ribose polymerase (PARP) represents a family of enzymes, of which at least 2 (PARP1 and PARP2) play important roles id deoxyribonucleic acid (DNA) repair. The study drug, talazoparib, is a potent and specific inhibitor of PARP 1 and 2 with activity in tumor cell lines bearing DNA repair deficiencies. PARP inhibition induces synthetic lethality in tumor cells bearing mutations in the genes encoding breast cancer susceptibility gene 1 (BRCA1) and breast cancer susceptibility gene 2 (BRCA2), both of which are key components in the pathway of repair for DNA double-strand breaks. Treatment with a PARP inhibitor results in cell cycle arrest and apoptosis.

### 2.10.1 Nonclinical Study Findings for Talazoparib

The nonclinical study findings for talazoparib are described in full in the IB. The main nonclinical findings were early hematological changes and subsequent bone marrow and lymphoid organ depletion, as well as focal necrosis, after repeat administration of talazoparib. These findings were in accordance with the mechanism of action and the exposure/ distribution pattern of the study drug and were reversible. The hematological changes, which consisted of decreases in the reticulocyte, platelet, red blood cell (RBC) and white blood cell (WBC) counts, were a sensitive and early marker of target organ toxicity and were used to clinically monitor safety.

### 2.10.2 Preliminary Clinical Study Findings for Talazoparib

Two Phase I studies (PRP-001 and PRP-002) of talazoparib are ongoing and one Phase 3 study (673-301) was initiated third quarter, 2013.

Medivation initiated the first-in-human study of talazoparib (PRP-001) in the first quarter of 2011. This is a Phase 1, single-arm, open-label, dose-escalation study of once daily, orally administered talazoparib for advanced or recurrent solid tumors (those that have defects in DNA repair). PRP-002, a Phase 1, 2-arm, open-label, dose-escalation study for talazoparib for the treatment of

subjects with advanced hematological malignancies was initiated in July 2011. This study enrolled subjects with acute myeloid leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia or mantle cell lymphoma.

The primary objective of the Phase 1 studies is to establish the maximum tolerated dose (MTD) of once daily, orally administered talazoparib, and to assess the safety, pharmacokinetics (PK), pharmacodynamics and preliminary efficacy in an expanded cohort of subjects with genetically defined tumors.

In June 2013, preliminary data from PRP-001 were presented at the American Society of Clinical Oncology (ASCO) 2013 that are described below [54]. As of June 2013, 70 subjects (60 women/10 men) enrolled into the study; 39 subjects (33 women/6 men) with solid tumors were enrolled in the dose escalation phase of the study in 9 cohorts ranging from 25 to 1100 µg/day that defined a MTD of 1000 µg/day. On defining the MTD, 31 subjects with breast cancer, ovarian, and pancreas cancer with deleterious germline mutations; a small cell lung cancer; and Ewing's sarcoma, were enrolled in the expansion phase of the study to further characterize safety and efficacy. The median (range) age for all 70 subjects was 51.5 years (18 to 81), performance status (PS) was 0 (0 to 1) and number of prior therapies was 4 (1 to 13), with 47 subjects having deleterious BRCA mutations. Tumors (number with deleterious BRCA ½ mutations) included 34 ovarian/primary peritoneal (28); 20 breast (18); 8 Ewing's; 4 pancreas; 2 colon; 1 prostrate (1), and 1 mullerian carcinosarcoma. A total of 27 and 21 subjects had BRCA1 and BRCA2 mutations, respectively.

Dose-limiting thrombocytopenia occurred in 1 of 6 subjects at 900 µg/day and 2 of 5 subjects at 1100 µg/day, respectively. Based on these results, the MTD was defined at a dose of 1000 µg/day. Related adverse events (AEs) occurring in >10% of all 70 subjects included fatigue (30%), nausea (29%), alopecia (21%), anemia (20%), thrombocytopenia (19%), and neutropenia (11%). One subject had drug-related Grade 4 thrombocytopenia. Grade 3 related AEs included fatigue in 1 subject (1%), anemia and thrombocytopenia each in 9 subjects (13%) and neutropenia in 4 subjects (6%). Dose reductions occurred in 11 subjects due to myelosuppression. No subjects discontinued due to AEs.

Inhibition of PARP activity in peripheral blood mononuclear cell was observed at doses > 100 µg/day. Talazoparib plasma concentrations peaked 1 to 2 hours post-dose; in general, exposure increased dose proportionally. Steady state plasma concentrations were reached by the end of the second week of daily dosing; mean maximum plasma concentration (Cmax): 0.30 to 25.4 ng/mL and area under the concentration time curve from 0 to 24 hours (AUC0-24): 3.96 to 203 ng-hr/mL across the 25 to 1100 µg/day dose range after 28 days of daily dosing.

Objective (response evaluation criteria in solid tumors [RECIST] v.1.1) and/or cancer antigen (CA)-125 responses occurred at doses > 100 µg/day in 11 of 25 (44%) and 19 of 27 (70%) subjects with BRCA-carrier ovarian and peritoneal cancer, respectively. Clinical benefit (complete response [CR]/partial response [PR]/stable disease [SD]>24 weeks) occurred in 23 of 28 subjects (82%) with BRCA-carrier ovarian and peritoneal cancer.

Objective responses (ORs) occurred in 10 of 18 (56%) BRCA-carrier breast-cancer subjects. Clinical benefit (CR/PR/SD>12 weeks) occurred in 14 of 18 (78%) of BRCA-carriers.

Overall, talazoparib was well tolerated with impressive anti-tumor activity in subjects with BRCA mutations with a single agent recommended Phase 2 trial dose of 1000 μg/day due to dose- limiting thrombocytopenia.

Study 673-301, initiated on 30 October 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 locally advanced and/or metastatic breast cancer. As of 30 November 2013, a total of 3 subjects had been enrolled in the study.

### 2.10.3 Preliminary Findings from this Trial as of 3/11/2016.

As this study was initially written as a feasibility to see if patients could tolerate therapy and if 20 patients could accrue within 2 years, the team has reviewed the current status of this trial as of 3/11/2016. At this time 13 patients have been enrolled. Although approval was 04/2016, it was not until 08/2016 when enrollment was able to initiate and in that time 13 patients have been accrued. Therefore the concern that this trial could not accrue is no longer present. Additionally, the second objective was to review for Grade IV toxicity and to date there have been no reported Grade IV toxicities. When evaluating the 3 dimensional volume of an oval in this setting, there has been dramatic reductions in the size of the tumors with 2 months of talazoparib. In the first 11 patients who have completed 2 months of therapy, the average shrinkage has been 76% decrease (Length x width x height x π)/6, (range =29-97% decrease in volume). One of the 13 patients have completed all therapy and has obtained a pathologic complete response. Given the extraordinary amount of response with this single agent therapy, obtaining an estimate of pathologic response will be necessary in order to properly construct and power a potential registration neoadjuvant trial.

In the first 13 patients enrolled in the pilot study, we observed 0 grade 4 or higher AEs. To estimate the probability of excessive toxicity given that we have observed 0/11 toxicities, we invoke the beta-binomial probability model. Assuming an uninformative beta (1, 1) prior, the posterior probability that the toxicity rate > 30% (i.e., Pr (Ptox > 0.3 | data)) is 1.4%. A 90% credible interval on the estimated toxicity rate is 0% to 22%.

## 3.0 RATIONALE FOR THE CURRENT STUDY

Patients with BRCA mutations have tumors that have demonstrated defects in homologous recombination (HR) and have been shown in several trials to have response to PARP inhibitors. Therefore understanding the mechanisms of response and resistance to PARP inhibitors as well as identifying patients who may not avoid prolonged cytotoxic therapy would be best studied in the neoadjuvant setting.

It is important prior to the outset of a larger randomized clinical trial to evaluate this strategy in a pilot setting. First we need to understand if it is safe to give preoperative talazoparib under close monitoring. If we discover significant benefit, we may proceed with tailoring the definitive clinical trial by evaluating pCR as an endpoint that may include less toxic regimens due to response to PARPi.

Secondly, we need to assess the feasibility of accruing to such a study as patients may not wish to extend their preoperative therapy and combination studies of PARPi with chemotherapy has been limited due to overlapping toxicities of cytopenias, nor will they want to wait the 2 weeks until BRCA testing results become available, although this has not been shown to be detrimental to outcomes to date and is a current strategy in other molecular triaging protocols.

Also, this study will be an information rich study to understand mechanism and resistance to PARPi in the setting of preoperative chemotherapy as well as the importance of developing patients derived xenografts of BRCA mutation carriers as well as mammosphere cultures as these do not yet exist to our knowledge and will be important models to move forward in studying response and resistance.

Expansion Phase: After the first 13 patients were enrolled, discussions with the investigators and the sponsors discussed the results available from these patients with an average tumor volume decrease of 76%, median decrease of 88% after just 2 months of therapy. Given that it was felt that an amendment would be pursued and once approved by the IRB and IND offices, to cease the feasibility portion of the study and to move forward with an expansion cohort where patients who are responding to oral therapy could continue to 4 and up to 6 months of therapy, proceed to surgery so that a pathologic response could be estimated to inform a randomized neoadjuvant clinical trial.

## 4.0 TREATMENT PLAN

### 4.1 Study Design

This is a non-randomized pilot study to assess feasibility and safety of using talazoparib in the neoadjuvant setting for women with invasive breast cancer who carry a BRCA deleterious mutation. An initial feasibility portion of the study was conducted to estimate toxicity, response, and ability to accrue. After 13 patients were accrued to the study an expansion cohort was added and once approved by the IRB, would close the feasibility portion of this study.

### 4.2 Eligibility

#### 4.2.1 Inclusion Criteria:

**To be included in the study, the subject must have:**

1) Signed, written informed consent

2) Histologically confirmed primary invasive adenocarcinoma of the breast with the size of the primary tumor being at least 1 cm on imaging by either mammography, ultrasound or breast MRI.

3) Negative HER-2/neu - disease defined as patients with FISH ratio <2.0 or <6.0 HER2 gene copies per nucleus, and IHC staining scores of 0, 1+, or 2+.

4) No treatment for current primary invasive adenocarcinoma of the breast such as irradiation, chemotherapy, immunotherapy, investigational therapy or surgery. Previous treatment for breast and/or ovarian cancer with chemotherapy, endocrine therapy, surgery and radiation are all allowed if >/= 3 years prior to current diagnosis and there is no clinical evidence of metastatic disease.

5) ECOG performance status of 0-1.

6) Baseline MUGA or echocardiogram scans with LVEF of > 50%.

7) Patient must have adequate organ function as determined by the following laboratory values:
   a. ANC≥1,500 /μL
   b. Platelets ≥100,000 / μL
   c. Hgb ≥ 9 g/dL
   d. Creatinine clearance >50 ml/min
   e. Total bilirubin ≤ 1.5 X ULN
   f. ALT and AST < 2.5 X ULN

8) Men or women 18 years of age or older.

9) Negative serum or urine pregnancy test for women within 72 hours of receiving the first dose of the study medication for women of childbearing potential as per institutional guidelines. Women will be considered not of childbearing potential and exempt from pregnancy testing if they are either a) older than 50 and amenorrheic for at least 12 consecutive months following cessation of all exogenous hormonal treatments, or b) have documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy, but not tubal ligation.

10) Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 8 weeks after the last dose of investigational product. Men on study also must be using contraception.

11) Identified deleterious mutation in BRCA 1 or 2 genes (this does not include variants of uncertain significance).

12) Eligible to receive standard of care chemotherapy and/or surgery based upon standard practices or institutional guidelines.

### 4.2.2 Exclusion Criteria:

1) Women who are pregnant (including positive pregnancy test at enrollment or prior to study drug administration) or breast-feeding.

2) Disease free of prior malignancy for < 3 years with the exception of curatively treated basal carcinoma of the skin or carcinoma in situ of the cervix.

3) Any other previous antitumor therapies for the current cancer event.

4) Has had major surgery within 21 days before Cycle 1, Day 1

5) Gastrointestinal tract disease or defect with associated malabsorption syndrome.

6) Uncontrolled inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)

7) Myocardial infarction within 6 months before starting therapy, symptomatic congestive heart failure (New York Heart Association > class II), unstable angina, or unstable cardiac arrhythmia requiring medication

8) Serious intercurrent infections or non-malignant medical illness that are uncontrolled or the control of which may be jeopardized by this therapy.

9) Psychiatric disorders or other conditions rendering the subject incapable of complying with the requirements of the protocols.

10) Unable to take oral medications

11) Known to be human immunodeficiency virus positive

12) Known active hepatitis C virus, or known active hepatitis B virus

13) Concurrent disease or condition that would interfere with study participation or safety, such as any of the following:

- Active, clinically significant infection either grade > 2 by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 or requiring the use of parenteral anti-microbial agents within 14 days before Day 1 of study drug

- Clinically significant bleeding diathesis or coagulopathy, including known platelet function disorders

- Non-healing wound, ulcer, or bone fracture

14) Known hypersensitivity to any of the components of talazoparib

**4.3 Treatment Administration Plan**

All subjects will be registered in CORe and the data will be entered in PMDS/CORe, the electronic CRF. Given the early responses seen in the first 11 patients with 2 months of talazoparib, understanding the pCR rate of single agent talazoparib in this setting will be

paramount to developing the randomized neoadjuvant trial. Therefore after the first 13 patients were accrued, the trial was amended to change to an expansion cohort to better estimate pathologic response.

EXPANSION COHORT

An expansion cohort of 20 patients will be accrued. Talazoparib will be administered orally at 1 mg per day for at least 4 and up to 6 cycles. Each cycle will consist of 28 days (+/-3 days). At the time of surgery, residual disease will be quantified by residual cancer burden. After surgery, the patient and physician may proceed to receive or not receive physician's choice of systemic therapy. Dose modifications will continue as per section 4.6.

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.

Once the Expansion cohort amendment portion of this trial is approved by the IRB and ready to initiate accrual, we will stop accruing to the feasibility portion of this trial.

### 4.3.1 Study Visits

Study visits are as outlined in Section 10. Due to scheduling, these visits can occur +/- 3 days from the required time of follow-up. Given that there may be cytopenias associated with this therapy, weekly CBCs will be obtained (+/- 7 days). During the expansion phase CBC's will be every 2 weeks x 3 and then monthly after that. On days where no other testing is required these blood tests can occur at any CLIA-certified laboratory (Cycle 1, Day 15). The Principal Investigator or treating physician must review all outside lab results, determine clinical significance for abnormal labs, and sign and date the report.

### 4.3.2 Biopsies/Correlative Studies

Ideally up to 4 core biopsies will be obtained at each time point if enough material is available, for a total of up to 12 core biopsies for the trial. Up to two fine needle aspirates (FNAs) will also be obtained at each time point for a total of up to 6 FNA's for the trial, which will be used for the patient derived xenograft models. Pre-study biopsies, as well as biopsies within 7 days prior to the completion of 2 months of talazoparib will be collected via diagnostic imaging, in addition to a portion of the surgical specimen at the time of the definitive surgery.
For the expansion cohort, only pre-study biopsies will be collected.
Ultrasounds will be done after cycle 1 and cycle 2 on the pilot phase of the protocol. For the expansion cohort, breast ultrasounds will be performed after every 2 cycles (+/- 7 days). Therapy will be discontinued if the Physician or PI indicates clinically significant progression of disease. A biopsy of the tumor at the time of progression will be obtained prior to switching to the standard of care treatment of the physician's choice. Tissue samples at the time of progressive disease may

occur at the time of surgery in the form of residual tissue and therefore a biopsy would not be required.

During the expansion phase of this trial, ultrasounds will be obtained every 2 cycles (+/- 1 week), and at progression with biopsy if progression occurs and further systemic therapy is given prior to definitive surgery.

These tissue specimens will be evaluated for response and biological markers of response and/or resistance.

### 4.3.3 Progression While on Study

Subjects who progress while on talazoparib will automatically be considered non-responders to talazoparib and will proceed to the standard of care therapy of the treating physician's choice or proceed to surgery if the treating physician feels that is in the patient's best interest. A biopsy of the tumor will be obtained prior to switching to the standard of care regimen of the physician's choice.

If progressive disease occurs while on standard of care treatment, the subjects should remain in the study until after they have undergone definitive surgery.

As an exploratory endpoint, during the tumor core biopsy, patients will also be offered an optional contralateral breast core biopsy to evaluate biomarker changes in the unaffected, yet high risk, breast tissue. BRCA mutation carriers have an up to 60% risk of developing new contralateral breast cancer. Since no prevention agents exist for BRCA mutation carriers, this preliminary data would help us to further understand the potential (preventative) effects of PARP inhibitors in high risk breast tissue. Without any preliminary knowledge, it will not be possible to conduct a preventative study with PARP inhibitors in women without breast cancer. Biomarkers that will be evaluated will be similar to the ones that will be evaluated in the tumor core biopsy (section 1.2.1) with the exception of the generation of PDX models and transcriptional profile to assess TNBC subtype. Currently there is no data in the literature related to biomarker changes in high risk breast tissue in women treated with PARP inhibitors.

### 4.3.4 Surgery

In the initial cohort, patients will undergo definitive breast surgery 4 -6 weeks from last dose of systemic chemotherapy.
For those patients that are a part of the Expansion Cohort, they will undergo definitive breast surgery within 6 weeks of the last dose of talazoparib. Tumors must be removed by either lumpectomy or mastectomy with clinically appropriate axillary surgery. The surgical specimens (breast and axillary lymph node tissue) will be evaluated for pathological complete response (defined per protocol) by central Pathologists at M.D. Anderson Cancer Center. Any further post-operative therapy, either local or systemic will be at the discretion of the treating physician.

## 4.4 Duration of Study

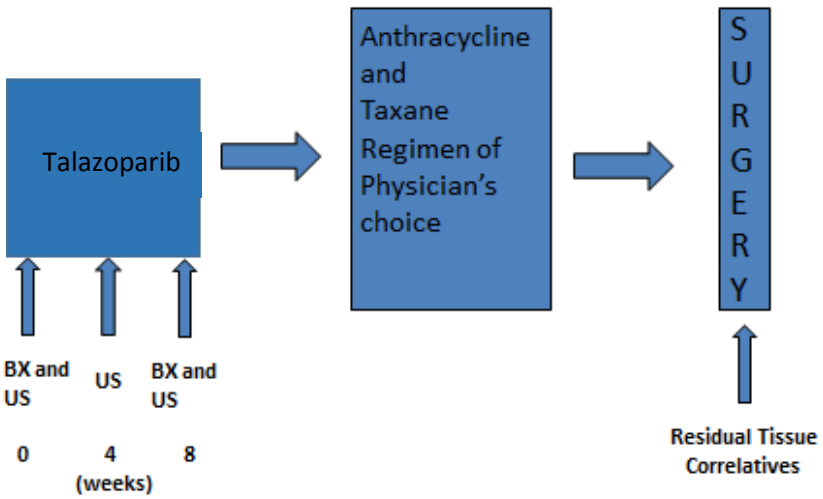
The study is expected to complete accrual within 3 years from study initiation. The duration of chemotherapy treatment per subject will be approximately 2 months on talazoparib followed by 6 months of a standard of care regimen of the treating physician's choice.

Additionally, from data presented at the San Antonio Breast Cancer Symposium in 2013 by Sikov, et al[26] evaluating the addition of both carboplatin as discussed in the background, the treating physician may choose to add or not add carboplatin to this standard of care regimen as well.

For those patients participating in the Expansion Cohort, all systemic therapy will be at the discretion of the treating physician after surgery.

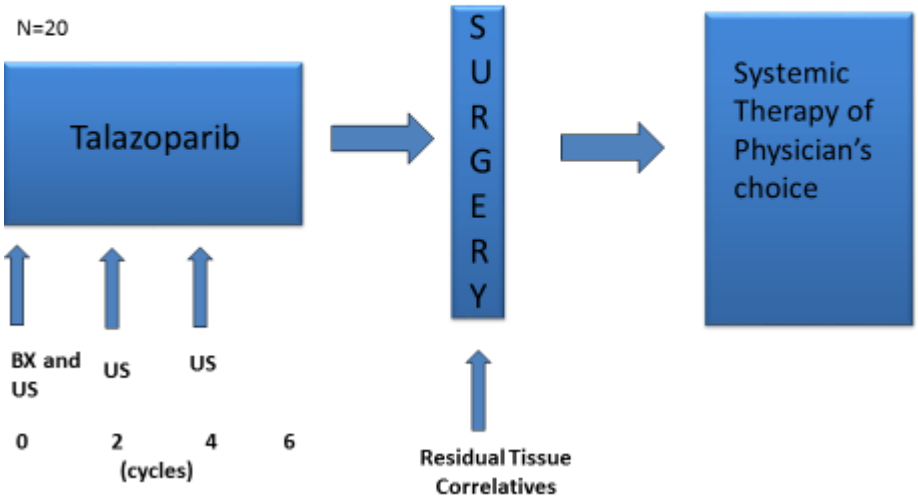
Participants will be followed until the time of surgery. Any available remaining tissue collected from this surgery will be used for the correlative studies.

## 4.5 STUDY DESIGN SCHEMA (Original Study Schema)




* Therapy will be discontinued at progression of disease. A biopsy of the tumor at the time of progression will be obtained prior to switching to the standard of care regimen of the physician's choice. Tissue samples at the time of progressive disease may occur at the surgical visit in the form of residual tissue and therefore a biopsy would not be required. (See Section 4.3.2).

**Expansion Cohort**




*Therapy will be discontinued at progression of disease. A biopsy of the tumor at the time of progression will be obtained prior to switching to the standard of care regimen of the physician's choice. Tissue samples at the time of progressive disease may occur at the surgical visit in the form of residual tissue and therefore a biopsy would not be required.

During the expansion phase, ultrasounds will be obtained every 2 cycles (+/- 1 week), and at progression with a biopsy if progression occurs and further systemic therapy is given prior to definitive surgery.

## 4.6 Dose modification

Talazoparib Dosing

Talazoparib should be taken orally once daily (i.e., continuous daily dosing) at approximately the same time each day (preferably in the morning).
Patients will document the time of dosing on a "pill diary calendar". This will be reviewed by the study team at the end of each cycle, along with reconciliation and documentation of any remaining study drug. The completed pill diaries will be kept by the study team.
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 a discussion between sponsor or designee and investigator if evidence of response or clinical benefit to talazoparib is noted.

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 (e.g. 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 (e.g., from 1.0 mg/day to 0.75 mg/day, 0.75 mg/day to 0.5 mg/day) when toxicity resolves to grade 1 or returns to baseline. Subject must discontinue study drug and move to standard therapy if drug is held more than 28 days.

- Grade 4 toxicity: Daily dosing should be stopped.
  With the approval of the PI, talazoparib may be resumed at a lower dose level (1 or 2 dose level decrease) when the toxicity has resolved to grade 1 or baseline. Subject must discontinue study drug and move to standard therapy if drug is held more than 28 days.

| **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 |

## 4.7 Concurrent and supportive care

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient are allowed, including drugs given prophylactically (e.g., Antiemetics +/- steroids, colony stimulating factors), with the following exceptions:

- No other investigational therapy should be given to patients.

- No anticancer agents other than the study medications administered as part of this study protocol should be given to patients.

The concurrent use of all other drugs, over-the-counter medications, or alternative therapies including herbal supplements will be captured in the electronic medical record.

## 4.8 Criteria for discontinuation of study drug

All patients will be analyzed on an intent-to-treat basis. Treatment will continue until one of the following criteria is met:

Patients who develop progression of disease while on talazoparib therapy will proceed with standard of care therapy. Management of the systemic therapy and further local therapy will then be per the treating physician's preferences.

If a patient develops unacceptable toxicity (defined as toxicity necessitating the discontinuation of study drug) the patient will be removed from the study treatment plan. Further treatment will be individualized for these patients.

Completion of all prescribed protocol therapy.

In the judgment of the investigator that the treatment is not in the best interest of the patient.
Removal from study
Data will be collected until the day after surgery. The patient will then come off study with regards to data collection.

Should a patient withdraw consent, the patient will be removed from study at that time and no further data will be collected.

## 4.9 Criteria for Feasibility and Response

A primary objective of this study is to assess the toxicity profile of women taking single agent talazoparib prior to surgery. A secondary objective is preliminary correlation of biomarkers with treatment efficacy.

As there is currently no data available regarding these endpoints, this feasibility study will provide the first available data in order to plan a larger randomized clinical trial with pCR as an endpoint.

We will start monitoring the aggregate toxicity rate after 7 patients have been enrolled. If greater than 33% of the patients enrolled have either a grade 4 toxicity possibly, probably, or definitely related to the treatment as attributed by the Principal Investigator, or requires a delay in treatment for greater than 4 weeks due to toxicity, we will suspend accrual to the trial

The secondary endpoint will be to assess response as per radiographic evaluation of the tumor by ultrasound during the 2 cycles of single agent talazoparib. Bi-dimensional measurements will be used to evaluate response. A 20% increase in bi-dimensional primary tumor size or 20% increase in the size of any measurable, biopsy-proven regional lymphadenopathy will constitute progression and removal from the talazoparib single agent treatment. In addition, pathologic complete response (pCR) and RCB will be measured and documented in the pathology report. pCR is defined in this study as complete absence of any viable invasive cancer cells in the resected breast and lymph nodes.

In cases where 3 dimensional measurements are given by the radiologist, the volume of the lesion will be estimated by:

(Length x width x height x π)/6. And changes in tumor volume can then be estimated. If using the 3 dimensional measurements, there is a > 20% increase in the volume measurement, the patient will be taken off of study and then proceed with physician's choice chemotherapy.

In the Expansion Cohort, the endpoint will be pathologic response and residual cancer burden (RCB).

In the initial phase of this study, feasibility will be considered achieved if the treatment is proven safe and all 20 patients are able to be accrued within 2 years from initiating accrual.

However, after the initial 13 patients were accrued, given the significant response to single agent therapy, the protocol was amended to allow an expansion group of patients to continue to 4 and up to 6 months, then proceed to surgery and receive systemic therapy after surgery in the adjuvant setting.

### 4.10 Definition of Residual Cancer Burden

The residual cancer burden (RCB) as a continuous variable derived from the primary tumor dimensions, cellularity of the tumor bed, and axillary nodal burden. RCB can also be divided into four classes (RCB-0 to RCB-III) and may be collected as part of the study when all information is available in order to calculate.
RCB-0 (pCR), Minimal RCB (RCB-I), Moderate RCB (RCB-II), and Extensive RCB (RCB-III).
The following parameters are required from pathologic examination in order to calculate Residual Cancer Burden (RCB) after neoadjuvant treatment:

1. The largest two dimensions (mms) of the residual tumor bed in the breast (largest tumor bed if multicentric disease)

2. Submission of the entire largest cross-sectional area of the residual tumor bed for histologic mapping, with specific identification of those slides in the pathology report (e.g. "the largest cross-sectional area of primary tumor bed was submitted in cassettes A5 - A9")

    - If the residual tumor is large (i.e. largest di > 5 cm), then at least 5 representative cassettes from the largest cross-sectional area are sufficient, but should be identified in the original pathology report (e.g. "representative sections from the largest cross- sectional area of primary tumor bed were submitted in cassettes A5 - A9")

3. Histologic assessment of the percentage of the tumor bed area that contains carcinoma (all carcinoma, i.e. invasive and in situ), select one of the following:

    0%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%

    - To assess cellularity it is helpful to scan across the sections of tumor bed and then estimate the average cellularity from the different microscopic fields.

- When estimating percentage cancer cellularity in any microscopic field, compare the involved area with obvious standards, e.g. more or less than half, one quarter, one fifth, one tenth, one twentieth, etc.

- Expect there to be variable cellularity within the cross section of any tumor bed, but estimate the overall cellularity from the average of the estimates in different microscopic fields of the tumor bed.

- e.g. if cellularity in different fields of the tumor bed were estimated as 20%, 10%, 20%, 0%, 20%, 30%, then an average estimate of overall cellularity would be 20%.

4. Histologic estimate of the percentage of the carcinoma in the tumor bed that is in situ, select one of the following:

   0%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%

5. The number of positive (metastatic) lymph nodes

6. The largest diameter (mm) of the largest nodal metastasis

The RCB can be accessed online: www.mdanderson.org/breastcancer_RCB

## 5.0 CORRELATIVE STUDIES

### 5.1 Biopsies

Up to four core biopsies at each time point, will be obtained prior to initiation of therapy with talazoparib, within 7 days prior to the completion of talazoparib (prior to initiation of systemic chemotherapy) and residual tissue available after surgery will be collected once all diagnostic testing needed for patient care is completed. Additionally, up to two FNA's will be collected at each time point to be used for the patient derived xenograft models. For expansion cohort patients, biopsies will only be obtained prior to the initiation of therapy. Tissue collected from participating subjects will be de- linked from all personal identifiers per institutional tissue banking procedures.

The following tissue analyses will be completed if sufficient tissue is able to be obtained:

- Targeted or whole exome sequencing for BRCA pathway mutations and other somatic and germline alterations
- RNA sequencing
- Evaluation of changes in immune response
- Transcriptional profile to assess TNBC subtype, BRCA-ness signature and putative PARP sensitivity predictors
- Functional proteomics with reverse phase protein array (RPPA)
- Generate PDX models and mammosphere cultures from patient derived tumors
- PTEN, gamma-H2A.X, Ki-67 and cleaved caspase 3 by IHC

### 5.2 Patient Derived Xenografts (PDX)

Fresh tumor tissue obtained from patients with BRCA1/2 mutant breast cancer will be used to:

- Process the tumor for implanting into the humanized mammary fat pads of NOD SCID mice to create a collection of HIM/PDX models of BRCA1/2 deficient breast cancer.

- Process the tumor to generate mammosphere cultures for performing comprehensive functional genomic screens in vivo.

We intend to build a collection of Human-In-Mouse (HIM) models of BRCA1/2 mutant breast cancer. These models will be used to understand the basic biology of BRCA-mutant breast cancer and to explore the efficacy of novel targeted therapies. To create these models, we "humanize" the 4th mammary fat pads of NOD SCID mice by removing mouse mammary epithelia and engrafting immortalized human breast fibroblasts to create a human stromal microenvironment. Tumor cells obtained from patients with BRCA1/2 mutant breast cancer are then engrafted into the humanized mammary fat pads of these mice. A major strength of the HIM model is that it uses tumors that are obtained directly from patients and immediately transplanted and propagated in the context of humanized mammary fat pads of recipient mice, resulting in a closer resemblance to the human tumor counterpart than established cell lines. Once established, the tumors will be expanded in mice to generate a collection of BRCA1/2-mutant HIM models. To ensure that our HIMs maintain their similarity to the initial tumors we will perform gene expression analysis and IHC at regular intervals. We will use these established models as pre- clinical models of BRCA1/2-mutant tumors to test the efficacy of various chemotherapeutic agents on human tumors. For example, we will assess the anti-tumor effect of cell cycle checkpoint inhibitors alone or in combination with DNA damaging agents and PARP inhibitors. Models established from tumors that do not respond to therapy will be used to understand resistance mechanisms.

Methods:
In parallel with establishing the HIM models, we will culture BRCA1/2-mutant tumor cells under conditions that enrich for tumor initiating cells (TICs). TICs are reportedly responsible for the establishment and maintenance of all primary breast tumors and their metastases. TICs can be maintained in culture by growing breast cancer cells in defined, serum-free media (Mammocult) on low binding plates. Under these conditions, cells do not attach to the plate, but rather grow as spheres (mammospheres) that retain a relatively high frequency of TICs. Mammosphere cultures will be established by dissociating fresh tumors (obtained directly from biopsies) into single cells suspensions and culturing them in vitro in Mammocult media (STEM cell technologies) on ultralow attachment plates. These cells can be manipulated in vitro and then placed back in the mice for phenotypic analysis. We will use these cultures to perform both gain of function and loss of function screens to identify tumor dependencies. In addition, synthetic lethal screens will be conducted in vivo to identify tumor vulnerabilities.

Mouse surgical procedures
Epithelium will be removed from fat pads of the 4th mammary gland to create "cleared fat pads" in NOD-SCID mice. Three week old female mice will be anesthetized with ketamine (86.98 mg/kg body weight) and xylazine (13.4 mg/kg body weight) via IP injection. When asleep, tape will be applied to the appendages to restrain the animal on its back. An inverted Y-shaped incision will be made along the thoracic-inguinal region to expose the mammary glands. Using the dissecting microscope, the 4th nipple is located and cauterized, as well as the blood vessel near the junction by the lymph node and vessel at a point on the fat pad bridge between the 4th and 5th fat pads. The epithelium area is carefully excised and discarded to create a "cleared fat pad" into which human

breast tissues can be transplanted without interference from the host's mammary epithelium. 250,000 human fibroblasts will be injected into the fat pads in a volume of 30 µl. The volume of matrigel will be 1/2 to 1/3 of the final volume. The skin will be gathered and the incision will be closed with wound clips. The approximate duration of the surgery will be 8-10 minutes. To maintain body temperature, mice will be put on bubble wrap during the surgery. After surgery, the body temperature will be maintained by placing a heat lamp at a distance which controls body heat throughout recovery. Wound clips will be removed after healing has occurred, typically 7-10 days. To avoid graft rejection, animals with a compromised immune system will be used as hosts for the transplants. 2-3 weeks later, human breast tumor organoids and fibroblasts will be injected into the fat pads for development of breast tumor xenografts. Once the xenograft from the first generation (P1) reaches a diameter of 1.5 cm – 2 cm, the mice will be euthanized for tumor tissue collection. Each tumor will be cut into three pieces. One will be snap frozen in liquid nitrogen for cDNA microarray and DNA sequence analysis. Another, will be fixed in formalin and embedded in paraffin for conventional pathological studies and immunohistochemistry. The last piece will be dissociated to generate organoids, part will be stored in liquid nitrogen and part will be passed into 10 NOD-SCID mice in the same manner to produce the next generation of tumor xenograft. When the xenografts of the second generation reach a diameter of 1.5 cm we will collect the tumors in the same manner as before. If all xenografts from the same patient have similar cDNA expression profiles and pathological characteristics, we will generate the third generation of xenografts. This will continue up until the 10th generation.

### 5.3 Circulating Biomarkers

Blood will be collected for germline normal comparisons. One lavender top tube will be collected and isolated for PBMC and cfDNA analysis. PBMCs will be collected at pre-treatment on Day 1, on week 2 (Day 8), and week 4 (Day 22) for assessment of PARP levels and PAR-producing activity. The collected blood will be institutionally logged using a research specific z-code.
For the Expansion Cohort - PBMCs will be collected at baseline and at Cycle 3 Day 1 - (Week 9 Day 1).

Plasma for cfDNA will be collected pre-treatment on Day 1, and within 7 days prior to the completion of the 2 months of talazoparib. Plasma will be collected for exploratory proteomic analysis.
During Expansion – cfDNA will be collected at baseline, Cycle 3 Day 1, and if necessary, at the time of progression prior to the patient being placed on chemotherapy treatment.

### 5.4 Sample and Data Sharing

Sample sharing: In some cases samples may be sent to or received from outside collaborators such as Broad Institute for next-generation sequencing and/or analysis. All samples will be sent under a specific contract or Material Transfer Agreement (MTA). We will protect participant's privacy by coding samples and keeping the master list of identifiers accessible to only key project staff. Data will be kept on secure computers and samples will be kept in freezers in locked laboratories and buildings. Additionally in some other cases, samples may be provided from outside collaborators or institutions for discovery and research purposes. In such cases, the samples should be obtained under IRB-approved protocols at these outside collaborators and institutions to allow them for participation

in this protocol and under a specific grant/ contract or Material Transfer Agreement (MTA) with MD Anderson Cancer Center.

Internal/External Sequencing may be done here at MD Anderson, in one of the Core labs such as Cancer Genomics Lab, but in some cases samples may be sent to outside collaborators for sequencing and/or analysis such as Broad Institute. Sequencing performed by Broad or any other external collaborator will be conducted under specific contract or Material Transfer Agreement (MTA).

Data Sharing: Researchers can do more powerful studies when they share with each other the information they get from studying human samples. NGS data may be placed in a local M.D. Anderson Institutional Data Repository (IDR), such as the access controlled Confederated Data Warehouse; where both deposition of and access to data require governance and approval. In some cases, grant requirements may require deposition of large-scale data into the public Genotypes and Phenotypes database (dbGaP) an access controlled database overseen by the National Center for Biotechnology Information (NCBI). In other cases peer reviewed Journals may require data to be shared through a resource such as dbGaP. Data submitted to those repositories will only be shared in a de-identified fashion and without associated clinical data or identifiers. This data will be used only for research purposes, and the data elements collected and analyzed will only be those that are necessary to conduct this research.

Database access additional protections: The precedent to publically broadcast sequence data has been set by large consortial projects, such as The Cancer Genome Atlas (TCGA) and the Encyclopedia of DNA Elements (ENCODE), in order to maximize data utility. However, we know there is the potential for privacy risks associated with the release of sequence data to databases and while the risk may be small it could grow in the future as technology advances. To minimize this potential, we will implement good faith efforts to ensure patient confidentiality and reduce patient exposure. The database of Genotypes and Phenotypes and others like it are extremely access restricted. Only authorized researchers may deposit or access the data and either or both efforts require MD Anderson institutional approval. Sequence data will only be broadcast through secure transmission processes. All samples will be de-identified with access to the linking table available only to the MD Anderson PI and his/her designees. Only non-identifiable data will be deposited to dbGaP i.e., no linking table or access to a linking table will be available. Research records will be kept separate from medical records and patients will not have access to any of the research data.

Protected health information (PHI) may be collected from medical records that are related to health and/or disease history including test results, medical procedures, and images (such as X-rays) in addition demographic and environmental factors may be requested. Researchers will use this information to better understand how genes affect health and response to treatment. All samples will be de-identified with access to the linking table available only to the MD Anderson PI and his/her designees.

# 6.0 STUDY DRUG COMPLIANCE AND ACCOUNTABILITY

## 6.1 Assessment of Compliance

To ensure that each patient has been complying adequately with his or her study regime, study medication will be returned, counted, and recorded at each patient visit. Copies of all forms documenting returned drug and drug accountability records will be retained by the site. If the records show that the patient is taking less than 80% of the required dose, the patient should be counseled about her compliance. If compliance continues to be a problem (as per the physician's discretion or his designated appointee) study drug should be stopped and patient removed from study.

## 6.2 Assessment of Accountability

The investigator, or an approved representative, e.g. pharmacist, will ensure that all investigational products are stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. All study drug supplies must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the investigator or other site personnel supply study drug to other investigators, patients, or clinics, or allow supplies to be used other than directed by this protocol. Institutional policies will be followed as applicable for drug accountability and disposal of investigational drugs.

# 7.0 ADVERSE EVENT REPORTING AND DATA COLLECTION

## 7.1 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.

## 7.2 Adverse Event Reporting Guidelines

Serious Adverse Event Reporting (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event). All SAEs (expected or unexpected, causally related or not) must also be reported to Pfizer's drug safety vendor, Pfizer U.S. Clinical Trial Department within 24 hours of the Investigator's awareness as follows:

  Pfizer U.S. Clinical Trial Dept.
  Fax: 1-866-997-8322

Protocol specific reporting criteria:

Pregnancy

Pregnancy in a subject being treated with the product should be reported immediately (within 24 hours of becoming aware of the pregnancy) to Pfizer U.S. Clinical Trial Department 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 U.S. Clinical Trial Department as follows:

Pfizer U.S. Clinical Trial Dept.
Fax: 866-997-8322

- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last study treatment/intervention, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

### 7.3 Investigator Communication with Supporting Companies

SAEs will be required to be reported from the time of first protocol-specific intervention, during the course of treatment and within 30 days after the last study visit or 30 days after the last dose of study medication, whichever comes first.

Beyond 30 days of treatment, completion of only those SAEs that, in the judgment of the investigator, are definitely, possibly or probably related to the study treatment will require reporting. Talazoparib serious, related, unlabeled, (unexpected) adverse events will be reported to the FDA as required by 21 CFR 312.32 by the Investigator/Sponsor. These reports may be filed

utilizing the MDACC SAE form. The Investigator/Sponsor will provide Pfizer Drug Safety, with a copy of this report.

All serious adverse events (SAEs) and pregnancy reports whether or not considered drug-related should be reported to Pfizer U.S. Clinical Trial Department (contact information below) within 24 hours of receipt by the investigator/sponsor by using the Pfizer SAE form.

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

Pfizer will review AE data as documented in the final study report submitted.

Clinicians should not wait to collect additional information that fully documents the event before notifying Pfizer U.S. Clinical Trial Dept. of an SAE or pregnancy. Pfizer may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore it is important that clinicians submit additional information requested by Pfizer U.S. Clinical Trial Dept. as soon as it becomes available.

Reporting of SAEs to the IRB will be done in compliance with the standard operating procedures and policies of the IRB and with applicable regulatory requirements.
Contact information for Pfizer U.S. Clinical Trial Department is as follows:

Pfizer U.S. Clinical Trial Depart.
Fax: 866-997-8322

### 7.4 Monitoring

This study will be monitored for compliance by the IND office.

### 7.5 Adverse Event Data Collection

The following information will be collected for all adverse events:

- Start and stop dates
- Severity (grade)
- Relationship to study drug (attribution)

Whether or not the subject discontinued treatment due to the AE

Note all AEs on the Adverse Event Case Report Form (CRF) whether or not related to study drug.

Adverse events will be graded using CTCAE (version 4.03).

AE grading and assignment of attribution require documentation by medical personnel who are directly involved in the clinical care of protocol subjects.

### 7.6 AE/SAE Follow up

All AEs/SAEs, including laboratory abnormalities, that in the opinion of the investigator are clinically significant, will be followed up according to good medical practices.

NOTE: If a subject begins a new anticancer therapy, the adverse event reporting period for non-serious adverse events ends at the time the new treatment is started. Death must be reported if it occurs during the serious adverse event reporting period after the last dose of investigational product, irrespective of any intervening treatment.

## 8.0 STATISTICAL ANALYSIS

Demographic and baseline characteristics will be summarized by treatment arm for all randomized patients using descriptive statistics. Toxicity will be monitored at each of the study visits and documented. The aggregate toxicity rate will be estimated along with 95% confidence intervals, as will the proportions of patients in each of the ultrasound response categories (responding, stable, progression) and the RCB categories along with 95% confidence intervals.

As there is currently no data available regarding these endpoints, this feasibility study will provide the first available data in order to plan a larger randomized clinical trial with pCR as an endpoint.

Feasibility will be considered to be achieved if the treatment is safe and all 20 patients are able to be accrued within 2 years from initiating accrual.

We will start monitoring the aggregate toxicity rate after 7 patients have been enrolled. If greater than 33% of the patients enrolled have either a grade 4 toxicity attributable to the treatment, or require a delay in treatment for greater than 4 weeks due to toxicity, we will suspend accrual to the trial.

Response as evidenced by ultrasonography will be documented. A partial response by ultrasound will be considered if the tumor's greatest dimension has decreased by 20% or greater. Progression will be documented if bi-dimensional primary tumor size or size of any measurable, biopsy-proven regional lymphadenopathy has increased by 20% or greater. Residual Cancer Burden will also be calculated when available at the time of definitive surgery.

Biomarker results will be compared between patients with and without pCR as well as by their radiographic response using the Wilcoxon rank sum test and Fisher's exact test.

Expansion Cohort:

After the first 13 patients were accrued and had significant response, with no grade 4 toxicities, an expansion cohort was planned to estimate pathologic response. As RCB0 and RCB1 has similar excellent outcomes, we will measure all pathologic response in an additional 20 patients. As this cohort will have both hormone receptor positive and negative patients, a single agent therapy with a

30% rate of RCB0 and RCB1 would warrant further investigation into a subsequent larger, randomized trial. This estimate will be needed to inform and plan for the subsequent definitive study. Should 6 patients of these 20 patients in the expansion experience an RCB0 or RCB1 pathologic response at the time of surgery, this would estimate the RCB0 + RCB1 response of 30% with a 95% confidence Interval of 12% - 54%.

## 9.0 PUBLICATION OF TRIAL RESULTS

Publications resulting from this trial may be developed by the investigator who will provide Pfizer an opportunity (within 30 days before submission or other public disclosure) to prospectively review any proposed publication, abstract or other type of disclosure that reports the results of the study.

## 10.0 STUDY CALENDAR

### 10.1 Original Study Schema

A +/- 3 day window is allowed for all study assessments.

| STUDY WEEK | | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **After surgery** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| STUDY DAY | **-28 to 0** | 1 | 8 | 15 | 22 | 29 | 36 | 43 | 50 | 57 | 64 | 71 | 78 | |
| Informed Consent | X | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | |
| General Physical | X | X[a] | | | | X | | | | X | | | | |
| Vitals Signs, Weight | X | X[a] | | | | X | | | | X | | | | |
| Performance Status | X | X[a] | | | | X | | | | X | | | | |
| Baseline Symptoms / Toxicities | X | X[a] | | | | X | | | | X | | | | |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CBC | X | X[a] | X | X | X | X | X | X | X | X | | | | |
| Chemistries<br>Chem 12 and LFTs | X | X[a] | | | | X | | | | X | | | | |
| Pregnancy Test<br>(Serum or urine) | X | | | | | | | | | | | | | |
| Cardiac Scan<br>(MUGA or 2DEcho) | X | | | | | | | | | | | | | |
| Breast Ultrasound | X | | | | X | | | | X | | | | | |
| Biopsies and<br>Correlative studies [b] | X | | | | | | | | X[b] | | | | | X |
| Blood for PBMCs | | X[d] | X | | X | | | | | | | | | |
| Blood for cfDNA | | X[d] | | | | | | | X[b] | | | | | |

a) If screening test performed > 10 days before start of treatment repeat test on Day 1.
b) Must be collected within 7 days prior to the completion of talazoparib treatment.
c) Four core biopsies and two FNA's will be collected at each time point.
d) At time points that require both PBMC and cfDNA sample collection, one lavender top tube will be used to collect blood. PBMC and cfDNA will be isolated from the one collection tube.
e) Negative serum of urine pregnancy test for women within 7 days of receiving the first dose of the study medication for women of childbearing potential. Women will be considered not of childbearing potential and exempt from pregnancy testing if they are either a) older than 50 and amenorrheic for at least 12 consecutive months following cessation of all exogenous hormonal treatments, or b) have documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy, but not tubal ligation

## 10.2 Expansion Cohort

A +/- 3 day window is allowed for all study assessments.

| STUDY WEEK | | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **13** | **17** | **21** | **25** | **At surgery** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| STUDY DAY | **-28 to 0** | 1 | 8 | 15 | 22 | 29 | 36 | 43 | 50 | 57 | 85 | 113 | 141 | 169 | |
| Informed Consent | X | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | |
| General Physical | X | X[a] | | | | X | | | | X | X | X | X | X | |
| Vitals Signs, Weight | X | X[a] | | | | X | | | | X | X | X | X | X | |
| Performance Status | X | X[a] | | | | X | | | | X | X | X | X | X | |
| Baseline Symptoms / Toxicities | X | X[a] | | | | X | | | | X | X | X | X | X | |
| CBC | X | X[a] | | X | | X | | | | X | X | X | X | X | |
| Chemistries Chem 12 and LFTs | X | X[a] | | | | X | | | | X | X | X | X | X | |
| Pregnancy Test (Serum or urine) | X | | | | | | | | | | | | | | |
| Cardiac Scan (MUGA or 2DEcho) | X | | | | | | | | | | | | | | |
| Breast Ultrasound | X | | | | | | | | | X | | X | | X | |
| Biopsies and Correlative studies[c] | X | | | | | | | | | | | | | | X |
| Blood for PBMCs | | X[d] | | | | | | | | X | | | | | |
| Blood for cfDNA | | X[d] | | | | | | | | X | | | | | |

a) If screening test performed > 10 days before start of treatment repeat test on Day 1.
c) Up to four core biopsies and up to two FNA's will be collected at baseline and if progression (Must be collected within 7 days prior to the completion of talazoparib treatment); then prior to the initiation of any systemic therapy.
d) At time points that require both PBMC and cfDNA sample collection, one lavender top tube will be used to collect blood. PBMC and cfDNA will be isolated from the one collection tube.
e) Negative serum of urine pregnancy test for women within 7 days of receiving the first dose of the study medication for women of childbearing potential. Women will be considered not of childbearing potential and exempt from pregnancy testing if they are either a) older than 50 and amenorrheic for at least 12 consecutive months following cessation of all exogenous hormonal treatments, or b) have documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy, but not tubal ligation.

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