CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Open-Label, Randomized, Parallel, 2-Arm, Multi-Center Study of Talazoparib (BMN 673) versus Physician's Choice in Germline BRCA Mutation Subjects with Locally Advanced and/or Metastatic Breast Cancer, Who Have Received Prior Chemotherapy Regimens for Metastatic Disease
Protocol Number:	673-301
Active Investigational Product:	Talazoparib (also known as MDV3800, BMN 673)
IND and EudraCT Numbers:	108708 and 2013-002716-28
Indication:	Locally advanced and/or metastatic breast cancer with germline BRCA1 or BRCA2 mutations
Sponsor:	Medivation, Inc. 525 Market Street, 36th Floor San Francisco, CA 94105 PPD
Development Phase:	Phase 3
Sponsor's Responsible Medical Monitor:	PPD, MD Telephone: PPD Email: PPD
Study Design:	Open-Label, Randomized, Parallel, 2-Arm
Comparison:	Active comparator – physician's choice
Duration of Subject Participation:	Until death
Dose:	1.0 mg/day
Study Population:	Locally advanced and/or metastatic breast cancer subjects with germline BRCA1 or BRCA2 mutations
Original Protocol:	**v1.0 – 17 July 2013**
Amendment 1	**v2.0 – 14 December 2015**

This study will be conducted according to the principles of Good Clinical Practice as described in International Conference on Harmonisation guidelines, including the archiving of essential documents.

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2 SYNOPSIS

NAME OF COMPANY Medivation, Inc. 525 Market Street, 36th Floor San Francisco, CA 94105 NAME OF FINISHED PRODUCT: Talazoparib NAME OF ACTIVE INGREDIENT: Talazoparib tosylate	SUMMARY TABLE Referring to Part of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:
TITLE OF STUDY: A Phase 3, Open-Label, Randomized, Parallel, 2-Arm, Multi-Center Study of Talazoparib (BMN 673) versus Physician's Choice in Germline BRCA Mutation Subjects with Locally Advanced and/or Metastatic Breast Cancer**,** Who Have Received Prior Chemotherapy Regimens for Metastatic Disease		
PROTOCOL NUMBER: 673-301		
STUDY SITES: This study will be conducted at approximately 230 sites internationally in 16 countries (United States, Brazil, Russia, Spain, United Kingdom, Israel, Australia, France, Germany, Italy, Belgium, Ireland, South Korea, Poland, Taiwan, Ukraine). Additional countries and sites may be added.		
PHASE OF DEVELOPMENT: Phase 3		
STUDY RATIONALE: The mutation that predisposes breast cancer susceptibility gene (BRCA) mutation carriers to cancer formation selectively renders tumor cells susceptible to poly ADP ribose polymerase (PARP) inhibition while sparing normal cells that, possessing a normal BRCA allele, are relatively resistant to PARP inhibition. The selection of appropriate therapy for metastatic breast cancer is complex because of the many treatment options and biologic heterogeneity of the disease, including several that have led to development of targeted therapeutics. Among others, the potential treatment options are influenced by estrogen and progesterone receptor and human epidermal growth factor receptor 2 (HER2) status of the tumor. Treatment options for subjects presenting with metastatic breast cancer may also be influenced by what adjuvant therapy was used, how soon after adjuvant therapy the subject relapses, and by sites of metastasis. No therapies have been approved to date that take advantage of the well-defined vulnerability of BRCA mutant tumors. It would be a significant advance to provide a therapy which exploits the vulnerability of BRCA-mutant bearing tumors while sparing normal cells carrying one healthy BRCA allele. However, the lack of prospective, controlled studies in BRCA1 and BRCA2-mutant disease, along		

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with the mixed data from small retrospective studies, underscores the lack of information for making treatment decisions for these subjects. The potential role of BRCA1 in mediation of taxane cytotoxicity is consistent with the observation that the taxanes may be less effective in treatment of BRCA1-associated metastatic breast cancer than sporadic disease.

This coupled with the potential to specifically target the underlying genetic abnormality of the disease highlights the unmet need as well as the need for prospective evaluation of a molecularly rational, targeted therapy in comparison to the standard drugs used. While several agents have been shown to prolong progression-free survival (PFS) and some have modestly improved survival in metastatic breast cancer, the disease is, nevertheless, nearly uniformly fatal. Moreover, standard, non-targeted therapies are associated with substantial toxicity, which limits the quality of life of subjects while they are undergoing treatment.

Two studies of the PARP inhibitor, olaparib, given as a single agent to breast cancer subjects have been published. In one study, subjects with germline BRCA mutations were treated with either 400 mg twice daily or 100 mg twice daily in a non-randomized fashion. Eleven of 27 subjects (41%) receiving the higher dose had objective responses while 6 of 27 (22%) of subjects receiving the lower dose responded. In a second trial, olaparib was evaluated in subjects with germline mutations as well as subjects with triple negative breast cancer in the absence of germline mutations. Ten subjects with germline mutations were enrolled, including 6 with measurable disease. While there were no objective responders, 5 subjects had stable disease. There were also no responders among 16 triple negative breast cancer subjects who either did not have germline BRCA mutations or had unknown BRCA status.

In the Phase 1 study of talazoparib (also known as MDV3800, BMN 673), PRP-001, 18 breast cancer subjects with germline BRCA mutations, who had previously been treated with more than one chemotherapy regimen (range: 1 to 13), were enrolled during dose escalation (n=6) and expansion (n=12) as of 31 Mar 2015. All 18 subjects were treated with talazoparib at dose levels of 900 to 1100 μg/day including 12 in the expansion phase at 1000 μg/day (9 of the 12 subjects have been in the study for ≥ 3 cycles). Eight of 18 subjects have had objective responses, including one confirmed complete response (CR) in a subject with a BRCA2 deleterious mutation.

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OBJECTIVES:

The primary objective of the study is to compare PFS of subjects treated with talazoparib as a monotherapy relative to those treated with protocol-specific physician's choice.

The secondary objectives of the study are to evaluate the following:

- Objective response rate (ORR)
- Overall survival (OS)
- Safety
- Pharmacokinetics of talazoparib

The exploratory objectives are to evaluate the following:

- Duration of response (DOR) for objective responders
- Quality of life for all enrolled subjects (European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire [QLC-C30]/ EORTC Quality of Life Questionnaire – Breast Cancer Module [QLQ-BR23])
- Research assessments related to blood and tumor sampling that includes characterization of tumor sensitivity and resistance to talazoparib

STUDY DESIGN AND PLAN:

The study is an open-label, 2-arm, 2:1 randomized trial of talazoparib versus protocol-specific physician's choice. Subjects with germline BRCA mutations who have received no more than 3 prior cytotoxic chemotherapy regimens for locally advanced and/or metastatic breast cancer will be enrolled. Options for protocol-specific physician's choice include one of the following single-agent chemotherapies:

- Capecitabine, eribulin, gemcitabine, vinorelbine
    - The protocol-specific physician's choice must be determined prior to randomization for each individual subject.

Subjects will be centrally randomized with stratification by the following:

- Number of prior cytotoxic chemotherapy regimens for locally advanced and/or metastatic disease (0 vs. 1, 2, or 3)
- Triple negative (estrogen-receptor negative, progesterone-receptor negative, HER2-negative)

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vs. non-triple negative status based on most recent biopsy

- History of central nervous system (CNS) metastases vs. no CNS metastases

Subjects must start treatment ≤ 5 days from randomization; starting later will be considered a protocol deviation. Treatment with talazoparib or protocol-specific physician's choice will continue until radiographic disease progression as determined by the central Independent Radiology Facility (IRF), unacceptable toxicity, consent withdrawal, physician's decision to terminate treatment, or Sponsor's decision to terminate the trial. Subjects who discontinue from study medication for any reason other than radiographic disease progression as determined by the IRF or initiation of a new antineoplastic therapy must be followed to radiographic progression by imaging assessments (eg, computed tomography [CT] scans). All subjects will be followed for anticancer treatment and survival status until death.

NUMBER OF SUBJECTS PLANNED:

Up to 429 subjects will be enrolled. Subjects randomized into the study will not be replaced.

DIAGNOSIS AND ALL CRITERIA FOR INCLUSION AND EXCLUSION:

Individuals eligible to participate in this study must meet all of the following criteria:

- Histologically or cytologically confirmed carcinoma of the breast
- Locally advanced breast cancer that is not amenable to curative radiation or surgical cure and/or metastatic disease appropriate for systemic single cytotoxic chemotherapy
- Documentation of a deleterious, suspected deleterious, or pathogenic germline BRCA1 or BRCA2 mutation from Myriad Genetics or other laboratory approved by the Sponsor; for data obtained regarding a BRCA1/2 mutation from a non-Myriad laboratory, the pathology report must be submitted to and approved by the Sponsor and a blood sample sent to Myriad for analysis before randomization may occur
- No more than 3 prior chemotherapy-inclusive regimens for locally advanced and/or metastatic disease (no limit on prior hormonal therapies or targeted anticancer therapies such as mechanistic target of rapamycin [mTOR] or CDK4/6 inhibitors, immuno-oncology agents, tyrosine kinase inhibitors, or monoclonal antibodies against CTL4 or VEGF)
- Prior treatment with a taxane and/or anthracycline in the neoadjuvant, adjuvant, locally advanced, or metastatic setting unless medically contraindicated
- 18 years of age or older

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- Have measurable or non-measurable, evaluable disease by the revised response evaluation criteria in solid tumors (RECIST) v.1.1
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
- Adequate organ function as defined below:
  - Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × upper limit of normal (ULN); if liver function abnormalities are due to hepatic metastasis, then AST and ALT ≤ 5 × ULN
  - Total serum bilirubin ≤ 1.5 × ULN (≤ 3 × ULN for Gilbert's syndrome)
  - Calculated creatinine clearance ≥ 30 mL/min by local laboratory or Cockcroft-Gault formula
  - Hemoglobin ≥ 9.0 g/dL with last transfusion at least 14 days before randomization
  - Absolute neutrophil count (ANC) ≥ 1500/mm^3
  - Platelet count ≥ 100,000/mm^3
- Able to take oral medications
- Willing and able to provide written, signed informed consent after the nature of the study has been explained, and prior to any research-related procedures
- A female of childbearing potential (defined in Section 9.7.4.6) must not be pregnant and must agree to avoid pregnancy during the study by using a highly effective birth control method (defined in Section 9.7.4.6) from the time of the first dose of study drug through 45 days after the last dose of study drug
- Male subjects must use a condom when having sex with a pregnant woman and when having sex with a woman of childbearing potential from the time of the first dose of study drug through 105 days after the last dose of study drug. Contraception should be considered for a nonpregnant female partner of childbearing potential
- Male and female subjects must agree not to donate sperm or eggs, respectively, from the first dose of study drug through 105 days and 45 days after the last dose of study drug, respectively
- Females of childbearing potential (defined in Section 9.7.4.6) must have a negative serum pregnancy test at Screening and be willing to have additional pregnancy tests during the study
- Willing and able to comply with all study procedures

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the

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study:

- First-line locally advanced and/or metastatic breast cancer with no prior adjuvant chemotherapy unless the Investigator determines that one of the 4 cytotoxic chemotherapy agents in the control arm would be otherwise offered to the subject
- Prior treatment with a PARP inhibitor (not including iniparib)
- Not a candidate for treatment with at least 1 of the treatments of protocol-specific physician's choice (ie, capecitabine, eribulin, gemcitabine, vinorelbine)
- Subjects who had objective disease progression while receiving platinum chemotherapy administered for locally advanced or metastatic disease; subjects who received low-dose platinum therapy administered in combination with radiation therapy are not excluded
- Subjects who have received platinum in the adjuvant or neoadjuvant setting are eligible; however, subjects may not have relapsed within 6 months of the last dose of prior platinum therapy
- Cytotoxic chemotherapy within 14 days before randomization
- Radiation or anti-hormonal therapy or other targeted anticancer therapy within 14 days before randomization
- Has not recovered from the acute toxicities of previous therapy, except treatment-related alopecia or laboratory abnormalities otherwise meeting the inclusion requirements stated in the inclusion criteria
- HER2 positive breast cancer
- Active inflammatory breast cancer
- CNS metastases
    - Exception: Adequately treated brain metastases documented by baseline CT or MRI scan that has not progressed since previous scans and that does not require corticosteroids (except prednisone ≤ 5 mg/day or equivalent) for management of CNS symptoms. A repeated CT or MRI following the identification of CNS metastases (obtained at least 2 weeks after definitive therapy) must document adequately treated brain metastases
    - Subjects with leptomeningeal carcinomatosis are not permitted

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- Prior malignancy except for any of the following:
  - Prior BRCA-associated cancer as long as there is no current evidence of the prior cancer
  - Carcinoma in situ or non-melanoma skin cancer
  - A cancer diagnosed and definitively treated ≥ 5 years before randomization with no subsequent evidence of recurrence
- Known to be human immunodeficiency virus positive
- Known active hepatitis C virus, or known active hepatitis B virus
- Use of any investigational product (IP) or investigational medical device within 14 days before randomization
- Major surgery within 14 days before randomization
- Myocardial infarction within 6 months before randomization, symptomatic congestive heart failure (New York Heart Association [NYHA] > class II), unstable angina, or unstable cardiac arrhythmia requiring medication)
- Female subjects who are breastfeeding at Screening or planning to become pregnant at any time during study participation through 45 days after the last dose of study drug; male subjects who are planning to impregnate a partner at any time during study participation through 105 days after the last dose of study drug
- 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 randomization
  - Clinically significant bleeding diathesis or coagulopathy, including known platelet function disorders
- Non-healing wound, ulcer, or bone fracture, not including a pathological bone fracture caused by a pre-existent pathological bone lesion
- Known hypersensitivity to any of the components of talazoparib

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INVESTIGATIONAL PRODUCT(S), DOSE, ROUTE AND REGIMEN:

Talazoparib will be administered orally once daily (ie, continuous dosing). Talazoparib should be taken at approximately the same time each day, preferably in the morning. Talazoparib will be swallowed whole, and may be taken with or without food. On days of clinic visits when PK samples are to be drawn, talazoparib should be taken at the clinic after completion of the pre-dose sampling and assessments.

The IP is talazoparib tosylate, a white to off-white crystalline powder. The drug substance is a 4-methylbenzenesulfonate (tosylate) salt of talazoparib free base, the active moiety. The drug product consists of the drug substance formulated with a pharmaceutically suitable excipient filled into hydroxymethylpropylcellulose capsules. Capsules will be provided to the sites in dose strengths of 0.25 mg and 1.0 mg capsules. The dosage strengths are based on the active moiety (talazoparib free base). The capsules for each dose strength are provided in dose-specific colors to provide a visual method of distinguishing dose strengths.

Talazoparib should be stored at room temperature (15 to 30°C; 59 to 86°F). The capsules are supplied in 30-count induction-sealed high-density polyethylene (HDPE) bottles.

Daily dosing of talazoparib can be interrupted for recovery from toxicity for up to 28 days. For interruptions longer than 28 days, treatment at the same or a reduced dose can be considered based on a discussion between the Sponsor or designee and Investigator if evidence of response or clinical benefit to talazoparib is noted. Dose modifications must be made based on observed toxicity as described in Section 9.4.7.1.

DURATION OF TREATMENT:

Subjects are eligible to receive treatment until radiographic disease progression as determined by the IRF, occurrence of unacceptable toxicity, subject or physician decision to stop treatment, or until the study is terminated by the Sponsor.

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REFERENCE THERAPIES, DOSE, ROUTE AND REGIMEN:

Treatment of protocol-specific physician's choice is to include any one of the single-agent chemotherapies listed below. Suggested dosing schedules are noted, but if institution dose and regimen guidelines differ, the site may utilize institution guidelines:

- Capecitabine: 1250 mg/m^2, oral, twice daily, from Day 1 through 14 of a 21-day cycle, 30 minutes after meal.
- Eribulin mesylate: 1.4 mg/m^2 (equivalent to eribulin 1.23 mg/m^2), infusion over 2-5 minutes, Days 1 and 8 of 21-day cycles
- Gemcitabine: 1250 mg/m^2, infusion over 30 minutes, Days 1 and 8 of 21-day cycles
- Vinorelbine: 30 mg/m^2, weekly infusion over 6 to 10 minutes, Days 1, 8 and 15 of 21-day cycles

Dose modifications and reductions are to occur per the package insert and institutional practice, and as described in Section 9.4.7.3.

CRITERIA FOR EVALUATION:

Efficacy:

The primary efficacy measure will be the ability of the treatment to delay progression of breast cancer, assessed using sequential imaging studies digitally submitted to and reviewed by the central IRF. Progression and response will be defined according to RECIST v.1.1 with modifications. Radiographic disease assessment (CT and/or magnetic resonance imaging [MRI]) will be performed within 28 days prior to randomization. Subjects will undergo radiographic disease assessment every 6 weeks (± 7 days) from the date of randomization for 30 weeks.

Thereafter, imaging assessments will be performed every 9 weeks (± 7 days) until progressive disease is radiographically documented as determined by the IRF or the time of initiation of a new antineoplastic therapy. Clinical disease progression should be verified by radiographic imaging as determined by the IRF before discontinuing study treatment (or the subject will not be considered to have a progressive disease event for the purposes of the analysis). Imaging assessments should continue according to the schedule of assessments until radiographic progression is observed by the IRF, unless the subject withdraws consent or initiates a new antineoplastic therapy.

The secondary efficacy measures include ORR (RECIST v.1.1 with modifications) as assessed by the IRF and OS. Confirmation of objective response (CR or partial response [PR]) is not required.

The exploratory efficacy measures are to evaluate DOR in responding subjects and quality of life

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(EORTC QLQ-C30/EORTC QLQ-BR23).

Safety:

The following safety outcome measurements will be assessed:

- Incidence of adverse events (AEs), including serious AEs (SAEs)
- Change in clinical laboratory tests (serum chemistry and hematology)
- Change in vital signs
- Change in physical examination
- Concomitant medication use

Pharmacokinetics:

The following PK parameters will be determined from plasma talazoparib concentrations:

- Trough concentrations of talazoparib

A population PK modeling approach will be used to estimate individual values of apparent clearance (CL/F) and central volume of distribution (V_c/F). Individual CL/F estimates will then be used to estimate individual area under the concentration time curve over a dosing interval (AUCτ).

STATISTICAL METHODS:

Primary Efficacy Analysis:

The primary efficacy analysis is the comparison of PFS in subjects treated with talazoparib versus treatments of protocol-specific physician's choice.

PFS is defined as time from randomization until the date of radiologic progressive disease (per RECIST v.1.1 with modifications as described in Section 24.3) as determined by the central IRF or death from any cause, whichever comes first.

The primary analysis will be conducted when at least 288 PFS events have been observed, and will be performed using the intent-to-treat (ITT) population, defined as all randomized subjects.

The primary analysis will include only radiographic progression events as determined by the central IRF per RECIST v.1.1 with modifications and deaths. Clinical deterioration or radiographic progression determined by Investigators will not be considered progression events for the primary analysis.

A stratified log-rank 2-sided test with a 0.05 level of significance will be used to compare treatment groups. The stratification factors will be the same as used to stratify the randomization schedule as documented in the interactive voice and Web response system (IXRS).

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The median PFS and the associated 95% confidence interval (CI) for each treatment arm will be estimated using the Kaplan-Meier method.

The hazard ratio (HR=$\lambda_{talazoparib}/\ \lambda_{control}$) and the associated 95% CI will be estimated using a Cox regression model with treatment group as the only main effect and stratifying by the same stratification factors as were used for the log-rank test. An unstratified HR and the associated 95% CI will also be presented.

If the p-value for the stratified log-rank test is statistically significant (< 0.05, two-sided) and the observed HR ($\lambda_{talazoparib}/\ \lambda_{control}$) is < 1, the null hypothesis of no difference in PFS will be rejected and it will be inferred that PFS is statistically prolonged in the group receiving talazoparib compared with the group receiving protocol-specific physician's choice of therapy.

Secondary Efficacy Analysis:

Secondary efficacy endpoints include ORR and OS. To maintain experiment-wise 2-sided type I error at 0.05, a detailed multiplicity adjusted inferential procedure for the primary and secondary efficacy analyses will be provided in the Statistical Analysis Plan.

The ORR will be determined by the IRF and is defined as the proportion of subjects with a partial or complete response as defined by RECIST v.1.1 with modifications.

The primary analysis of ORR will be performed among the subjects with baseline measurable disease in the ITT population. In the analysis of ORR, subjects who do not have any post-baseline adequate tumor assessments will be counted as non-responders. Formal hypothesis testing of ORR will be performed using the stratified Cochran-Mantel-Haenszel test. The stratification factors will be the same used to stratify the randomization schedule as documented in the IXRS. The CR responders will be reported separately for the non-measurable disease subjects.

OS is defined as the time from randomization to death due to any cause.

There will be an interim and final analysis for OS. The interim analysis of OS will be conducted at the time of the primary analysis of PFS. At the interim analysis, OS data will be summarized to detect a statistical trend in OS (no formal hypothesis testing). The formal analysis of OS will be conducted when approximately 321 deaths have been observed, and will be performed using the ITT population.

The testing of OS will be conducted using a stratified log-rank 2-sided test. The stratification factors will be the same used to stratify the randomization schedule as documented in the IXRS.

The median OS and the associated 95% CI for each treatment arm will be estimated using the Kaplan-Meier method. The HR and the associated 95% CI will be estimated using a Cox regression model with treatment group as the only main effect and stratifying by the same stratification factors as

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were used for the log-rank test. An unstratified HR and the associated 95% CI will also be presented.

Determination of Sample Size:

This study is designed to provide adequate power for PFS and OS.

For PFS, based on 2:1 randomization allocation ratio, a total of 288 events provide the study with 90% power for a 2-sided log-rank test with a 0.05 level of significance to detect a 50% increase in PFS (hazard ratio [HR]=0.67).

Assuming an exponential distribution of PFS, this corresponds to an increase in median PFS from 20 weeks to 30 weeks. In the current design, the minimum observed effect that would result in statistical significance for PFS is a 28% improvement (HR = 0.78) from 20 to 25.6 weeks.

Up to 429 subjects will be randomized (2:1) and followed to observe the required number of events within the planned study duration (approximately 39 months accrual; approximately 41 months total to observe the required PFS events).

For OS, approximately 321 death events will provide the study with 80% power for a 2-sided log-rank test with an overall 0.05 level of significance to detect a 39% increase in OS (HR=0.72). Assuming an exponential distribution of OS, this corresponds with an increase in median OS from 20 months to 27.8 months.

Safety Analysis:
The analyses of safety will include all subjects who receive any study drug (talazoparib or active control) throughout the study duration.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The Investigator will classify the severity of AEs using the CTCAE v 4.03. A treatment emergent adverse event (TEAE) is defined as any event with an onset date on or after date of first dose of study drug, or any event present before treatment that worsens after treatment. Only TEAEs with an onset date prior to date of last dose + 30 days or the date of initiation of a new antineoplastic therapy (whichever occurs first) will be tabulated in summary tables.

The number and percentage of subjects who experience AEs will be summarized by system organ class, preferred term, relationship to study drug, and severity for each treatment group. A by–subject listing will be provided for those subjects who experience an SAE, including death, or experience an AE associated with discontinuation from study drug.

Clinical laboratory data will be summarized by the type of laboratory test. The number and percentage of subjects who experience abnormal (ie, outside of reference ranges) and/or clinically significant abnormalities after study drug administration will be presented for each clinical laboratory measurement. For each clinical laboratory measurement, descriptive statistics will be provided for

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baseline and all subsequent post-treatment scheduled visits. Changes from baseline to the post-treatment visits will also be provided. Descriptive statistics of vital signs will also be provided in a similar manner. In addition, shift from baseline in CTCAE grade (where applicable) and by high/low flags (where CTCAE grades are not defined) will be presented by treatment group.		

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

ADL	activities of daily living
ADP	adenosine diphosphate
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
$AUC\tau$	area under the concentration time curve over a dosing interval
AUC_{0-24}	area under the concentration time curve from 0 to 24 hours
BOR	best overall response
BRCA1	breast cancer susceptibility gene 1
BRCA2	breast cancer susceptibility gene 2
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	apparent clearance
CMF	cyclophosphamide, methotrexate, and fluorouracil
C_{max}	maximum plasma concentration
CNS	central nervous system
CR	complete response
CRA	clinical research associate
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

EORTC	European Organization for Research and Treatment of Cancer
EU	European Union
EudraCT	EU Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
G-CSF	granulocyte-colony stimulating factor
GCP	Good Clinical Practice
HDPE	high density polyethylene
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
IB	Investigator Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH E6	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
IEC	independent ethics committee
IND	Investigational New Drug (application)
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRF	independent radiology facility
ITT	intent-to-treat
IXRS	interactive voice and Web response system
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NE	non evaluable
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival

PARP	poly(ADP-ribose) polymerase
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	prothrombin time
QLQ-BR23	Breast Cancer-Specific Quality of Life Questionnaire
QLQ-BR30	Quality of Life Questionnaire
RBC	red blood cell (count)
REB	research ethics board
RECIST v.1.1	revised response evaluation criteria in solid tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SPECT	single-photon emission computed tomography imaging
SWOG	South West Oncology Group
TEAE	treatment emergent adverse event
US	United States
ULN	upper limit of normal
Vc/F	apparent central volume of distribution
WBC	white blood cell (count)

Definition of Terms:

Investigational Product (IP): “A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use” (from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 [ICH E6]). The terms “IP” and “study drug” may be used interchangeably in the protocol.

5 ETHICS

5.1 Institutional Review Board or Independent Ethics Committee or Research Ethics Board

Prior to initiating the study, the Investigator will obtain written confirmation that the institutional review board (IRB), independent ethics committee (IEC) or Research Ethics Board (REB) is properly constituted and compliant with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and Good Clinical Practice (GCP) requirements, applicable laws and local regulations. A copy of the confirmation from the IRB/EC/REB will be provided to the Sponsor or designee. The Investigator or designee will provide the IRB/EC/REB with all appropriate material, including the protocol, Investigator Brochure (IB), the Informed Consent Forms (ICFs) including compensation procedures, and any other written information provided to the subjects, including all ICFs translated to a language other than the native language of the clinical site. The study will not be initiated and investigational product (IP) supplies will not be shipped to the site until appropriate documents from the IRB/EC/REB confirming unconditional approval of the protocol, the ICF and all subject recruitment materials (if any) are obtained in writing by the Investigator and copies are received by the Sponsor or designee. The approval document should refer to the study by protocol title and Sponsor protocol number (if possible), identify the documents reviewed, and include the date of the review and approval. The Sponsor will ensure that the appropriate reports on the progress of the study are made to the IRB/EC/REB and the Sponsor by the Investigator in accordance with applicable guidance documents and governmental regulations.

5.2 Ethical Conduct of Study

This study will be conducted in accordance with the following:

- United States (US) Code of Federal Regulations (CFR) sections that address clinical research studies, and/or other national and local regulations, as applicable
- ICH Harmonised Tripartite Guideline: Guideline for GCP E6 (ICH E6)
- The ethical principles established by the Declaration of Helsinki

Specifically, this study is based on adequately performed laboratory and animal experimentation. The study will be conducted under a protocol reviewed and approved by an IRB/EC/REB and will be conducted by scientifically and medically qualified persons. The benefits of the study are in proportion to the risks. The rights and welfare of the subjects will

be respected and subject participation continued as long as the Investigators conducting the study do not find the hazards to outweigh the potential benefits.

Each subject, or his/her legally authorized representative will provide written, informed consent before any study-related tests or evaluations are performed.

5.3 Subject Information and Informed Consent

A properly written and executed ICF, in compliance with the Declaration of Helsinki, ICH E6 (Section 4.8), US CFR, 21 CFR §50 and other applicable local regulations, will be obtained for each subject prior to entering the subject into the study. The Investigator or designee will prepare the ICF and provide the documents to the Sponsor for approval prior to submission to the IRB/EC/REB approval. The Sponsor and the IRB/EC/REB must approve the documents before they are implemented. A copy of the approved ICF from each investigational site and, if applicable, a copy of the approved subject information sheet and all ICFs translated to a language other than the native language of the clinical site, must also be received by the Sponsor or designee prior to any study-specific procedures being performed.

A main and a BRCA test ICF will be included as part of this clinical trial:

- The main ICF includes subject consent for all procedures that are part of this clinical trial (this informed consent must be completed by all subjects before any study-related procedures are performed, except BRCA1/2 mutation testing); the 28-day Screening Period starts when the subject signs the main informed consent
- The BRCA test ICF provides subject consent for only the blood test for determination of germline BRCA1/2 mutation status; it does not provide consent for other study-related procedures (a separate BRCA test ICF is not required if the subject has already signed the main informed consent)

Separate additional ICFs may be included as part of the trial according to country requirements (eg, certain countries may require separate ICFs for genetic and/or tissue sampling).

The Investigator will provide copies of the signed ICF to each subject (or the legally authorized representative of the subject) and will maintain the original in the record file of the subject. The Investigator will also fully document the informed consent process in the subject's source documents.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Prior to beginning the study, the Investigator at each site must provide to the Sponsor or designee, a fully executed and signed US Food and Drug Administration (FDA) Form FDA 1572, a current and signed Curriculum vitae and a Financial Disclosure Form. All sub-Investigators must be listed on Form FDA 1572. Financial Disclosure Forms must also be completed for all sub-Investigators listed on the Form FDA 1572 who will be directly involved in the treatment or evaluation of subjects in this study. Any change in the Principal Investigator at the site requires Sponsor approval.

The study will be administered by and monitored by employees or representatives of the Sponsor. Clinical Research Associates (CRAs) or trained designees will monitor each site on a periodic basis and perform verification of source documentation for each subject as well as other required review processes. The Sponsor Regulatory Affairs Department, in conjunction with the Drug Safety & Pharmacovigilance Department (or their respective designees) will be responsible for the timely reporting of serious adverse events (SAEs) to appropriate regulatory authorities as required.

Clinical laboratory evaluations will be performed at the local laboratories associated with the study sites, with the exception of the hematologic evaluations noted in Section 12.3.2. For subjects with acceptable retrospective BRCA testing, confirmation of BRCA carrier status will be done at a specific central laboratory. For all other subjects, prospective BRCA testing performed at a regional central laboratory is required before randomization. The specific laboratories and instructions for sample collection, processing and shipment are provided in the laboratory manual.

7 INTRODUCTION

A comprehensive review of talazoparib (also known as MDV3800, BMN 673) is contained in the Investigator Brochure (IB) supplied by the Sponsor. Investigators are to review this document prior to initiating this study.

7.1 Study Background

7.1.1 Talazoparib

Poly ADP-ribose polymerase (PARP) represents a family of enzymes, of which at least two (PARP1 and PARP2) play important roles in 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.

7.1.2 Nonclinical Study Findings for Talazoparib

The nonclinical study findings in the rat and the dog 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 tosylate, the drug substance containing 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.

7.1.3 Preliminary Clinical Study Findings for Talazoparib

Two Phase 1 studies (PRP-001 and PRP-002) of talazoparib were conducted; one Phase 2 study (673-201) has been initiated.

The first-in-human study of talazoparib (PRP-001) was initiated 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, 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 (de Bono, 2013, J.Clin Oncol.) and are described below. 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, ovarian, and pancreas cancer with deleterious germline mutations; 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 48 subjects having deleterious BRCA mutations. Tumors (number with deleterious BRCA 1/2 mutations) included 34 ovarian/ primary peritoneal (28); 20 breast (18); 8 Ewing's; 4 pancreas; 2 colon; 1 prostate (1), and 1 mullerian carcinosarcoma. A total of 27 and 21 subjects had BRCA 1 and 2 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.

- Subject PPD (0.9 mg/day): Grade 3 thrombocytopenia reported on Days 29-42 resolved after discontinuation of study drug; no hemorrhage was noted. Grade 3 anemia observed during this time also resolved
- Subject PPD (1.1 mg/day): Grade 3 thrombocytopenia reported on Days 22-26, became Grade 4 thrombocytopenia on Days 26-32. It resolved after discontinuation of study drug; the subject received a platelet transfusion. No hemorrhage was noted. The subject died on Day 52 due to invasive breast cancer
- Subject PPD (1.1 mg/day): Grade 3 thrombocytopenia reported on Days 28-32 resolved after discontinuation of study drug; no hemorrhage was noted

None of the 6 subjects who received a dose of 1 mg/day during the dose-escalation phase of this study had a dose-limiting toxicity, although Grade 3 anemia and neutropenia were observed in later treatment cycles. 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 without hemorrhage. 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.

After closure of enrollment to this study, 110 subjects had received at least one dose of talazoparib of which 77 subjects received the recommended dose of 1 mg/day. Dose reductions were reported for 26 (34%) of the 77 subjects treated at the recommended dose. The dose was reduced once (to 0.75 mg/day) for 14 subjects, twice (to 0.75 mg/day, then 0.5 mg/day) for 11 subjects, and three times (to 0.75 mg/day, 0.5 mg/day, then 0.25 mg/day) for one subject. In 20 (77%) of the 26 subjects with dose reductions, the dose reductions were due to an AE. The most frequently reported AEs leading to dose modification were thrombocytopenia and anemia, each reported for 20 subjects, followed by neutropenia reported for 12 subjects.

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. At the recommended dose of 1 mg/day, the mean maximum plasma concentration (C_{max}) was 10.6 (± 4.2) ng/mL on Day 1, and 21.0 (± 8.0) ng/mL on Day 35. The mean area under the concentration time curve from 0 to 24 hours (AUC_{0-24}) at the recommended dose of 1 mg/day was 85.1 (± 29.1) and 202.0 (± 54.0) ng-hr/mL on Day 1 and Day 35, respectively.

Objective (RECIST v.1.1) and/or CA-125 responses occurred at doses ≥ 100 µg/day in 11 of 25 subjects (44%) and 19 of 27 subjects (70%) 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 occurred in 8 of 18 (44%) BRCA-carrier breast cancer subjects. Clinical benefit (CR/PR/SD >12 weeks) occurred in 12 of 18 (67%) of BRCA-carriers.

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

7.2 Study Rationale

The mutation that predisposes BRCA mutation carriers to cancer formation selectively renders tumor cells susceptible to PARP inhibition while sparing normal cells that, possessing a normal BRCA allele, are relatively resistant to PARP inhibition.

The selection of appropriate therapy for metastatic breast cancer is complex because of the many treatment options and biologic heterogeneity of the disease, including several that have led to development of targeted therapeutics. Among others, the potential treatment options are influenced by estrogen and progesterone receptor and human epidermal growth factor receptor 2 (HER2) status of the tumor. Treatment options for subjects presenting with metastatic breast cancer may also be influenced by what adjuvant therapy was used, how soon after adjuvant therapy the subject relapses, and by sites of metastasis.

No therapies have been approved that take advantage of the well-defined vulnerability of BRCA mutant tumors. It would be a significant advance to provide a therapy which exploits the vulnerability of BRCA-mutant bearing tumors while sparing normal cells carrying one healthy BRCA allele.

Prognosis and best treatment practices in breast cancer subjects with germline BRCA1 or BRCA2 mutations have, for the most part, been characterized in retrospective studies from single institutions. When compared to sporadic primary breast cancer, BRCA1 disease is more likely to be hormone receptor negative and BRCA2 disease is more likely to be hormone receptor positive (Atchley, 2008, J.Clin.Oncol.), (Verhoog, 1999, J.Clin.Oncol.). BRCA1 and BRCA2 breast cancers have been reported to be higher grade and higher stage and to have more extensive and extracapsular lymph node involvement compared to non-BRCA cancers (Atchley, 2008, J.Clin.Oncol.), (Rennert, 2007, N.Engl.J.Med.).

However, a review of 20 studies regarding disease outcomes in primary BRCA-associated breast cancer concluded that while these subjects have an increased risk of contralateral breast cancer, the presence of the mutation provided no other prognostic information (Liebens, 2007, Eur.J.Cancer).

First-line therapy of metastatic breast cancer often includes an anthracycline and/or taxane. The combination of doxorubicin and paclitaxel in newly metastatic breast cancer was shown to improve response rates and time to treatment failure relative to either doxorubicin or paclitaxel given as single agents but had no significant impact on overall survival (OS) (Sledge, 2003, J.Clin.Oncol.). This supports the use of single-agent chemotherapy where survival is not adversely impacted while limiting the toxicity of therapy.

The utility of anthracyclines is also limited by cardiotoxicity concerns, particularly if the subject was exposed to anthracyclines in the adjuvant setting. In addition, growing evidence from nonclinical studies suggests that sensitivity to taxanes may require functional BRCA1 protein (Lafarge, 2001, Oncogene), (Quinn, 2003, Cancer Res.), (Tassone, 2003, Br.J.Cancer). In response to abnormal mitosis induced by taxanes, BRCA1 protein activates the mitotic spindle checkpoint and promotes apoptosis by the c-Jun-N-terminal kinase/stress-activated protein kinase pathway, leading to cell death (Harkin, 1999, Cell), (Quinn, 2009, Gynecol.Oncol.).

Responsiveness of BRCA-associated breast cancer to chemotherapy is poorly understood, and the data are conflicting. Retrospective neoadjuvant subject series have suggested that primary breast cancer in BRCA1 carriers is platinum-sensitive and relatively unresponsive to anthracyclines and/or taxanes (Byrski, 2010, J.Clin.Oncol.) while other studies have found that BRCA1 is relatively responsive to anthracyclines and/or taxanes while BRCA2 disease is less responsive than sporadic primary breast cancer to these drug classes (Arun, 2011, J.Clin.Oncol.). More recent data (Tutt, 2014, SABCS) demonstrated a prolonged median PFS in TNBC patients with a known deleterious BRCA1/2 mutation when carboplatin was administered compared with docetaxel.

The efficacy of standard chemotherapeutics in BRCA mutation carriers with metastatic breast cancer is unclear. In one retrospective review of first-line treatment of metastatic disease, BRCA1 subjects had a similar response rate and survival to those with sporadic disease treated with standard regimens (anthracycline-based, taxane-based or the combination regimen of cyclophosphamide, methotrexate, and fluorouracil [CMF]), while BRCA2 subjects appeared to have higher response rates with better survival than sporadic subjects (Kriege, 2009, J.Clin.Oncol.). In another series from the same institution evaluating taxane sensitivity in first- to third-line metastatic breast cancer, BRCA1 subjects appeared to be less responsive to docetaxel or paclitaxel than subjects with sporadic breast cancer, while BRCA2 subjects appeared to be more sensitive (Kriege, 2012, Cancer).

Sensitivity of BRCA1- and BRCA2-associated breast cancer to other standard chemotherapeutic agents has not been reported but is not generally perceived to be different from sporadic breast cancer. However, the lack of prospective, controlled studies in BRCA1 and BRCA2-mutant disease along with the mixed data from small retrospective studies underscores the lack of information for making treatment decisions for these subjects. The potential role of BRCA1 in mediation of taxane cytotoxicity is consistent with the observation that the taxanes may be less effective in treatment of BRCA1-associated metastatic breast cancer than sporadic disease. This, coupled with the potential to specifically

target the underlying genetic abnormality of the disease, highlights the unmet need as well as the need for prospective evaluation of a molecularly rational, targeted therapy in comparison to the standard drugs used.

While several agents have been shown to prolong progression-free survival (PFS) and some have modestly improved survival in metastatic breast cancer, the disease is, nevertheless, nearly uniformly fatal. Moreover, standard, non-targeted therapies are associated with substantial toxicity, which limits the quality of life of subjects while they are undergoing treatment.

Two studies of the PARP inhibitor, olaparib, given as a single agent to breast cancer subjects have been published. In one study, subjects with germline BRCA mutations were treated with either 400 mg twice daily or 100 mg twice daily in a non-randomized fashion. Eleven of 27 subjects (41%) receiving the higher dose had objective responses while 6 of 27 (22%) of subjects receiving the lower dose responded (Tutt, 2010, Lancet). In a second trial, olaparib was evaluated in subjects with germline mutations as well as subjects with triple negative breast cancer in the absence of germline mutations.

Ten subjects with germline mutations were enrolled, including 6 with measurable disease. While there were no objective responders, 5 subjects had stable disease. There were also no responders among 16 triple negative breast cancer subjects who either did not have germline BRCA mutations or had unknown BRCA status (Gelmon, 2011, Lancet Oncol.).

In talazoparib Phase 1 PRP-001, 18 breast cancer subjects with germline BRCA mutations, who have previously been treated with more than one chemotherapy regimen (range: 1 to 13), have been enrolled during dose escalation (n=6) and expansion (n=12) as of 31 Mar 2015. All 18 subjects were treated with talazoparib at dose levels of 900 to 1100 µg/day including 12 in the expansion phase at 1000 µg/day (9 of the 12 subjects have been in the study for ≥ 3 cycles). Eight of 18 subjects have had objective responses, including one confirmed CR in a subject with a BRCA2 deleterious mutation. Two of 2 BRCA breast responders had responded to prior platinum while 0 of 4 non-responders to prior platinum responded to talazoparib. Six of 12 BRCA breast subjects with no prior platinum have responded.

7.3 Summary of Overall Risks and Benefits

Talazoparib was selected for clinical evaluation in tumors with demonstrated or potential defects in DNA repair pathways, such as BRCA mutations based on its mechanism of action, preclinical activity and PK and toxicity profiles. Talazoparib has been shown to be a highly

selective and potent cytotoxic agent in human cancer cell lines and in animal models of tumors harboring mutations that compromise DNA repair pathways.

Preliminary data from PRP-001 show inhibition of PARP activity in peripheral blood mononuclear cell at doses ≥ 100 µg/day. Objective (RECIST v.1.1) and/or CA-125 responses occurred at doses ≥ 100 µg/day in 11 of 25 subjects (44%) and 19 of 27 subjects (70%) with BRCA-carrier ovarian and peritoneal cancer, respectively. Clinical benefit (CR/PR/SD >24 weeks) occurred in 23 of 28 (82%) BRCA-carrier ovarian and peritoneal cancer subjects. Objective responses occurred in 8 of 18 (44%) BRCA-carrier breast cancer subjects. Clinical benefit (CR/PR/SD >12 weeks) occurred in 12 of 18 (67%) of BRCA-carriers.

Pharmacokinetic parameters demonstrated a high bioavailability with a distribution profile indicating extensive tissue distribution, and a duration of exposure sufficient to support once daily dosing. Changes in hematology parameters were early markers of toxicology findings. Anemia, thrombocytopenia, and neutropenia have all been observed in the Phase 1 trials, including grade 3 to 4 events; however, these subjects did not require discontinuation of study drug or withdrawal from the study. All subjects are being monitored for myelosuppression in the ongoing studies. In PRP-001, 8 of 18 breast cancer subjects with germline BRCA mutations have had objective responses, including one confirmed CR.

These data, together with those reported from recent literature in the rationale section above, support the clinical investigation of talazoparib in a Phase 3 study in locally advanced or metastatic breast cancer subjects with germline BRCA1 or BRCA2 mutations.

8 STUDY OBJECTIVES

The primary objective of the study is to compare PFS of subjects treated with talazoparib as a monotherapy relative to those treated with protocol-specific physician's choice.

The secondary objectives of the study are to evaluate the following:

- Objective response rate (ORR)
- Overall survival (OS)
- Safety
- Pharmacokinetics of talazoparib

The exploratory objectives are to evaluate the following:

- Duration of response (DOR) for objective responders
- Quality of life for all enrolled subjects (European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire [QLC-C30]/ EORTC Quality of Life Questionnaire – Breast Cancer Module [QLQ-BR23])
- Research assessments related to blood and tumor sampling that includes characterization of tumor sensitivity and resistance to talazoparib

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

The study is an open-label, 2-arm, 2:1 randomized trial of talazoparib versus protocol-specific physician's choice. Subjects with germline BRCA mutations who have received no more than 3 prior cytotoxic chemotherapy regimens for locally advanced and/or metastatic breast cancer will be enrolled.

Options for protocol-specific physician's choice include one of the following single-agent chemotherapies:

- Capecitabine, eribulin, gemcitabine, vinorelbine
    - The protocol-specific physician's choice must be determined prior to randomization for each individual subject.

Subjects will be centrally randomized with stratification by the following:

- Number of prior cytotoxic chemotherapy regimens for locally advanced and/or metastatic disease (0 vs. 1, 2, or 3)
- Triple negative (estrogen-receptor negative, progesterone-receptor negative, HER2-negative) vs. non-triple negative breast cancer based on most recent biopsy
- History of central nervous system (CNS) metastases vs. no CNS metastases

A Screening visit will occur within 28 days before randomization and a baseline visit within 7 days before randomization.

Subjects must start treatment ≤ 5 days from randomization; starting later will be considered a protocol deviation. Subjects will present for weekly treatment visits for the first 2 cycles of talazoparib or protocol-specific physician's choice. Treatment with talazoparib or protocol-specific physician's choice will continue until radiographic disease progression as determined by the central Independent Radiology Facility (IRF), unacceptable toxicity, consent withdrawal, physician's decision to terminate treatment, or Sponsor's decision to terminate the trial.

Talazoparib will be administered orally daily for 21 days in repeated 21-day cycles at 1.0 mg/day with provision for dose modifications as described in Section 9.4.7.1. Protocol-specific physician's choice will also be administered in 21-day cycles in accordance with the dose and regimens suggested below unless institution dose and regimen guidelines differ in which case the site may utilize institution guidelines:

- Capecitabine: 1250 mg/m^2, oral, twice daily from Day 1 through 14 of 21-day cycles, 30 minutes after meal.

- Eribulin mesylate: 1.4 mg/m^2 (equivalent to eribulin 1.23 mg/m^2), infusion over 2-5 minutes, Days 1 and 8 of 21-day cycles
- Gemcitabine: 1250 mg/m^2, infusion over 30 minutes, Day 1 and 8 of 21-day cycles
- Vinorelbine: 30 mg/m^2, weekly infusion over 6-10 minutes, Day 1, 8, and 15 of 21-day cycles

Dose modifications and reductions for protocol-specific physician's choice are to occur per the package insert and institutional practice.

Tumor assessments will be performed for subjects by computed tomography (CT [preferred method]), magnetic resonance imaging (MRI), and x-ray. All subjects will also have nuclear medicine whole body bone scans within 12 weeks before randomization.

Tumor assessments are to be performed every 6 weeks (± 7 days) from the date of randomization for the initial 30 weeks, and every 9 weeks thereafter (± 7 days), regardless of any dose interruptions or dose delays until radiographic disease progression as determined by the IRF or initiation of a new antineoplastic therapy. Tumor assessments can occur as clinically indicated anytime during the study, and at the time of clinical suspicion of disease progression. Optional tumor marker assessments (eg, CA15-3 or CA27-29) are to be performed every 6 weeks (± 7 days) from the date of randomization for the initial 30 weeks, every 9 weeks thereafter (± 7 days), and at the End of Treatment but should not be repeated if normal at baseline. If bone metastasis is seen at Baseline, bone scans will be repeated every 12 weeks (± 7 days) until radiographic disease progression as determined by the IRF or initiation of a new antineoplastic therapy and as clinically indicated. In subjects without baseline bone lesions, bone scans should be repeated only as clinically indicated.

An End of Treatment visit will be performed for subjects 30 days (-3 or +10 days postdose) after the last dose of study drug.

Subjects who discontinue from study drug for reasons other than radiographic disease progression as determined by the IRF or initiation of a new antineoplastic therapy should be followed to radiographic progression by imaging assessments (eg, CT scans) unless the subject withdraws consent. Clinical disease progression should be verified by radiographic imaging as determined by the IRF; study treatment should continue until radiographic progression has occurred. All subjects will be followed for anticancer treatment and survival status. Survival follow-up will continue until death. Follow-up for anticancer therapy and survival status will occur every 60 days (± 7 days) after the last dose of study drug for 1 year and every 90 days (± 14 days) thereafter, or when requested by the Sponsor.

A summary of events and assessments are provided by visit in Table 9-1.

Table 9-1: Schedule of Events

	Screening/ Baseline [a]		Cycles 1 - 2 [c]			Cycles ≥ 3[c]			Every 6 Weeks (for 1st 30 weeks)	Every 9 Weeks (starting 39 weeks after randomization)	Unsch[j]	End of Treat ment Visit [e]	Long-Term Follow-Up [f]
Procedure/Assessment [b]	**(Day -28 to -1)**	**(Day -7 to -1)**	**Day 1**	**Day 8 [c] (± 3)**	**Day 15 (± 3)**	**Day 1**	**Day 8 [d] (± 3)**	**Day 15 [d] (± 3)**	**Weeks 6, 12, 18, 24, 30 (± 7)**	**Weeks 39+ (± 7)**	**na**	**30 days postdose(-3 to +10)**	**See footnote [f] for schedule**
Informed consent [g]	X												
Medical history [h]	X												
Vital signs [i]	X	X	X	X	X	X					[X]	X	
Physical examination [k]	X	X	X			X					[X]	X	
ECOG assessment [l]	X		X			X						X	
Tumor assessment [m]	X								X	X	[X]	X	
Optional tumor marker assessment (eg, CA15-3, CA27-29) [m]	[X]								[X][m]	[X][m]		[X]	
Brain CT or MRI[m]	X								[X]	[X]	[X]		
Bone scan[m]	X								Every 12w	Every 12w	[X]		
PK blood sampling [n]			X			X					[X]		
Clinical laboratory tests [o]													
Hematology [o]	X	X	X	X	X	X	[X[o]]	[X[o]]			[X]	X	
Serum chemistry [o]	X	X	X			X					[X]	X	
Coagulation/urinalysis [o]		X											
Calculated creatinine clearance [o]	X												
Serum pregnancy test [p]	X		[X]			[X]					[X]	[X]	
Urine pregnancy test[p]			X			X					[X]	X	
Quality of life questionnaire[q]		X	X			X						X	
AEs and SAEs [r]	X	X	X	X	X	X	[X]	[X]			X	X	

	Screening/ Baseline [a]		Cycles 1 - 2 [c]			Cycles ≥ 3[c]			Every 6 Weeks (for 1st 30 weeks)	Every 9 Weeks (starting 39 weeks after randomization)	Unsch[j]	End of Treat ment Visit [e]	Long-Term Follow-Up [f]
Procedure/Assessment [b]	**(Day -28 to -1)**	**(Day -7 to -1)**	**Day 1**	**Day 8 [c] (± 3)**	**Day 15 (± 3)**	**Day 1**	**Day 8 [d] (± 3)**	**Day 15 [d] (± 3)**	**Weeks 6, 12, 18, 24, 30 (± 7)**	**Weeks 39+ (± 7)**	na	**30 days postdose(-3 to +10)**	**See footnote [f] for schedule**
ECG [s]		X									[X]	X	
Concomitant medications [t]	X	X	X	X	X	X	[X]	[X]			X	X	
Subject contact: OS, obtain cancer treatment													X
Talazoparib treatment [u]			Once-daily dosing										
Chemotherapy treatment [v]			X	[X]	[X]	X	[X]	[X]					
Documentation of BRCA1, BRCA2 mutation [w]	X												
Blood sample (germline BRCA assay) [x]	X												
Blood sample (Genomic) [y]	X											[X]	
Tumor tissue collection [z]	X												
Optional tumor biopsy [aa]	[X]											[X]	

[X] denotes an optional test.

Abbreviations: AE, adverse event; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; MRI, magnetic resonance imaging; na, not applicable; OS, overall survival; PK, pharmacokinetics; SAE, serious adverse event; unsch, unscheduled; w, week

[a] The Screening visit must occur within 28 days before randomization, and the baseline visit must occur within 7 days before randomization. If Screening is performed within 7 days before randomization, physical examination, vital signs, and clinical laboratory assessments do not need to be repeated at baseline. Screening and baseline procedures may be performed on the same day as long as it is within 7 days before randomization. Subjects must receive their first treatment with talazoparib or protocol-specific physician's choice within 5 days of being randomized.

[b] All assessments will be performed before dosing except as indicated.

[c] Each cycle will be 21 days long, with daily dosing with talazoparib on Days 1 to 21. The first day of treatment in Cycle 1 is defined as Day 1; a ± 3 day window (relative to Day 1) is allowed for any Day 8 or Day 15 clinic visit.

[redacted]

[d] The Day 8 or Day 15 visit may be omitted in Cycles ≥ 3 for subjects not experiencing significant toxicities. Subjects assigned to talazoparib or capecitabine are not required to ingest the Day 8 or Day 15 dose at the clinic on a day the visit is optional. A Day 8 or Day 15 visit may not be required for a hematology assessment as the hematology assessment can be performed at a local laboratory outside of the investigational site laboratory as long as laboratory reports are provided to the Investigator for evaluation 24 hours prior to dosing.

[e] This visit may occur 27 to 40 days after the last dose of study drug. Tumor assessments are only required if not performed in the previous 28 days.

[f] Long-term Follow-up: Subject contact for: survival, cause of death, and additional cancer treatment every 60 days (± 7 days) after last dose for 1 year, every 90 days (± 14 days) thereafter, or when requested by the Sponsor.

[g] Written informed consent using the main informed consent form is required before any protocol-specified procedures or assessments are performed. Written informed consent for only the BRCA1/2 mutation testing blood test may be obtained at any time (including prior to the screening period).

[h] Includes full oncologic history, prior treatments, and demographics.

[i] Systolic and diastolic blood pressure, heart rate, respiration rate, and temperature at scheduled time points; weight only at Screening, baseline, Cycle 1 Day 1 pre-dose, Day 1 of each Cycle pre-dose, End of Treatment; height at Screening only.

[j] Anytime necessary to assess or follow up AEs, to perform scans, at the subject request, or at the Investigator request. Record the date and reason for the unscheduled visit in the source documentation. Perform study procedures as clinically appropriate. Imaging may be performed, as appropriate, for subjects who are symptomatic and/or for whom radiographic disease progression or response is being determined.
For subjects assigned to talazoparib only, obtain PK samples as appropriate.

[k] Screening/baseline physical examination to be a complete exam; subsequent examinations to be focused on physical examinations at the discretion of the Investigator based on the subject's clinical condition.

[l] ECOG performance status.

[m] CT (preferred), MRI, or X-ray.
A brain MRI or CT is to be performed at Screening/baseline to evaluate subjects for presence/absence of brain metastases. Newly diagnosed CNS metastases at Baseline/Screening makes a patient ineligible until such time as it can be adequately treated, at which point the patient may be re-screened. If adequately treated metastatic disease to the brain is present at Screening/Baseline, an MRI or CT will be performed during the study as clinically indicated. Post-baseline assessments should be performed using the same technique used at Screening/Baseline. CT/MRI scans performed as standard of care before the main ICF was signed and within the 28-day screening period may be used as the Screening tumor assessments if the scans were completed per the specific study requirements (as specified in the Imaging Manual).
Tumor assessment to be performed every 6 weeks (± 7 days) from the date of randomization for initial 30 weeks, and every 9 weeks thereafter (± 7 days), regardless of any dose interruptions or dose delays. Tumor assessments can occur as clinically indicated anytime during the study, and at the time of clinical suspicion of disease progression. Clinical disease progression should be verified by radiographic imaging as determined by the IRF; study treatment should continue until radiographic progression has occurred. Tumor assessments will also continue to be performed for subjects who discontinue from study drug for reasons other than radiographic disease progression as determined by the IRF or initiation of a new antineoplastic therapy. Post-baseline tumor assessments should be performed using the same technique used at Screening/baseline.
Optional tumor marker assessments (eg, CA15-3, CA27-29) are to be performed every 6 weeks (± 7 days) for the initial 30 weeks, every 9 weeks (± 7 days) thereafter, and at the End of Treatment, but should not be repeated if normal at baseline.
Bone scan will be performed at Screening/baseline (a bone scan obtained up to 12 weeks before randomization may be substituted). If metastatic disease to the bone is present at Screening/Baseline, a bone scan will be performed every 12 weeks (± 7 days) and as clinically indicated. Post-baseline assessments should be performed using the same technique used at Screening/Baseline.

[n] Sparse PK samples will be collected on Day 1 of Cycles 1 through 4 from subjects randomized to receive talazoparib. Sparse PK sampling will consist of a pre-dose sample collected ≤ 60 minutes prior to dosing, and 2 post-dose samples collected ≥ 30 minutes after dosing. For the pre-dose sample, collection of whether the subject has or has not eaten within 2 hours before dosing should also be performed. The collection times of the 2 post-dose samples will be separated by ≥ 2 hours. Within individual subjects, efforts should be made to collect PK samples at different times relative to dosing across the study days with PK assessments. Samples may be collected at unscheduled visits. In the event of a dose delay on Day 1 of Cycles 1-4, the pre and post-dose PK sample should be drawn on the day the subject resumes their next dose of talazoparib.

[o] Hematology: hemoglobin, hematocrit, platelet count, red blood cell (RBC), white blood cell (WBC) count, absolute neutrophil count (ANC), and WBC differential (absolute and/or percent) (refer to Table 9-6). Weekly blood counts are to be obtained during the first 2 cycles. Starting with Cycle 3, hematology counts will be obtained in each cycle on Day 1 and on either Day 8 (± 3 days) or Day 15 (± 3 days). Hematology assessments done at visits other than Day 1 of each cycle may be performed at a local laboratory outside of the investigational site laboratory as long as laboratory reports are provided to the Investigator for evaluation 24 hours prior to dosing. Hematology assessments scheduled for the day of the dosing must be available and assessed for abnormalities before dosing. The sampling for the hematology assessment can be drawn within 72 hours prior to dosing.
Serum chemistry: total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase (LDH), total protein, albumin, sodium, potassium, chloride, carbon dioxide (or bicarbonate), calcium, phosphorus, magnesium, blood urea nitrogen (BUN; also called urea), creatinine, uric acid, glucose. Coagulation: activated partial thromboplastin time (aPTT) and prothrombin time (PT)/international normalized ratio (INR); will be assessed only at baseline.
Urinalysis (dipstick): pH, specific gravity, protein, glucose, ketones, bilirubin, blood, leukocyte esterase. Microscopy is required if dipstick results for blood and leukocyte esterase are positive; will be assessed only at baseline.
Calculated creatinine clearance: to be performed at Screening. Use local laboratory results or calculate by Cockcroft-Gault formula.
Serum chemistry can be drawn within 72 hours prior to dosing.

[p] For women of child-bearing potential only. The protocol definition of “women not of childbearing potential” is provided in Section 9.7.4.6. Local urine or serum (as per local regulations/practice) pregnancy test should be performed at Day 1 of each cycle, prior to administration of study medication; if a urine pregnancy test is positive, study drug must be interrupted and a serum pregnancy test performed. Additional pregnancy testing may be performed throughout the study as clinically indicated.

[q] EORTC QLQ-C30/EORTC QLQ-BR23 quality of life questionnaire

[r] After written informed consent but before study drug initiation, only SAEs associated with protocol-imposed interventions will be recorded. For Cycles ≥ 3 Day 8 or Day 15, if the subject is not seen in clinic, the subject should be contacted by phone and assessed for AEs or SAEs. After the first dose of study drug, all SAEs and AEs will be recorded until 30 days after the last dose of study drug (permanent discontinuation) or before initiation of a new antineoplastic therapy, whichever occurs first. For events outside of this reporting period, only SAEs assessed as related to study drug will be reportable. SAEs, AEs and pregnancies ongoing at the End of Treatment visit will be followed until resolution or until the condition is considered stable by the Investigator.

[s] Baseline 12–lead ECG; End of Treatment, if clinically indicated.

[t] All concomitant medications or therapies, including herbal supplements, taken from 28 days before randomization to 30 days after the last dose will be recorded. For Cycles ≥ 3 Day 8 or Day 15, if the subject is not seen in clinic, the subject should be contacted by phone and assessed for concomitant medications.

[u] Talazoparib will be administered orally daily for 21 days in repeated 21-day cycles. On selected days of clinic visits, the drug will be taken at the clinic to allow pre-dose collection of safety data.

[v] Chemotherapy treatment: See Study Reference Manual

[w] Documentation of a deleterious, suspected deleterious, or pathogenic germline BRCA1 or BRCA2 mutation may be provided for enrollment based on a prior analysis. The pathology laboratory must be pre-approved by the Sponsor.

[x] For subjects who have prior documentation of BRCA carrier status, blood sample for BRCA germline testing will be collected at any time during the Screening/baseline period (Day -28 to Day -1). For subjects who must undergo prospective BRCA germline testing, blood sample testing must be collected as early as possible during the screening period.

[y] Blood sample for disease-related research, including but not limited to genomic analysis. Genomic blood sample will be collected at any time during the Screening/baseline period (Day -28 to Day -1) and at radiographic disease progression (+ 35 days).

[z] Archival formalin-fixed paraffin-embedded (FFPE) tumor tissue slides. Tumor blocks may be submitted with Sponsor approval. A subject may be randomized without availability of tumor tissue slides or blocks. See the Laboratory Manual for preparation of slides or tumor blocks.

[aa] Optional tumor biopsy to be performed only if subject consent is provided. Biopsy will be collected at any time during the Screening/baseline period (Day -28 to Day -1) and at radiographic disease progression (+ 35 days) or at the time of discontinuation of study treatment.

9.2 Discussion of Study Design, Including Choice of Control Group

This is a Phase 3, open-label, randomized, parallel, 2-arm, multi-center study of talazoparib vs. protocol-specific physician's choice in germline BRCA mutation subjects with locally advanced and/or metastatic breast cancer, who have received no more than 3 prior cytotoxic chemotherapy regimens for locally advanced and/or metastatic disease.

The rationale for this study is outlined below and described in detail in Section 7.2.

The subject population of germline BRCA mutation subjects with locally advanced and/or metastatic breast cancer was chosen for this study as there is a current unmet need to treat this population and interim results from the Phase 1 study (PRP-001) indicated objective responses to talazoparib in 8 of 18 subjects, including one confirmed CR.

An open-label design was selected as a double-blind design was not possible given the different chemotherapy cycle regimens for talazoparib vs. the control group regimens.

A 2-arm, randomized, parallel-group design was chosen as this was considered most suitable for assessing the safety and efficacy endpoints in the talazoparib group compared with the control group.

Talazoparib will be administered as a single agent in this study at a dose of 1.0 mg/day with provision for dose reductions to 0.75 mg/day and 0.5 mg/day (or lower) in case of toxicity. This dose regimen was chosen based on preliminary results from the Phase 1 clinical trial (PRP-001) involving breast cancer subjects, which reported good tolerability of talazoparib up to 1000 μg/day but dose-limiting thrombocytopenia at higher doses (1100 μg/day).

The control group in this study is treatment by protocol-specific physician's choice of any one of the single-agent chemotherapies: capecitabine, eribulin, gemcitabine or vinorelbine. These reference chemotherapies were chosen as they are considered to be standard single-agent therapies for subjects with locally advanced and/or metastatic breast cancer. Dose modifications and reductions are permitted per the package inserts and institutional practice.

The study drug will be administered until radiographic disease progression as determined by the IRF, occurrence of unacceptable toxicity, subject or physician decision to stop treatment or until the study is terminated by the Sponsor.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

Individuals eligible to participate in this study must meet all of the following criteria:

- Histologically or cytologically confirmed carcinoma of the breast
- Locally advanced breast cancer that is not amenable to curative radiation or surgical cure and/or metastatic disease appropriate for systemic single cytotoxic chemotherapy
- Documentation of a deleterious, suspected deleterious, or pathogenic germline BRCA1 or BRCA2 mutation from Myriad Genetics or other laboratory approved by the Sponsor; for data obtained regarding a BRCA1/2 mutation from a non-Myriad laboratory, the pathology report must be submitted to and approved by the Sponsor and a blood sample sent to Myriad for analysis before randomization may occur
- No more than 3 prior chemotherapy-inclusive regimens for locally advanced and/or metastatic disease (no limit on prior hormonal therapies or targeted anticancer therapies such as mechanistic target of rapamycin [mTOR] or CDK4/6 inhibitors, immuno-oncology agents, tyrosine kinase inhibitors, or monoclonal antibodies against CTL4 or VEGF)
- Prior treatment with a taxane and/or anthracycline in the neoadjuvant, adjuvant, locally advanced, or metastatic setting unless medically contraindicated
- 18 years of age or older
- Have measurable or non-measurable, evaluable disease by the revised response evaluation criteria in solid tumors (RECIST) v.1.1
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
- Adequate organ function as defined below:
    - Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × upper limit of normal (ULN); if liver function abnormalities are due to hepatic metastasis, then AST and ALT ≤ 5 × ULN
    - Total serum bilirubin ≤ 1.5 × ULN (≤ 3 × ULN for Gilbert's syndrome)
    - Calculated creatinine clearance ≥ 30 mL/min by local laboratory or Cockcroft-Gault formula
    - Hemoglobin ≥ 9.0 g/dL with last transfusion at least 14 days before randomization
    - Absolute neutrophil count (ANC) ≥ 1500/mm^3
    - Platelet count ≥ 100,000/mm^3
- Able to take oral medications

- Willing and able to provide written, signed informed consent after the nature of the study has been explained, and prior to any research-related procedures
- A female of childbearing potential (defined in Section 9.7.4.6) must not be pregnant and must agree to avoid pregnancy during the study by using a highly effective birth control method (defined in Section 9.7.4.6) from the time of the first dose of study drug through 45 days after the last dose of study drug
- Male subjects must use a condom when having sex with a pregnant woman and when having sex with a woman of childbearing potential from the time of the first dose of study drug through 105 days after the last dose of study drug. Contraception should be considered for a non-pregnant female partner of childbearing potential
- Male and female subjects must agree not to donate sperm or eggs, respectively, from the first dose of study drug through 105 days and 45 days after the last dose of study drug, respectively
- Females of childbearing potential (defined in Section 9.7.4.6) must have a negative serum pregnancy test at Screening and be willing to have additional pregnancy tests during the study.
- Willing and able to comply with all study procedures

9.3.2 Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

- First-line locally advanced and/or metastatic breast cancer with no prior adjuvant chemotherapy unless the Investigator determines that one of the 4 cytotoxic chemotherapy agents in the control arm would be otherwise offered to the subject
- Prior treatment with a PARP inhibitor (not including iniparib)
- Not a candidate for treatment with at least 1 of the treatments of protocol-specific physician's choice (ie, capecitabine, eribulin, gemcitabine, vinorelbine)
- Subjects who had objective disease progression while receiving platinum chemotherapy administered for locally advanced or metastatic disease; subjects who received low-dose platinum therapy administered in combination with radiation therapy are not excluded
- Subjects who have received platinum in the adjuvant or neoadjuvant setting are eligible; however, subjects may not have relapsed within 6 months of the last dose of prior platinum therapy
- Cytotoxic chemotherapy within 14 days before randomization
- Radiation or anti-hormonal therapy or other targeted anticancer therapy within 14 days before randomization

- Has not recovered from the acute toxicities of previous therapy, except treatment-related alopecia or laboratory abnormalities otherwise meeting the inclusion requirements stated in the inclusion criteria
- HER2 positive breast cancer
- Active inflammatory breast cancer
- CNS metastases
    - Exception: Adequately treated brain metastases documented by baseline CT or MRI scan that has not progressed since previous scans and that does not require corticosteroids (except prednisone ≤ 5 mg/day or equivalent) for management of CNS symptoms. A repeat CT or MRI following the identification of CNS metastases (obtained at least 2 weeks after definitive therapy) must document adequately treated brain metastases
    - Subjects with leptomeningeal carcinomatosis are not permitted
- Prior malignancy except for any of the following:
    - Prior BRCA-associated cancer as long as there is no current evidence of the prior cancer
    - Carcinoma in situ or non-melanoma skin cancer
    - A cancer diagnosed and definitively treated ≥ 5 years before randomization with no subsequent evidence of recurrence
- Known to be human immunodeficiency virus positive
- Known active hepatitis C virus, or known active hepatitis B virus
- Use of any IP or investigational medical device within 14 days before randomization
- Major surgery within 14 days before randomization
- Myocardial infarction within 6 months before randomization, symptomatic congestive heart failure (New York Heart Association [NYHA] > class II), unstable angina, or unstable cardiac arrhythmia requiring medication
- Female subjects who are breastfeeding at Screening or planning to become pregnant at any time during study participation through 45 days after the last dose of study drug; male subjects planning to impregnate a partner at any time during study participation through 105 days after the last dose of study drug
- 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 AEs (CTCAE) v4.03 or requiring the use of parenteral anti-microbial agents within 14 days before randomization

    - Clinically significant bleeding diathesis or coagulopathy, including known platelet function disorders
- Non-healing wound, ulcer, or bone fracture, not including a pathological bone fracture caused by a pre-existent pathological bone lesion
- Known hypersensitivity to any of the components of talazoparib

9.3.3 Removal of Subjects from Study or from Study Treatment

Subjects should be encouraged to continue to provide study data until the primary outcome of radiographic disease progression as determined by the IRF or death has occurred. This is to avoid any potential for bias or mis-estimation of treatment effect as a result of missing and therefore censored data. This encouragement should continue even in the event of discontinuation of study drug administration. Notwithstanding the above, subjects may withdraw their consent to participate in the study and Investigators may withdraw subjects at any time without prejudice. Subjects may withdraw consent for study drug treatment (only), for any follow-up radiographic imaging, or for long-term follow-up for survival status and anticancer therapy. The specific type of withdrawal of consent should be documented in the medical chart. When possible, the tests and evaluations listed for the End of Treatment visit should be carried out.

The Sponsor must be notified of all subject withdrawals as soon as possible. The Sponsor also reserves the right to discontinue the study at any time for either clinical or administrative reasons and to discontinue participation by an individual Investigator or site for poor enrollment or noncompliance.

Reasons for which the Investigator or Sponsor may discontinue administration of study drug include, but are not limited to, the following:

- Subject experiences a serious or intolerable AE or clinically significant laboratory abnormality (see Section 9.4.7)
- Subject requires medication or medical procedure prohibited by the protocol (Section 9.3.6)
- Subject does not adhere to study requirements specified in the protocol
- Subject was erroneously admitted into the study or does not meet entry criteria
- Subject is lost to follow-up

- Subject becomes pregnant (refer to Section 10.4 for details on the reporting procedures to follow in the event of pregnancy)
- Subjects may be removed from study if considered by the Investigator or Sponsor to be in the best interest of the subject

If a subject discontinues from treatment but remains on study, every effort should be made to continue the subject's assessments according to the schedule of assessments (Table 9-1) through the end of the study. For subjects who withdraw from the study, procedures and assessments for the End of Treatment visit (Section 12.4) should be performed (unless the subject withdraws consent to do so).

If a subject fails to return for scheduled visits, a documented effort must be made to determine the reason. If the subject cannot be reached by telephone, study site personnel may contact the subject's family member or legally authorized representative, if appropriate. A certified letter should be sent to the subject (or the subject's legally authorized representative, if appropriate) requesting contact with the Investigator. As permitted by local law, study site personnel may use public databases, perform an internet search, or review obituaries to determine date of death. This information should be recorded in the study records.

The Investigator or designee must explain to each subject, before enrollment into the study, that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and IRB/IEC/REB. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as the Health Insurance Portability and Accountability Act (HIPAA) in the US, from each subject, or if appropriate, the subject's legally authorized representative. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the subject and the subject will be removed from the study.

9.3.4 Subject Identification and Replacement of Subjects

All reports and subject samples will be identified only by a subject identification number and actual initials (if permitted) or mock initials and date of birth (month/year only if no date is permitted) to maintain subject confidentiality. This unique identifier will be on all electronic case report form (eCRF) pages. A new subject identification number will be assigned to any subjects who are re-screened after a screen failure. Subjects who discontinue the study will not be replaced.

9.3.5 Duration of Subject Participation

Subjects will attend a Screening visit within 28 days before randomization and a baseline visit within 7 days before randomization.

Subjects must start treatment ≤ 5 days from randomization; starting later will be considered a protocol deviation. Talazoparib or protocol-specific physician's choice will be administered in repeated 21-day cycles. Subjects will present for weekly treatment visits for the first 2 cycles of talazoparib or protocol-specific physician's choice. Treatment with talazoparib or protocol-specific physician's choice will continue until radiographic disease progression as determined by the central IRF, unacceptable toxicity, consent withdrawal, physician's decision to terminate treatment, or Sponsor's decision to terminate the trial. Tumor assessments are to be performed every 6 weeks (± 7 days) from the date of randomization for the initial 30 weeks, and every 9 weeks thereafter (± 7 days), regardless of any dose interruptions or dose delays until radiographic disease progression as determined by the IRF or initiation of a new antineoplastic therapy.

An End of Treatment visit will be performed for subjects 30 days (-3 days or +10 days) after the last dose of study drug.

Subjects who discontinue from the study drug for any reason other than radiographic disease progression as determined by the IRF or initiation of a new antineoplastic therapy will also be followed to radiographic progression by imaging assessments (eg, CT scans) unless the subject withdraws consent. All subjects will be followed for anticancer treatment and survival status. Survival follow-up will continue until death. Follow-up for anticancer therapy and survival status will occur every 60 days (± 7 days) after the last dose of study drug for 1 year and every 90 days (± 14 days) thereafter, or when requested by the Sponsor.

9.3.6 Prohibited Medications

The following medications and procedures are prohibited through study drug discontinuation:

- Any investigational agent other than talazoparib
- Any anticancer treatment other than talazoparib, the protocol-specified comparator agents, bisphosphonates and denosumab

Bisphosphonates and the monoclonal antibody denosumab are permitted for treatment, or prophylaxis, of bone metastases as per local standards of care. Examples of other permitted medications are outlined in Section 9.4.9.

9.4 Treatments

9.4.1 Treatments Administered

The Sponsor and/or its designee will provide the study site with a supply of talazoparib sufficient for the completion of the study.

All physician's choice drugs are commercially available in all planned study countries, except for eribulin, which is not available in some of the planned study countries. All physician's choice comparator drugs should be supplied by the local pharmacy (if possible per local regulations). The physician's choice drugs are to be labeled, packaged, and stored according to local regulations and manufacturer's instructions. Physician's choice drug costs will be reimbursed by the Sponsor where necessary.

9.4.2 Identity of Investigational Product

9.4.2.1 Product Characteristics and Labeling

The IP is talazoparib tosylate, a white to off-white crystalline powder. The drug substance is a 4-methylbenzenesulfonate (tosylate) salt of talazoparib free base, the active moiety.

The drug product consists of the drug substance formulated with a pharmaceutically-suitable excipient filled into hydroxymethylpropylcellulose capsules.

Capsules will be provided to the sites in dose strengths of 0.25 mg and 1.0 mg capsules. The dosage strengths are based on the active moiety (talazoparib free base). The capsules for each dose strength are provided in dose-specific colors to provide a visual method of distinguishing dose strengths. The capsules will be supplied in 30-count induction-sealed high density polyethylene (HDPE) bottles.

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 (Goodin, 2011, J.Oncol.Pract.). 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.

The label will vary in content and/or language, depending upon requirements of individual countries and the design of the clinical trial. At a minimum, each bottle label will provide the following information: study Sponsor identification, dosage form, route of administration, quantity and potency, batch number, directions for use, required storage conditions, caution statements (including "for clinical trial use only" language), study identification, and product retest or expiration date.

9.4.3 Physician's-Choice Comparator

Treatment of protocol-specific physician's choice is to include any one of the following single-agent chemotherapies: capecitabine, eribulin, gemcitabine or vinorelbine. All physician's choice comparator drugs should be supplied by the local pharmacy (except where not allowed by local law). Some subjects will receive protocol-specific physician's choice study drug by mail-order pharmacy. They are to be labeled, packaged, and stored according to local regulations and manufacturer's instructions. Comparator drug costs will be reimbursed by the Sponsor where necessary.

9.4.4 Storage

At the study site, all talazoparib must be stored under the conditions specified in the IB in a secure area accessible only to the designated pharmacists and clinical site personnel. Talazoparib must be stored at room temperature (15 to 30°C; 59 to 86°F), inventoried and the inventories must be carefully and accurately documented according to applicable state, federal and local regulations, ICH GCP, and study procedures.

The protocol-specific physician's choice comparators should be stored per the package insert and institutional practice.

9.4.5 Directions for Administration

Talazoparib will be taken orally once daily (i.e., continuous dosing). Talazoparib should be taken at approximately the same time each day, preferably in the morning. Talazoparib will be swallowed whole and may be taken with or without food. If a subject vomits a dose, the subject should not take a second dose that calendar day. The subject should resume daily dosing the next day. On days of clinic visits when PK samples are to be drawn, talazoparib should be taken at the clinic after completion of the pre-dose sampling and assessments.

The protocol-specific physician's choice comparators should be administered per the package insert or institutional practice. Suggested dosing schedules are provided in Section 9.1.

9.4.6 Method of Assigning Subjects to Treatment Groups

Subjects will be randomized (2:1) centrally based on the following stratifications:

- Number of prior cytotoxic chemotherapy regimens for locally advanced and/or metastatic disease (0, vs 1, 2, or 3)
- Triple negative (estrogen-receptor negative, progesterone-receptor negative, HER2-negative) vs. non-triple negative status based on the most recent biopsy
- History of CNS metastases vs. no CNS metastases

Assignment to study drug arms will be based on a computer-generated schedule before the start of the study. The schedule will be developed according to the Randomization Plan. The approved randomization schedule will be implemented in an interactive voice and Web response system (IXRS). The IXRS will assign a subject to talazoparib or protocol-specific physician's choice based on the subject's strata and allocate a randomization number. For subjects assigned to the physician's choice arm, the protocol-specific physician's choice should be determined prior to randomization. A subject may only receive one randomization number; each randomization number may only be assigned to one subject.

A subject will be considered randomized into the study when a randomization number is assigned. At the end of the trial the completed randomization schedule will be transferred to the Sponsor.

9.4.7 Selection of Doses Used in the Study

The selection of doses used in this study is described in Section 7.2 and Section 9.2.

9.4.7.1 Talazoparib: Timing of Administration and Dose Reduction Guidelines

Talazoparib should be taken orally once daily (ie, continuous daily dosing) at approximately the same time each day (preferably in the morning). On days of clinic visits when PK samples are to be drawn, talazoparib should be taken at the clinic after completion of pre-dose sampling and assessments; on these PK sample dates, the clinic visit should be scheduled for approximately the same time of day that the dose is typically taken.

Daily dosing of talazoparib can be interrupted for recovery from toxicity for up to 28 days. For interruptions longer than 28 days, treatment at the same or a reduced dose can be considered based on a discussion between the Sponsor or designee and Investigator if evidence of response or clinical benefit to talazoparib is noted.

Dose modifications should be made based on the observed toxicity, as summarized in Table 9-2.

Table 9-2: Dose Modifications Based on Hematologic or Nonhematologic Toxicity

Toxicity	Recommended Dose Modification
Liver test abnormalities	Refer to the liver safety test monitoring and assessment rules in Section 9.4.7.3. Dose interruption and/or dose reduction may be required for Grade 2 AST or ALT values, depending on the liver test values at Screening.

Toxicity	Recommended Dose Modification
Grade 1 or 2 toxicity (other than liver test abnormalities)	No requirement for dose interruption or dose reduction. If the toxicity persists at Grade 2 (for ≥ 7 days), a dose reduction to the next lower dose level (eg, from 1.0 mg/day to 0.75 mg/day) may be implemented at the discretion of the Investigator.
Grade 3 nonhematologic toxicity (other than liver test abnormalities)	Daily dosing must be held for Grade 3 AEs considered related to talazoparib. Supportive care should be implemented as appropriate (eg, anti-emetics, anti-diarrheal agents). Talazoparib dosing may resume at the next lower dose level (eg, from 1.0 mg/day to 0.75 mg/day, 0.75 mg/day to 0.5 mg/day to 0.25 mg/day) when toxicity resolves to Grade 1 or returns to baseline.
Grade 3 hematologic toxicity	Daily dosing must be held for Grade 3 laboratory abnormalities known to be associated with talazoparib per the current IB. Supportive care should be implemented as appropriate (eg, growth factor support, blood products). Talazoparib dosing may resume at the next lower dose level when toxicity resolves to Grade 1 or would meet the eligibility criteria (Section 9.3).
Grade 4 nonhematologic toxicity (other than liver test abnormalities)	Daily dosing must be held for Grade 4 AEs (regardless of relationship to talazoparib). Supportive care should be implemented as appropriate (eg, anti-emetics, anti-diarrheal agents). Talazoparib may resume at a lower dose level (1-2 dose level decrease) when toxicity resolves to Grade 1 or returns to baseline.
Grade 4 hematologic toxicity	Daily dosing must be held for Grade 4 laboratory abnormalities (regardless of relationship to talazoparib). Supportive care should be implemented as appropriate (eg, growth factor support, blood products). Talazoparib may resume but must be at a lower dose level when toxicity resolves to Grade 1 or would meet the eligibility criteria (Section 9.3); this should be a 1-2 dose level decrease per Investigator discretion.

Refer to Table 9-3 for additional information.

Table 9-3: Dose Modifications for Toxicities

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

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

9.4.7.2 Protocol-Specific Physician's-Choice Comparators: Timing of Administration and Dose Reduction Guidelines

Treatment of protocol-specific physician's choice is to include any one of the single-agent chemotherapies listed below. Suggested dosing schedules are noted, but if institution dose and regimen guidelines differ, the site may utilize institution guidelines:

- Capecitabine: 1250 mg/m^2, oral, twice daily from Days 1 through 14 of a 21-day cycle, 30 minutes after meal
- Eribulin mesylate: 1.4 mg/m^2 (equivalent to eribulin 1.23 mg/m^2), infusion over 2-5 minutes, Days 1 and 8 of 21-day cycles
- Gemcitabine: 1250 mg/m^2, infusion over 30 minutes, Days 1 and 8 of 21-day cycles
- Vinorelbine: 30 mg/m^2, weekly infusion over 6-10 minutes, Days 1, 8 and 15 of 21-day cycles

Dose modifications and reductions are to occur per the package insert and institutional practice. Dose adjustments based on abnormal liver test results should follow the instructions in Section 9.4.7.3. Dose adjustments based on renal insufficiency should follow the Summary of Product Characteristics or manufacturer's prescribing information.

Toxicities will be managed as defined in the Summary of Product Characteristics or manufacturer's prescribing information and institutional practice.

9.4.7.3 Liver Safety Test Monitoring and Assessments (Talazoparib or Protocol-Specific Physician's Choice Comparators)

Subjects who develop abnormal liver tests (ie, AST, ALT, total bilirubin) and/or international normalized ratio [INR] values, and/or signs/symptoms of hepatitis during the study treatment period, may meet the criteria for withholding or permanent discontinuation of study drug

(talazoparib or treatment of physician's choice) as specified in US FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation (2009).

Subjects who meet permanent discontinuation criteria or temporary withholding criteria, or who do not meet permanent discontinuation criteria or temporary withholding criteria but who have abnormal liver tests are to be followed according to the recommendations in this section.

It is recommended that study drug (talazoparib or treatment of physician's choice) be withheld for any one of the liver test abnormalities listed in Table 9-4.

Table 9-4: Liver Test Abnormalities That May Require Dose Modifications

Baseline AST or ALT Value	**Elevation**
≤ 3 × ULN	> 5 × ULN to ≤ 8 × ULN
> 3 to ≤ 5 × ULN	> 8 × ULN
Baseline Total Bilirubin Value	**Elevation**
≤ 1.5 × ULN	> 3 × ULN

Study drug (talazoparib or treatment of physician's choice) should be withheld pending investigation into alternative causes of drug-induced liver injury (DILI). If study drug is withheld, the subject should be followed for possible DILI. Rechallenge may be considered if an alternative cause for the impaired liver tests (ie, ALT, AST, total bilirubin) is discovered and the laboratory abnormalities resolve to normal or baseline values.

The decision to rechallenge the subject should be discussed and agreed on unanimously by the subject, Investigator, and Sponsor. Following rechallenge, subjects should be closely monitored for signs and symptoms of hepatitis, and/or abnormal liver test results. If signs or symptoms recur with rechallenge, study drug (talazoparib or treatment of physician's choice) should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation should never be rechallenged.

Study drug should be discontinued permanently if ALL of the following 4 criteria are met (ie, potential severe DILI/Hy's Law case):

1. AST or ALT increases to ≥ 3 × ULN (> 5 × ULN if baseline ALT/AST is > 3 and ≤ 5 × ULN)
2. Total bilirubin increases to > 2 × ULN and/or INR > 1.5
3. Alkaline phosphatase (ALP) value does not reach 2 × ULN

4. No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes include, but are not limited to:
    - Hepatobiliary tract disease
    - Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, parvovirus)
    - Congestive heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia
    - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms
    - Alcoholic hepatitis
    - Non-alcoholic steatohepatitis (NASH)
    - Autoimmune hepatitis
    - Wilson's disease and hemochromatosis
    - Alpha-one antitrypsin deficiency

If an alternative cause for hepatotoxicity is identified or if the liver test abnormalities do not reach the specified severity, study drug should be withheld or permanently discontinued, as appropriate for the safety of the subject based on the patient population and/or severity of the hepatotoxicity or event.

All subjects in whom study drug is withheld (either conditionally or permanently) due to a potential DILI are to undergo a period of "close observation" until the liver test abnormalities return to baseline or normal values. The evaluations listed in Table 9-5 should be performed.

Table 9-5: Liver Monitoring After Events Meeting Hy's Law Criteria or Suggesting Potentially Severe Drug-Induced Liver Injuries

Results	Frequency for Repeating Liver (AST, ALT, Bilirubin [Total and Direct]) and INR Tests
After the initial liver test abnormality	Within 24 hours
If AST or ALT ≥ 3 × ULN (> 5 × ULN if baseline ALT/AST is > 3 and ≤ 5 × ULN), and total bilirubin > 2 × ULN or INR > 1.5	Every 24 hours until laboratory abnormalities improve
If ALT or AST ≥ 3 × ULN (> 5 × ULN if baseline ALT/AST is > 3 and ≤ 5 × ULN) and total bilirubin and/or INR are normal	Every 48 to 72 hours until laboratory abnormalities improve
If the liver test abnormalities improve AND the subject is asymptomatic	Frequency may decrease

As DILI is a diagnosis of exclusion, it is important to initiate investigation of alternative causes for abnormal liver tests; this may include consultation with a hepatologist. The medical monitor should be contacted for questions regarding adequate follow-up tests.

9.4.8 Blinding

This is an open-label study. No blinding will be performed. Steps will be taken to ensure designated Sponsor staff responsible for study conduct and IRF members are appropriately blinded to subject treatment identity throughout the study.

9.4.9 Prior and Concomitant Medications

All prescription and over-the-counter medications taken by a subject for 28 days before randomization will be recorded on the designated eCRF. The Investigator may prescribe additional medications during the study, as long as the prescribed medication is not prohibited by the protocol (Section 9.3.6). In the event of an emergency, any needed medications may be prescribed without prior approval, but the medical monitor or designee must be notified of the use of any contraindicated medications immediately thereafter. Any concomitant medications added or discontinued during the study will be recorded on the eCRF, including the start and end dates of treatment, as applicable.

Supportive medications may be provided prophylactically or therapeutically at the Investigator's discretion, with the exception that granulocyte-colony stimulating factor (G-CSF) is only allowed in the rescue setting. Allowed medications include (but are not limited to) anti-emetics, such as dexamethasone, metoclopramide, ondansetron, or aprepitant; anti-diarrheals, such as loperamide hydrochloride; and appetite stimulants such as megestrol acetate. Bisphosphonates and the monoclonal antibody denosumab are also permitted for treatment, or prophylaxis, of bone metastases as per local standards of care.

Guidelines for concomitant use of talazoparib with inhibitors or inducers of P-glycoprotein (P-gp) or inhibitors of breast cancer resistance protein (BCRP) are as follows

- Use of strong P-gp inhibitors (eg, dronedarone, itraconazole, quinidine, ranolazine, verapamil), P-gp inducers (eg, rifampin, tipranavir/ritonavir), or BCRP inhibitors (eg, elacridar [GF120918]) should be avoided
- Caution should be used for coadministration of other P-gp inhibitors (eg, amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, erythromycin, felodipine, ketoconazole, lopinavir, ritonavir, quercetin), P-gp inducers (eg, avasimibe, carbamazepine, phenytoin, St John's wort), or BCRP inhibitors (eg, cyclosporine, eltrombopag, gefitinib)

- Refer to the following website for a complete list: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inhibitors

External beam radiotherapy will be allowed, following consultation with the medical monitor.

Subjects may not receive any other systemic anticancer therapies while on study prior to radiographic disease progression as determined by the IRF.

A subject may be referred for surgery of metastatic lesion(s), when it is in the best interest of the subject. The subject may continue on study if the subject is receiving clinical benefit from the study drug per Investigator discretion. If the target lesions are removed, the subject will be excluded from the measurable disease population. Resection of a subject's target lesion(s) should be discussed with the Medical Monitor prior to surgery.

9.4.10 Treatment Compliance

Subjects will be instructed to bring all used and unused study drug containers to each study visit. Subject compliance with the dosing regimen of oral therapy (talazoparib and capecitabine) will be assessed by reconciliation of the used and unused study drug at least once per cycle. The quantity dispensed, returned, used, lost, etc. must be recorded by the Investigator or designee on the dispensing log provided for the study at least once per cycle.

9.5 Investigational Product Accountability

The Investigator or designee is responsible for maintaining accurate records (including dates and quantities) of IP(s) received, subjects (or their primary caregiver) to whom IP is dispensed (subject-by-subject dose specific accounting), and IP lost or accidentally or deliberately destroyed. The Investigator or designee must retain all unused or expired study supplies until the study monitor (on-site CRA) has confirmed the accountability data and the Sponsor has approved return or destruction.

9.5.1 Return and Disposition of Clinical Supplies

Unused study drug (including talazoparib and any other Investigational Medicinal Products provided by the Sponsor) must be kept in a secure location for accountability and reconciliation by the study monitor. The Investigator or designee must provide documentation for any destroyed or missing study drug or study materials.

Unused study drug may be destroyed on site, per the site's standard operating procedures, but only after the Sponsor or designee has granted approval for drug destruction. The monitor

must account for all study drug in a formal reconciliation process, prior to study drug destruction (if possible). All study drug destroyed on site must be documented.

Documentation must be retained in the Investigator study files. If a site is unable to destroy study drug, the site can return unused study drug to a central location for drug destruction. The return of study drug or study drug materials must be documented on the study drug return form.

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures.

9.6 Dietary or Other Protocol Restrictions

Not applicable.

9.7 Efficacy and Safety Variables

9.7.1 Efficacy and Safety Measurements Assessed

The Schedule of Events in Section 9.1 describes the timing of required evaluations.

9.7.2 Primary Efficacy Variable

The primary efficacy measure will be the ability of the treatment to delay radiographic progression of breast cancer, assessed using sequential imaging studies digitally submitted to and reviewed by the central IRF (refer to Section 16).

Progression and response will be determined by the IRF and defined according to RECIST v.1.1 (Eisenhauer, Eur. J. Cancer. 2009) with modifications. Radiographic disease assessment (CT and/or MRI) will be performed within 28 days before randomization. Subjects will undergo radiographic disease assessment every 6 weeks (± 7 days) from the date of randomization for 30 weeks.

Thereafter, imaging assessment will be performed every 9 weeks (± 7 days) until radiographic disease progression as determined by the IRF or the time of initiation of a new antineoplastic therapy. Clinical disease progression should be confirmed by radiographic imaging as determined by the IRF before discontinuing study treatment (or the subject will not be considered to have a progressive disease event for the purposes of the analysis). If a subject is suspected to have disease progression based on clinical signs or symptoms, the site should complete and submit the appropriate forms and scans for IRF determination. Imaging assessments should continue according to the schedule of assessments (Table 9-1) until

radiographic progression is observed by the IRF, unless the subject withdraws consent or initiates a new antineoplastic therapy.

The assessment of tumor response via RECIST v.1.1 with modifications is described in full in Section 24.3.

9.7.3 Secondary Variables

The secondary efficacy measures include ORR (RECIST v.1.1 with modifications) as assessed by the IRF and OS. Confirmation of objective response (CR or PR) is not required.

The assessment of tumor response via RECIST v.1.1 with modifications is described in full in Section 24.3.

9.7.3.1 Pharmacokinetics

The following PK parameters will be determined from plasma talazoparib concentrations:

- Trough concentrations of talazoparib

A population PK modeling approach will be used to estimate individual values of apparent clearance (CL/F) and central volume of distribution (Vc/F).

Individual CL/F estimates will then be used to estimate individual exposure parameters (eg, area under the concentration time curve over a dosing interval [AUCτ]). The association between talazoparib exposure parameters and efficacy and safety outcomes may be explored.

9.7.3.2 Exploratory Efficacy Variables

The exploratory efficacy variables are DOR in responding subjects via RECIST v.1.1 with modifications (Section 24.3) and EORTC QLQ-C30/EORTC QLQ-BR23 (Section 24.4).

9.7.4 Safety Variables

The following safety variables will be assessed:

- The incidence of AEs, including SAEs
- Change in clinical laboratory tests (serum chemistry and hematology)
- Change in vital signs
- Change in physical examination
- Concomitant medication use

9.7.4.1 Adverse Events

The determination, evaluation and reporting of AEs will be performed as outlined in Section 10. Assessments of AEs will occur at the time points shown in Table 9-1.

9.7.4.2 Clinical Laboratory Assessments

Specific visits for obtaining clinical laboratory assessment samples are provided in Table 9-1. The scheduled clinical laboratory tests are listed in Table 9-6.

Refer to the Study Laboratory Manual for instructions on obtaining and shipping blood and tissue samples.

Any abnormal test results determined to be clinically significant by the Investigator should be repeated (at the Investigator's discretion) until the cause of the abnormality is determined, the value returns to baseline or to within normal limits, or the Investigator determines that the abnormal value is no longer clinically significant.

All abnormal clinical laboratory result pages should be initialed and dated by an Investigator, along with a comment regarding whether or not the result is clinically significant. An abnormal laboratory result should be recorded as an AE if it meets the criteria listed in Section 10.1.

The diagnosis, if known, associated with abnormalities in clinical laboratory tests that are considered clinically significant by the Investigator will be recorded on the AE eCRF.

[redacted]

Table 9-6: Clinical Laboratory Tests

Blood Chemistry	Hematology	Urinalysis (dipstick)[a]	Other
Albumin	Hemoglobin	pH	Serum or urine pregnancy test, if applicable
Alkaline phosphatase	Hematocrit	Specific gravity	
ALT	WBC count	Ketones	PK
AST	RBC count	Protein	
Total bilirubin	Platelet count	Glucose	
BUN (or urea)	ANC [b]	Bilirubin	
Calcium	WBC differential (absolute / percent)	Leukocyte esterase	
Chloride		Blood	
CO_2 (or bicarbonate)			
Creatinine		**Coagulation**	
Glucose		aPTT (or TCA)	
LDH		PT	
Magnesium		INR	
Phosphorus			
Potassium			
Total protein			
Sodium			
Uric acid			

Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; aPTT, activated partial thromboplastin time; PK, pharmacokinetic; PT, prothrombin time; INR, international normalized ratio; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CO_2, carbon dioxide; LDH, lactate dehydrogenase; RBC, red blood cell; TCA, temps de céphaline active; WBC, white blood cell.

[a] Microscopy is required if dipstick results for blood or leukocyte esterase are positive.

[b] For sites that do not provide an ANC, this should be calculated as WBC multiplied by percentage of neutrophils (or percentage of segmented neutrophils plus bands).

Blood samples for hematology assessments are to be obtained on a weekly basis (ie, Day 1, Day 8 and Day 15) during the first 2 cycles of treatment, as well as at Screening/baseline and End of Treatment. Starting with Cycle 3, hematology counts should be obtained in each cycle on Day 1 and on either Day 8 (± 3 days) or Day 15 (± 3 days). Hematology assessments obtained on days other than Day 1 of a Cycle may be performed at a local laboratory outside of the investigational site laboratory as long as laboratory reports are provided to the Investigator for evaluation 24 hours prior to dosing. Hematology assessments scheduled for

the day of dosing must be available and assessed for toxicity prior to dosing. Blood samples for hematology assessments can be drawn within 72 hours prior to dosing.

Blood samples for serum chemistry assessments are to be obtained on Day 1 of each treatment cycle, as well as at Screening/baseline and End of Treatment. Blood samples for serum chemistry assessments can be drawn within 72 hours prior to dosing.

For hematology and serum chemistry assessments, at least 1 blood sample must be collected before randomization (Screening/Baseline) and 1 blood sample must be collected after randomization and before dosing on Cycle 1 Day 1.

Calculated creatinine clearance will be assessed at Screening using the value provided by the local laboratory or using the Cockcroft-Gault formula.

Coagulation parameters will be assessed only at baseline.

Urinalysis (dipstick) parameters will be assessed only at baseline; microscopy is required if dipstick results for blood and leukocyte esterase are positive.

9.7.4.3 Pharmacokinetic Assessments

For the evaluation of plasma concentrations of talazoparib, sparse blood samples for PK analysis will be collected on Day 1 of treatment cycles 1 through 4 for subjects randomized to receive talazoparib. Sparse PK sampling will consist of a pre-dose sample collected ≤ 60 minutes prior to dosing, and 2 post-dose samples collected ≥ 30 minutes after dosing. The collection times of the 2 post-dose samples will be separated by ≥ 2 hours. Within individual subjects, efforts should be made to collect PK samples at different times relative to dosing across the study days with PK assessments. In the event of a dose delay on Day 1 of Cycles 1 to 4, the pre- and postdose PK blood sample should also be delayed until the subject resumes their next dose of talazoparib.

On study days with PK assessments, the dose of talazoparib will be administered in the clinic, and the dose amount, food status (within 2 hours before taking the talazoparib dose), and dosing date and time will be recorded in the eCRF. The dose amount and dosing date and time for the dose taken on the day before the study days with PK assessments will also be recorded in the eCRF.

PK samples will be collected at all study sites except those that are unable to perform PK studies with the agreement of the Sponsor.

9.7.4.4 Research Exploratory Assessments

Blood and tumor samples will be collected for exploratory research to characterize tumor sensitivity and resistance to talazoparib, and for other disease-related research. Analyses will include but not be limited to genomic/genetic, cellular, molecular, histochemical, and biochemical assays.

9.7.4.5 Vital Signs, Physical Examinations and Other Observations Related to Safety

Vital signs including systolic blood pressure, diastolic blood pressure, heart rate, respiration rate and temperature will be assessed at Screening, baseline, on relevant treatment days (Table 9-1) and at the End of Treatment. Any change in vital signs will be recorded as an AE if it meets the criteria listed in Section 10.1.

Weight will be assessed at Screening, baseline, prior to dosing on Day 1 of each treatment cycle, and at the End of Treatment. Height will be assessed at Screening only.

Standard 12-lead electrocardiograms (ECGs) will be performed at baseline and if clinically indicated, at End of Treatment. Any change in the 12-lead ECGs will be recorded as an AE if it meets the criteria listed in Section 10.1.

9.7.4.6 Reproductive Considerations

Female Subjects

Female subjects of childbearing potential must use a highly effective form of contraception. from the time of the first dose of study drug through 45 days after the last dose of study drug, defined as:

- Established use of an oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
- Established use of an oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Placement of an intrauterine device or intrauterine hormone-releasing system
- Bilateral tubal ligation for ≥ 6 months before randomization
- Partner vasectomized for ≥ 6 months before randomization
- Sexual abstinence when in relation to the preferred and usual lifestyle of the subject

Female subjects of childbearing potential will have a serum pregnancy test performed at Screening. Female subjects with a positive pregnancy test at Screening do not meet eligibility criteria for enrollment.

A local serum or urine pregnancy test (per local regulations/practice) will be performed for female subjects of childbearing potential at Day 1 of each cycle and the End of Treatment. If a urine pregnancy test is positive or there is a clinical question regarding possible pregnancy, dosing will be interrupted. Any positive urine pregnancy test result will be confirmed by a serum pregnancy test. Urine pregnancy tests must have a limit of detection of 25 IU/L (or equivalent units) for human chorionic gonadotropin.

Additional pregnancy tests will be performed if clinically indicated at any visit in which pregnancy status is in question.

Females considered not of childbearing potential include those who are surgically sterile (bilateral salpingectomy, bilateral oophorectomy, or hysterectomy) or who are post-menopausal, defined as:

- ≥ 55 years of age with no spontaneous menses for ≥ 12 months before randomization
- < 55 years of age with no spontaneous menses for ≥ 12 months before randomization and with a postmenopausal follicle-stimulating hormone (FSH) concentration > 30 IU/L (or meeting criteria for post-menopausal status by the local laboratory)

Male Subjects

Male subjects with partners of childbearing potential must use a condom and contraception should be considered for the female partner from the time of the first dose of study drug through 105 days after the last dose of study drug. Male subjects whose partners are pregnant should use condoms for the duration of the pregnancy.

Refer to Section 10.4 for details on the reporting procedures to follow in the event of pregnancy.

10 REPORTING ADVERSE EVENTS

10.1 Adverse Events

- For this protocol, a reportable AE is any untoward medical occurrence (eg, sign, symptom, illness, disease or injury) in a subject administered study drug or other protocol-imposed intervention, regardless of attribution. Examples of AEs include the following:
- A worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition
- Development of an intercurrent illness during the study
- Development of symptoms that may or may not be related to the use of a concomitant medication or investigational product
- Injury or accidents: If a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (eg, for a fall secondary to dizziness, both “dizziness” and “fall” should be recorded separately)
- Investigational abnormalities (eg, laboratory parameters, vital signs, ECG data) should be defined as AEs only if the abnormality meets one of the following criteria:
    - Induces clinical signs or symptoms
    - Needs active intervention
    - Needs interruption or discontinuation of study medication
    - Abnormality or investigational value is clinically significant in the opinion of the Investigator

An AE does not include the following:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an AE
- Pre-existing diseases or conditions present or detected before the start of study drug administration that do not worsen
- Situations where an untoward medical event has not occurred (eg, planned hospitalization for an elective procedure as known at the time of informed consent)

<u>Events of special interest</u>: Adverse events of special interest are any events identified for intensive monitoring during the study. For 673-301, events of special interest include overdose (Section 10.3), pregnancy in the subject or partner (Section 10.4), and specified liver test abnormalities (Section 10.5).

An adverse drug reaction is any AE for which there is a reasonable possibility that study drug caused the AE. “Reasonable possibility” means there is evidence to suggest a causal relationship between study drug and the AE.

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of terms relating to a diagnosis or a surgical procedure.

The reporting period for non-serious AEs is the period from the time of **initial dose of study drug** through 30 days after the last dose of study drug (permanent discontinuation of talazoparib or physician’s choice), or before initiation of a new antineoplastic therapy, whichever occurs first. If a non-serious AE remains unresolved at the conclusion of the study, the Investigator will assess whether continued follow-up of the AE is warranted, and the results of this assessment must be documented. Resolution is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic. The Investigator should follow all unresolved AEs until the events are resolved or stabilized, the subject is lost to follow-up, or it has been determined that the study drug or participation is not the cause of the AE. Resolution of AEs (with dates) should be documented on the appropriate eCRF page(s) and in the subject’s medical record.

The criteria for determining, and the reporting of, SAEs is provided in Section 10.2.

The Investigator responsible for the care of the subject or qualified designee will assess AEs for severity, for relationship to study drug, and seriousness (refer to Section 10.2 for SAE definition).

Severity (as in mild, moderate or severe myocardial infarction) is not equivalent to seriousness, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

The Investigator will determine the severity of each event by using NCI CTCAE v4.03. Adverse events that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v4.03 as stated below.

Grade	Description
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)[a]
3	Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
4	Life threatening or debilitating: consequences; urgent intervention indicated
5	Death related to AE

[a] Instrumental ADL refer to the following examples: preparing meals, shopping for groceries or clothes, using the telephone, managing money.

[b] Self-care ADL refer to the following examples: bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, not bedridden.

The study Investigator responsible for the subjects care (or qualified designee) will assess causality of reportable AEs/SAEs. The causal attribution guidance in Table 10-1 will be applied.

Table 10-1: Causal Attribution Guidance

Is there a reasonable possibility that the AE/SAE was caused by the study drug based on facts (evidence) or arguments to suggest a causal relationship?	
YES (Possible, probable or definite)	If there is a plausible temporal relationship between the onset of the AE/SAE and study drug administration and the AE/SAE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE/SAE follows a known pattern of response to study drug; and/or the AE/SAE abates or resolves upon discontinuation of study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO (Not related or remote)	If data are available to identify a clear alternative cause for the AE/SAE other than study drug; such as the subject's clinical state, concomitant therapy, and/or other interventions. OR The AE/SAE has no plausible temporal relationship to administration of study drug (eg, cancer diagnosed 2 days after first dose of study drug).

The Investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual AE/SAE reports, the Sponsor will promptly evaluate all reported safety information against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators and applicable regulatory authorities.

10.2 Serious Adverse Events

An SAE is any untoward medical occurrence that meets 1 or more of the following criteria:

- Is fatal
- Is life threatening

  Note: Life-threatening refers to an event that places the subject at immediate risk of death. This definition does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Requires or prolongs in-patient hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect in the child or fetus of a subject exposed to IP prior to conception or during pregnancy
- Is an important medical event or reaction, including events requiring medical intervention to prevent worsening to any of the previously noted seriousness criteria

  Grade 4 laboratory abnormalities are not by definition serious, unless the subject was at immediate risk of death, prolonged hospitalization or was considered an important medical event.

The safety reporting period for SAEs begins from the time of signing of the main ICF through 30 days after the last dose of study drug (permanent discontinuation of talazoparib or physician's choice), or before initiation of a new antineoplastic therapy, whichever occurs first.

Any SAE, whether or not considered related to study drug, must be reported immediately (within 24 hours of knowledge of the event) to the Sponsor Pharmacovigilance by fax or email using the study-specific SAE Report Form. Each SAE must also be reported on the appropriate eCRF page(s). Investigators should not wait to collect information that fully documents the event before notifying the Sponsor Pharmacovigilance of an SAE. The Sponsor 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 Investigators submit any information requested by the Sponsor as soon as it becomes available. As additional information becomes available, including but not limited to the outcome of the SAE and any

medication or other therapeutic measures used to treat the event, it must be reported within 24 hours by fax or email (using the study-specific SAE Report Form).

If an SAE remains unresolved at the conclusion of the study, follow-up will be done until the event is assessed by the Investigator as having resolved or improved to a stable, chronic condition, or the subject becomes lost to follow-up. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic. Serious adverse events reported to the Investigator after the safety reporting period should be reported to the Sponsor if the Investigator assesses the event as related to the study drug.

Reporting of SAEs to the IRB/IEC/REB will be done in compliance with the standard operating procedures and policies of the IRB/IEC/REB and with applicable regulatory requirements. Adequate documentation must be obtained by the Sponsor showing that the IRB/IEC/REB was properly and promptly notified as required.

10.3 Overdose

10.3.1 Talazoparib

The medical monitor must be contacted in the event of a study drug overdose. An overdose is defined as any dose greater than the protocol-specified dose of talazoparib 1.0 mg once daily. In the event of an overdose, treatment with study drug should be stopped and general supportive measures initiated, taking into consideration the half-life is 53.5 and 40 hours (comparing Day 1 and Day 35 of talazoparib). There is no known antidote to overdose.

All overdose events are to be reported as events of special interest within 24 hours of awareness by the study site according to Section 10.7, whether or not the event meets AE criteria.

10.3.2 Treatment of Physician's choice

The medical monitor must be contacted in the event of a study drug overdose. Overdose for a protocol-specified treatment of physician's choice is any dose greater than the protocol-specified dose as follows:

- Capecitabine: 1250 mg/m^2, oral, twice daily, from Day 1 through 14 of a 21-day cycle, 30 minutes after meal.
- Eribulin mesylate: 1.4 mg/m^2 (equivalent to eribulin 1.23 mg/m^2), infusion over 2-5 minutes, Days 1 and 8 of 21-day cycles
- Gemcitabine: 1250 mg/m^2, infusion over 30 minutes, Days 1 and 8 of 21-day cycles

- Vinorelbine: 30 mg/m^2, weekly infusion over 6 to 10 minutes, Days 1, 8 and 15 of 21-day cycles

In the event of an overdose, treatment with study drug should be stopped and general supportive measures initiated, taking into consideration the half-life of the respective drug. The Package Insert or Summary of Product Characteristics for the treatment of physician's choice should be followed regarding patient management in a setting of an overdose.

All overdose events are to be reported as events of special interest within 24 hours of awareness by the study site according to Section 10.7, whether or not the event meets AE criteria.

10.4 Pregnancy

Pregnancy in a subject or subject's partner should be reported within 24 hours of the site becoming aware of the pregnancy by faxing or emailing the Pregnancy Form in the study reference materials to the Sponsor Drug Safety & Pharmacovigilance Department. In addition, pregnancy in a subject is also reported on the end of study eCRF. The Investigator must make every effort to follow the subject through resolution of the pregnancy (delivery or termination) and to report the resolution on the pregnancy follow-up form in the study reference materials. In the event of pregnancy in the partner of a study subject, the Investigator should make every reasonable attempt to obtain the woman's consent for release of protected health information. This consent for release of protected medical information will be documented on the pregnancy and pregnancy follow-up report forms and will be maintained in the subject's research record. Should the pregnancy result in an abortion of any kind, stillbirth, or if the infant is born with a congenital anomaly, these events should be reported as an SAE rather than as a pregnancy report.

10.5 Reporting Liver Test Abnormalities

The following liver test abnormalities must be reported to the Sponsor as SAEs within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations are concluded):

- AST or ALT $\geq 3 \times$ ULN ($> 5 \times$ ULN if baseline ALT/AST is > 3 and $\leq 5 \times$ ULN), and total bilirubin $> 2 \times$ ULN or INR > 1.5
- AST or ALT $\geq 3 \times$ ULN with signs and symptoms consistent with hepatitis
- Other events of hepatotoxicity and potential drug-induced liver injury that meet the criteria for an SAE

10.6 Urgent Safety Measures

The regulations governing clinical trials state that the Sponsor and Investigator are required to take appropriate urgent safety measures to protect subjects against any immediate hazards that may affect the safety of subjects, and that the appropriate regulatory bodies should be notified according to their respective regulations. According to the European Union (EU) Clinical Trial Directive 2001/20/EC, "…in the light of the circumstances, notably the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the Sponsor and the Investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard. The Sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the IRB/EC/REB is notified at the same time." The reporting period for these events which may require the implementation of urgent safety measures is the period from the time of signing of the main ICF through permanent discontinuation of talazoparib or physician's choice, or before initiation of a new antineoplastic therapy, whichever occurs first. Investigators are required to report any events that may require the implementation of urgent safety measures to the Sponsor Drug Safety & Pharmacovigilance Department within 24 hours.

Examples of situations that may require urgent safety measures include discovery of the following:

- An immediate need to revise the IP administration (ie, modified dose amount or frequency not defined in protocol)
- Lack of study scientific value, or detrimental study conduct or management
- Discovery that the quality or safety of the IP does not meet established safety requirements

10.7 Serious Adverse Event and Event of Special Interest Reporting

Study site personnel will collect SAE information from the time the subject signs the informed consent form through screen failure, 30 days after the last dose of study drug (permanent discontinuation), or before initiation of a new antineoplastic therapy, whichever occurs first. Serious adverse events reported to the Investigator after the safety reporting period should be reported to the Sponsor if the Investigator assesses the event as related to the study drug.

Using an SAE report form, all SAEs, events of overdose, and specified liver test abnormalities (Section 10.1) must be reported **within 24 hours** of the study site personnel's knowledge of the event, regardless of the Investigator assessment of the relationship of the

event to study drug. The contact information for submission of SAEs and 24-hour reports for events of overdose and specified liver test abnormalities is as follows:

Name:	PPD
Fax:	PPD (United States)
	or designated regional toll-free number
Backup Fax:	PPD (United Kingdom)
Email:	PPD
Phone:	PPD

The initial report should include, at minimum, the following:

- Study number (673-301)
- Site name and number
- Investigator name
- Subject number, sex, and age
- Details of study drug administration
- The date of the report
- A description of the SAE (event term, seriousness of the event)
- Causal relationship to the study drug

If the subject died, the report should include the cause of death as the event term (with fatal outcome) and whether or not the event leading to death was related to study drug, as well as the autopsy findings if available.

10.8 Clarification in Reporting of Deaths

As overall survival is one of the study endpoints, all subjects must be followed for survival status until death, and information relating to the death (eg, date and primary cause) should be obtained and recorded. Fatal events (regardless of relationship to study drug) should be reported as SAEs during the safety reporting period (through 30 days after permanent treatment discontinuation).

Death is not an AE but is an outcome of an AE. For this protocol, reports of death without an AE will be managed as expedited reports (SUSARs) until the Sponsor receives additional information.

10.9 Clarification in Reporting of Disease Progression as an Adverse Event

Disease progression is not unexpected in this study population and the term “disease progression” should not be reported as an AE unless a more specific clinical term is not defined or available. When clinical disease progression is identified, the clinical event that identifies the disease progression, if known, should be reported as the AE.

11 APPROPRIATENESS OF MEASUREMENTS

Efficacy endpoints will be assessed in this study using RECIST v.1.1, an internationally standardized and widely accepted standard for measuring response to treatment in cancer (Eisenhauer, Eur. J. Cancer. 2009). Modifications to the criteria, regarding progression by bone metastasis and a requirement for progression by imaging (omitting progression by digital photography or physical examination for superficial lesions), will be employed (detailed in Section 24.3). Efficacy endpoints based on tumor assessments have been increasingly used in drug development, and both PFS and time to tumor progression (TTP) have been accepted as markers of clinical benefit for drug approval. PFS is available earlier than OS, is less likely than OS to be influenced by competing causes of death, and is not influenced by treatments administered after progression in a given trial (Everardo D. Saad., 2011). PFS is subject to measurement error and bias. Measurement error may result from inconsistent use of definitions and standards among Investigators and bias may result from unblinded ascertainment of progression and from the fact that the date at which progression is verified radiographically is a proxy for the true progression date, which lies somewhere within two successive assessments (Everardo D. Saad., 2011).

Overall survival has historically been considered the most important endpoint in medical oncology due to its objective measurement and the unquestionable benefit derived by patients. The US FDA considers OS a direct measure of treatment benefit; according to that agency, OS is usually the preferred endpoint when studies can be conducted to adequately assess survival (US Department of Health and Human Services, May 2007). However, OS is increasingly an elusive endpoint, mostly because it may be confounded by the use of treatments administered to patients after participation in a trial (Everardo D. Saad., 2011).

The European Medicine's Agency (EMA), Committee for Medicinal Products for Human Use (CHMP) Guideline on the Evaluation of Anticancer Medicinal Products in Man (EMA/CPMP/205/95/Rev.4, 2012) states that OS and PFS are acceptable endpoints and recommends that if PFS is selected as the primary endpoint, OS should be selected as a secondary endpoint.

In this study, PFS (defined as time from randomization until the date of radiologic progressive disease [per RECIST v.1.1 with modifications] as determined by the central IRF, or death from any cause, whichever comes first) has been selected as the primary endpoint. The potential for measurement error and bias, outlined above, has been reduced in this study by the use of a blinded central IRF and the use of a randomized study design in which a similar evaluation schedule is used for all treatment arms. Overall survival has been selected

as a secondary endpoint in this study in accordance with the regulatory guidance described above.

The secondary efficacy measure of ORR and exploratory efficacy measure of DOR are well accepted efficacy endpoints in clinical development for oncology studies and in line with recommendations in the EMA CHMP Guideline on the Evaluation of Anticancer Medicinal Products in Man (EMA/CPMP/205/95/Rev.4, 2012); and the US FDA Guidance for Industry on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (US Department of Health and Human Services, May 2007).

Quality of life will be assessed as an exploratory endpoint in this study using the EORTC QLQ-C30/ EORTC QLQ-BR23, which is a validated instrument for assessing quality of life in breast-cancer subjects.

The safety and PK endpoints in this study are standard and well-understood endpoints in clinical oncology.

12 STUDY PROCEDURES

12.1 Pre-study

A subject may sign the BRCA test ICF that permits BRCA1/2 testing at any time. A subject may enter the 28-day screening period and be randomized after the main ICF is signed and dated by the subject, the Investigator or designee, and witness (if required) before any other study-related procedures are performed.

12.2 Screening/Baseline Visits

There will be a Screening visit within 28 days before randomization and a baseline visit within 7 days before randomization. If the Screening visit occurs within 7 days before randomization, physical examination, vital signs, and clinical laboratory assessments do not need to be repeated at baseline. All Screening and baseline procedures may be performed on the same day as long as it is within 7 days before randomization.

At the Screening visit (within 28 days before randomization), the following procedures and assessments will be performed:

- Record full medical history, including oncologic history, prior treatments, and demographics
- Collect vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and temperature), record height and weight
- Perform a full physical examination
- ECOG assessment
- Perform baseline tumor assessments. Tumor measurements will be based on computed tomography (CT; preferred), magnetic resonance imaging (MRI), or X-ray. CT/MRI scans performed as standard of care before the main ICF was signed and within the 28-day screening period may be used as the Screening tumor assessments if the scans were completed per the specific study requirement (as specified in the Imaging Manual)
- Perform optional tumor marker (eg, CA15-3, CA27-29) assessments
- MRI or CT to be performed to evaluate subjects for presence/absence of brain metastases

- If newly diagnosed CNS metastases are discovered at Screening, the subject is not eligible for enrollment until the CNS disease has been adequately treated with radiotherapy and/or surgery. Following treatment, if the CNS metastases are adequately controlled and do not require corticosteroids (except prednisone ≤ 5 mg/day or equivalent) for management of CNS symptoms, the subject may be re-screened for eligibility. A repeat CT/MRI following the identification of brain metastases (obtained at least 2 weeks after definitive therapy) must document adequately treated brain metastases

- Acquire whole body nuclear medicine bone scan within 12 weeks before randomization
- Collect samples for clinical laboratory tests (hematology and serum chemistry and a serum pregnancy test for women of childbearing potential)
- Calculate creatinine clearance (see Section 9.7.4.2)
- Record any SAEs occurring after signing of the informed consent and related to study procedures or study conduct as outlined in Section 10.2
- Record all concomitant medications or treatments (including herbal therapies) that the subject has received within 28 days before randomization
- Documentation of deleterious, suspected deleterious, or pathogenic germline BRCA1 or BRCA2 mutation must be provided for enrollment from prior analysis by Myriad Genetics or laboratory approved by the Sponsor
- Obtain blood sample for germline BRCA assay. For subjects who have prior documentation of BRCA carrier status, a blood sample for retrospective BRCA germline testing will be collected during the Screening/baseline period (Day -28 to Day -1). Retrospective testing will be performed at the central laboratory. For subjects who must undergo prospective BRCA germline testing, blood sample must be collected as early as possible during the Screening period. Prospective BRCA testing will be performed at the central laboratory. Specific laboratories and instructions on collection, processing, and shipment are provided in the laboratory manual
- Obtain blood sample for disease-related research, including but not limited to genomic analysis
- Confirm availability of archived tumor tissue slides (formalin-fixed paraffin-embedded [FFPE]) and ship as instructed in laboratory manual; tumor blocks may be substituted if approved by the Sponsor. A subject may be randomized without availability of tumor tissue slides or blocks. See the Laboratory Manual for preparation of slides or tumor blocks
- Collect a fresh tumor biopsy sample (this procedure is optional and should only be performed if the subject has consented. The biopsy will be collected at any time during the Screening/baseline period (Day -28 to Day -1))

At the Baseline visit (within 7 days before randomization), the following procedures and assessments will be performed:

- Collect vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and temperature), record weight
- Perform a full physical examination
- Collect samples for clinical laboratory tests (hematology, serum chemistry, coagulation, and dipstick urinalysis). The laboratory tests may be omitted if the Screening samples were obtained within 7 days before randomization. (At least 1 set of laboratory tests must be collected before randomization.)
- EORTC QLQ-C30/EORTC QLQ-BR23 (see Section 24.4)
- Record any SAEs occurring after signing of the informed consent and related to study procedures or study conduct as outlined in Section 10.2
- Record any changes to the subject's concomitant medications or treatments (including herbal therapies) since the previous visit
- Obtain a 12-lead ECG

12.3 Treatment Visits

Throughout the study, hematology assessments scheduled for the day of the dosing must be available and assessed for abnormalities requiring dose adjustment before dosing. The sampling for the hematology assessment can be drawn within 72 hours prior to dosing. In addition, serum chemistry, coagulation and urinalysis can be drawn within 72 hours prior to dosing.

The first day of treatment is defined as Day 1; a ± 3-day window is allowed for Day 8 and 15 visits for all Cycles. If initiation of a new cycle is delayed, the Day 1 procedures for that cycle will be performed on the day that dosing is resumed.

12.3.1 Cycles 1 and 2

Weekly blood counts are to be obtained during the first 2 cycles. Hematology assessments obtained on days other than Day 1 of a Cycle may be performed at a local laboratory outside of the investigational site laboratory, as long as laboratory reports are provided to the Investigator for evaluation 24 hours before dosing.

For subjects assigned to talazoparib, daily dosing will begin on Day 1 and continue up to Day 21 for each cycle as described in Section 9.4.5.

For subjects assigned to protocol-specific physician's choice, the following dosing schedules will apply for each cycle (unless institution dosing guidelines differ) as described in Section 9.4.5:

- Capecitabine will be administered twice daily on Day 1 through Day 14
- Eribulin will be administered on Day 1 and 8
- Gemcitabine will be administered on Day 1 and 8
- Vinorelbine will be administered on Day 1, 8, and 15

12.3.1.1 Cycles 1 and 2, Day 1

On Day 1, the following procedures and assessments will be performed before dosing with talazoparib or protocol-specific physician's choice:

- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and temperature) and weight
- Focused physical examination at the discretion of the Investigator based on the subject's clinical condition
- ECOG assessment
- For women of childbearing potential only: serum or urine pregnancy test
    - If urine pregnancy test is positive, interrupt study drug treatment and confirm with a serum pregnancy test
- For subjects assigned to talazoparib only: Collect pre-dose PK blood sample (within 60 minutes prior to dosing)
    - Also collect whether subject had or had not eaten within 2 hours before collection of PK sample
- Collect samples for clinical laboratory tests (hematology and serum chemistry)
- EORTC QLQ-C30/EORTC QLQ-BR23 (see Section 24.4)
- Record any AEs observed or reported since the previous visit (Cycle 2, Day 1 only)
- Record any SAEs occurring after signing of the informed consent and related to study procedures or study conduct (Cycle 1, Day 1), and any SAEs observed or reported since the previous visit (Cycle 2, Day 1) as outlined in Section 10.2
- Record any changes to the subject's concomitant medications or treatments (including herbal therapies) since the previous visit

After completion of the pre-dose assessments, the following will occur:

- Subjects assigned to talazoparib only will swallow the Day 1 dose of talazoparib at the clinic. The site will dispense sufficient talazoparib to last for one cycle. The subject will be instructed to take the assigned dose of talazoparib at approximately the same time each day, preferably in the morning
- Subjects assigned to protocol-specific physician's choice will receive the Day 1 dose of capecitabine, eribulin, gemcitabine, or vinorelbine. For subjects assigned to capecitabine, the site will dispense sufficient capecitabine to last for one cycle

For subjects assigned to talazoparib only: After talazoparib dosing, the following procedures and assessments will be performed:

- Collect sparse PK blood samples ≥ 30 minutes after dosing. Two post-dose samples will be collected, separated by ≥ 2 hours

12.3.1.2 Cycles 1 and 2, Day 8 (± 3 days)

On Day 8, the following procedures and assessments will be performed before dosing with talazoparib or protocol-specific physician's choice:

- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and temperature)
- Collect samples for clinical laboratory tests (hematology only); review the laboratory results for abnormalities before dosing
- Record any AEs, including SAEs, observed or reported since the previous visit
- Record any changes to the subject's concomitant medications or treatments (including herbal therapies) since the previous visit

After completion of the pre-dose assessments the following will occur:

- Subjects assigned to talazoparib only will swallow the Day 8 dose of talazoparib at the clinic
- Subjects assigned to protocol-specific physician's choice will receive the Day 8 dose of capecitabine, eribulin, gemcitabine, or vinorelbine

12.3.1.3 Cycles 1 and 2, Day 15 (± 3 days)

On Day 15, the following procedures and assessments will be performed before dosing with talazoparib or protocol-specific physician's choice:

- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and temperature)

- Collect samples for clinical laboratory tests (hematology only); review the laboratory results for abnormalities before dosing
- Record any AEs, including SAEs, observed or reported since the previous visit
- Record any changes to the subject’s concomitant medications or treatments (including herbal therapies) since the previous visit

After completion of the pre-dose assessments the following will occur:

- Subjects assigned to talazoparib only will swallow the Day 15 dose of talazoparib at the clinic
- Subjects assigned to protocol-specific physician’s choice of vinorelbine will be administered the Day 15 dose of vinorelbine. Subjects assigned to protocol-specific physician’s choice of eribulin, gemcitabine and capecitabine will resume treatment at the next scheduled visit

12.3.2 Cycles ≥ 3

Subjects who do not experience radiographic disease progression as determined by the IRF, unacceptable toxicity, or other discontinuation criteria at the end of Cycle 2 may continue to receive treatment in additional 21-day cycles.

For subjects assigned to talazoparib, daily dosing will begin on Day 1 and continue up to Day 21 for each cycle as described in Section 9.4.5.

For subjects assigned to protocol-specific physician’s choice, the following proposed dosing schedules will apply (unless institution dosing guidelines differ) as described in Section 9.4.5:

- Capecitabine will be administered twice daily on Day 1 through Day 14 of each cycle
- Eribulin will be administered on Day 1 and 8
- Gemcitabine will be administered on Day 1 and 8
- Vinorelbine will be administered on Days 1, 8, and 15

In Cycles ≥ 3, the Day 8 and Day 15 clinic visits may be omitted for subjects assigned to talazoparib or capecitabine not experiencing significant toxicities. Similarly, the Day 15 clinic visit may be omitted for subjects assigned to eribulin, gemcitabine or vinorelbine (depending on schedule of administration or toxicity). A hematology assessment must be performed on either Day 8 or Day 15; this may occur at a local laboratory outside of the investigational site laboratory as long as laboratory reports are provided to the Investigator for evaluation 24 hours before dosing. Subjects who do not come to the clinic for Day 8 or

Day 15 visits should be contacted by phone to review AEs and concomitant medications. The phone review should be documented in the subject's source documents.

12.3.2.1 Cycle ≥ 3, Day 1

On Day 1, the following procedures and assessments will be performed before dosing with talazoparib or protocol-specific physician's choice:

- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and temperature) and weight
- Focused physical examination at the discretion of the Investigator based on the subject's clinical condition
- ECOG assessment
- For women of childbearing potential only: serum or urine pregnancy test
  - If urine pregnancy test is positive, interrupt study drug treatment and confirm with a serum pregnancy test
- For subjects assigned to talazoparib only in Cycles 3 and 4 only: Collect pre-dose PK blood sample (within 60 minutes prior to dosing)
  - Also collect whether subject had or had not eaten within 2 hours before collection of PK sample
- Collect samples for clinical laboratory tests (hematology and serum chemistry); review the laboratory results for abnormalities before dosing
- EORTC QLQ-C30/EORTC QLQ-BR23 (see Section 24.4)
- Record any AEs, including SAEs, observed or reported since the previous visit
- Record any changes to the subject's concomitant medications or treatments (including herbal therapies) since the previous visit

After completion of the pre-dose assessments, the following will occur:

- Subjects assigned to talazoparib will swallow the Day 1 dose of talazoparib at the clinic. The site will dispense sufficient talazoparib to last for one cycle
- Subjects assigned to protocol-specific physician's choice will receive the Day 1 dose of capecitabine, eribulin, gemcitabine, or vinorelbine. For subjects assigned to oral capecitabine, the site will dispense sufficient capecitabine to last for one cycle

For subjects assigned to talazoparib only, in Cycles 3 and 4 only: After talazoparib dosing, the following procedures and assessments will be performed:

- Collect sparse PK blood samples ≥ 30 minutes after dosing. Two post-dose samples will be collected, separated by ≥ 2 hours (for Cycle 3 and 4 only)

12.3.2.2 Cycles ≥ 3, Day 8 (± 3 days)

On Day 8, the following procedures and assessments will be performed before dosing with talazoparib or protocol-specific physician's choice:

- Collect samples for clinical laboratory tests (hematology only); review the laboratory results for abnormalities before dosing
    - Note: Starting with Cycle 3, hematology counts should be obtained in each cycle on either Day 8 (± 3 days) or Day 15 (± 3 days)
- Record any AEs, including SAEs, observed or reported since the previous visit; this information may be obtained via telephone for subjects who do not come to the clinic
- Record any changes to the subject's concomitant medications or treatments (including herbal therapies) since the previous visit; this information may be obtained via telephone for subjects who do not come to the clinic

12.3.2.3 Cycles ≥ 3, Day 15 (± 3 days)

On Day 15, the following procedures and assessments will be performed before dosing with talazoparib or protocol-specific physician's choice:

- Collect samples for clinical laboratory tests (hematology only); review the laboratory results for abnormalities before dosing
    - Note: Starting with Cycle 3, hematology counts should be obtained in each cycle on either Day 8 (± 3 days) or Day 15 (± 3 days)
- Record any AEs, including SAEs, observed or reported since the previous visit; this information may be obtained via telephone for subjects who do not come to the clinic
- Record any changes to the subject's concomitant medications or treatments (including herbal therapies) since the previous visit; this information may be obtained via telephone for subjects who do not come to the clinic

12.3.3 Unscheduled Visits

Unscheduled visits may be performed if a subject comes in for a visit and the dose is delayed due to an AE. Unscheduled visits may also be performed anytime to assess or follow up AEs, to perform scans, at the subject request, or at the Investigator request. The date and reason for the unscheduled visit must be recorded in the source documentation.

A review of AEs and changes to the subject's concomitant medications or treatments (including herbal therapies) occurring since the previous visit should be performed at unscheduled visits. Other study procedures may be performed as clinically appropriate. Imaging may be performed, as appropriate, for subjects who are symptomatic and/or for whom radiographic disease progression or response is being determined.

12.3.4 Timing of Tumor Assessments

Tumor assessments will be performed by CT (preferred), MRI or X-ray. A brain MRI or CT is required at Screening/Baseline. Newly diagnosed CNS metastases at Baseline/Screening makes a patient ineligible for enrollment until such time as the CNS disease has been adequately treated by radiotherapy and/or surgery and the CNS disease is adequately controlled as described in Section 12.2. At that point, the patient is eligible for re-screening. If adequately controlled metastatic disease in the brain is present at Screening/Baseline, the brain MRI or CT will be repeated as clinically indicated. Post-baseline tumor assessments should be performed using the same technique used at Screening/Baseline.

Tumor assessments are to be performed at Screening, every 6 weeks (± 7 days) for the initial 30 weeks from the date of randomization, and every 9 weeks thereafter (± 7 days), regardless of any dose interruptions or dose delays until radiographic disease progression as determined by the IRF or initiation of a new antineoplastic therapy. Tumor assessments can occur as clinically indicated, and at the time of clinical suspicion of disease progression. Post-baseline tumor assessments should be performed using the same technique used at Screening/baseline.

Optional tumor marker assessments (eg, CA15-3, CA27-29) may be performed at baseline, every 2 cycles (± 7 days) and at the End of Treatment. Tumor marker assessments will not be repeated if normal at baseline.

A bone scan is required at Screening/Baseline (or within 12 weeks before randomization). If bone metastasis is present at Screening/Baseline, a bone scan will be repeated every 12 weeks (± 7 days) and as clinically indicated. Post-baseline assessments should be performed using the same technique used at Screening/Baseline.

12.3.5 Timing of Quality of Life Assessments

EORTC QLQ-C30/EORTC QLQ-BR23 assessments will be performed at baseline, Day 1 of each treatment cycle, and at the End of Treatment. The EORTC QLQ-C30/EORTC QLQ-BR23 is included in Section 24.4.

12.4 End of Treatment and Follow-up Visits

Following permanent treatment discontinuation, for any reason, the subject will return to the site 30 days (-3 days or +10 days [27-40 days postdose]) after the last dose of study drug for an End of Treatment visit. At the End of Treatment visit, the following procedures and assessments will be performed (tumor assessments may be skipped if performed in the previous 28 days):

- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and temperature) and weight
- Perform focused physical examination
- ECOG assessment
- For women of childbearing potential only: Urine or serum pregnancy test (per local regulations):
  - If urine pregnancy test is positive, confirm with a serum pregnancy test
- Perform tumor assessments by using the same techniques used at baseline (if not performed within the previous 28 days)
- Optional tumor marker assessment (only for subjects with abnormal results at baseline)
- Genomic blood sample at radiographic disease progression (+ 35 days)
- Collect samples for clinical laboratory tests (hematology and serum chemistry only)
- EORTC QLQ-C30/EORTC QLQ-BR23 (see Section 24.4)
- Perform 12-lead ECG (if clinically indicated)
- Record any changes to the subject's concomitant medications or treatments (including herbal therapies) since the previous visit; note whether anticancer treatment has been provided since the last dose of study drug
- Collect a fresh tumor biopsy sample (this procedure is optional and should only be performed if the subject has consented. The biopsy will be collected at radiographic disease progression [+ 35 days] or at the time of discontinuation of study treatment)

AEs will continue to be recorded until 30 days after the last dose of study drug (permanent discontinuation) or before initiation of a new antineoplastic therapy, whichever occurs first. For events occurring outside of this reporting period, only SAEs occurring greater than 30 days after last dose of study medication and assessed as related to study drug will be reportable.

Long-term follow-up: Subjects will be contacted after the End of Treatment visit to determine survival status, cause of death (if applicable) and subsequent anti-cancer treatment every 60 days (± 7 days) after last dose for the first year, every 90 days (± 14 days) thereafter, and when requested by the Sponsor.

13 DATA QUALITY ASSURANCE

Sponsor personnel or designees will visit the study site prior to initiation of the study to review with the site personnel information about the IP, protocol and other regulatory document requirements, any applicable randomization procedures, source document requirements, eCRFs, monitoring requirements, and procedures for reporting AEs, including SAEs.

At visits during and after the study, a CRA will monitor the site for compliance with regulatory documentation, with a focus on accurate and complete recording of data on eCRFs from source documents, adherence to protocol, randomization (if applicable), SAE reporting and drug accountability records.

Data quality control and analysis will be performed by the Sponsor or a designee, based on a predefined analysis plan.

[redacted]

14 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

14.1 Statistical and Analytical Plans

The statistical analysis plan (SAP) will provide additional details on the planned statistical analysis.

14.1.1 Interim Analyses

There will be an interim and the final analysis for OS. An interim analysis of OS will be conducted at the time of the primary analysis of PFS. As the OS data are not expected to be mature at the time of interim analysis, OS data will be summarized to detect a statistical trend. The formal analysis of OS will be conducted when approximately 321 death events have been observed.

14.1.2 Procedures for Accounting for Missing, Unused and Spurious Data

All available data will be used. No efficacy or PK data will be imputed; missing values will be treated as missing.

14.2 Primary Efficacy Analysis

The primary efficacy analysis is the comparison of PFS in subjects treated with talazoparib versus treatments of protocol-specific physician’s choice.

The primary endpoint is PFS, which is defined as time from randomization until the date of radiologic progressive disease per RECIST v.1.1 with modifications as determined by the central IRF or death from any cause, whichever comes first. The primary analysis of PFS will be conducted when at least 288 PFS events have been observed.

The primary analysis of PFS will be performed using the intent-to-treat (ITT) population, defined as all randomized subjects, and will include only radiographic progression events as determined by the central IRF per RECIST v.1.1 with modifications and deaths. Clinical deterioration or radiographic progression determined by Investigators will not be considered progression events for the primary analysis.

A stratified log-rank 2-sided test with a 0.05 level of significance will be used to compare treatment groups. The stratification factors will be the same used to stratify the randomization schedule as documented in the interactive voice and Web response system (IXRS).

The median PFS and the associated 95% confidence interval (CI) for each treatment arm will be estimated using the Kaplan-Meier method. The hazard ratio (HR; $\lambda_{talazoparib}/\ \lambda_{control}$) and the associated 95% CI will be estimated using a Cox regression model with treatment group as the only main effect and stratifying by the same stratification factors as were used for the log-rank test. An unstratified HR and the associated 95% CI will also be presented.

If the p-value for the stratified log-rank test is statistically significant (< 0.05, two-sided) and the observed HR ($\lambda_{talazoparib}/\ \lambda_{control}$) is < 1, the null hypothesis of no difference in PFS will be rejected and it will be inferred that PFS is statistically prolonged in the group receiving talazoparib compared with the group receiving protocol-specific physician's choice of therapy.

14.3 Secondary Efficacy Analysis

Secondary efficacy endpoints include ORR and OS. To maintain experiment-wise 2-sided type I error at 0.05, a detailed multiplicity adjusted inferential procedure for the primary and secondary efficacy analyses will be provided in the Statistical Analysis Plan.

Objective Response Rate

The ORR will be determined by the IRF and is defined as the proportion of subjects with a partial or complete response as defined by RECIST v.1.1 with modifications.

The primary analysis of ORR will be performed among the subjects with baseline measurable disease in the ITT population. In the analysis of ORR, subjects who do not have any post-baseline adequate tumor assessments will be counted as non-responders. Formal hypothesis testing of ORR will be performed using the stratified Cochran-Mantel-Haenszel test. The stratification factors will be the same used to stratify the randomization schedule as documented in the IXRS. The CR responders will be reported separately for the non-measurable disease subjects.

Overall Survival

OS is defined as the time from randomization to death due to any cause.

There will be an interim and final analysis for OS. The interim analysis of OS will be conducted at the time of the primary analysis of PFS. At the interim analysis, OS data will be summarized to detect a statistical trend in OS (no formal hypothesis testing). The formal analysis of OS will be conducted when approximately 321 deaths have been observed, and will be performed using the ITT population.

The testing of OS will be conducted using a stratified log-rank 2-sided test. The stratification factors will be the same used to stratify the randomization schedule as documented in the IXRS.

The median of OS and the associated 95% CI for each treatment arm will be estimated using the Kaplan-Meier method. The HR and the associated 95% CI will be estimated using a Cox regression model with treatment group as the only main effect and stratifying by the same stratification factors as were used for the log-rank test. An unstratified HR and the associated 95% CI will also be presented.

14.4 Exploratory Efficacy Analysis

The exploratory efficacy endpoints are duration of response in responding subjects and quality of life for all enrolled subjects, assessed using the EORTC QLQ-C30 / EORTC QLQ-BR23.

Duration of response is defined, for subjects with an objective response, as the time from first radiographic documentation of CR or PR to disease progression by RECIST v.1.1 with modifications as determined by the IRF or death due to any cause, whichever occurs first. Median duration of response and its associated 95% CI will be estimated, by treatment group, using Kaplan-Meier methods. The difference between treatment groups will be analyzed using a stratified log-rank test, using the same stratification that was used for randomization.

The EORTC QLQ-C30 / EORTC QLQ-BR23 is composed of a global health status scale, 5 functional scales (physical, role, emotional, cognitive, and social), 3 symptom scales (fatigue, nausea & vomiting, and pain), and several single items, as well as a module designed specifically for breast cancer.

Summary statistics will be presented, by treatment group, at Baseline, at Day 1 of each cycle and at End of Treatment for the global health status scale, the functional and symptom scales, and the breast cancer module. Summary statistics for change from baseline will be presented at Day 1 of each cycle and at the End of Treatment. Differences between treatment groups will be analyzed using repeated measures analysis methods if applicable.

Blood and tumor samples will be collected for future exploratory research to identify additional marker profiles that indicate potential sensitivity to PARP inhibition, to characterize tumor sensitivity and resistance to talazoparib, and for other disease-related research. Analyses will include but not be limited to genomic/genetic, cellular, molecular, histochemical and biochemical assays.

14.4.1 Pharmacokinetic Analyses

The PK analysis will include all subjects who receive at least 1 dose of talazoparib and provide at least 1 evaluable PK assessment. The pharmacokinetics of talazoparib will be evaluated by summary statistics of trough plasma concentrations collected on Day 1 of Cycles 2, 3, and 4.

A population PK modeling approach will be used to estimate individual values of apparent clearance (CL/F) and central volume of distribution (Vc/F) from the sparse post-dose PK samples. Individual CL/F estimates will then be used to estimate individual exposure parameters (eg, area under the concentration time curve over a dosing interval [AUC_{τ}]). The association between talazoparib exposure parameters and efficacy and safety outcomes may be explored.

14.5 Safety Analysis

The analyses of safety will include all subjects who receive any study drug (talazoparib or active control) throughout the study duration.

All AEs will be coded using MedDRA. The Investigator will classify the severity of AEs using the CTCAE v 4.03. A treatment emergent AE (TEAE) is defined as any event with an onset date on or after date of first dose of study drug, or any event present before treatment that worsens after treatment. Only TEAEs with an onset date prior to date of last dose + 30 days or the date of initiation of a new antineoplastic therapy (whichever occurs first) will be tabulated in summary tables.

The number and percentage of subjects with AEs will be summarized by system organ class, preferred term, relationship to study drug, and severity for each treatment group. A by-subject listing will be provided for those subjects who experience an SAE, including death, or experience an AE associated with discontinuation of study drug.

Clinical laboratory data will be summarized by the type of laboratory test. The number and percentage of subjects who experience abnormal (ie, outside of reference ranges) and/or clinically significant abnormalities after study drug administration will be presented for each clinical laboratory measurement. For each clinical laboratory measurement, descriptive statistics will be provided for baseline and all subsequent post-treatment scheduled visits. Changes from baseline to the post-treatment visits will also be provided. Descriptive statistics of vital signs will also be provided in a similar manner. In addition, shift from baseline in CTCAE grade (where applicable) and by high/low flags (where CTCAE grades are not defined) will be presented by treatment group.

14.6 Determination of Sample Size

This study is designed to provide adequate power for PFS and OS.

For PFS, based on 2:1 randomization allocation ratio, a total of 288 events provide the study with 90% power for a 2-sided log-rank test with a 0.05 level of significance to detect a 50% increase in PFS (hazard ratio [HR]=0.67). Assuming an exponential distribution of PFS, this corresponds to an increase in median PFS from 20 weeks to 30 weeks. In the current design, the minimum observed effect that would result in statistical significance for PFS is a 28% improvement (HR = 0.78) from 20 to 25.6 weeks.

Up to 429 subjects will be randomized (2:1) and followed to observe the required number of events within the planned study duration (approximately 39 months accrual; approximately 41 months total to observe the required PFS events).

For OS, approximately 321 events will provide the study with 80% power for a 2-sided log-rank test with an overall 0.05 level of significance to detect a 39% increase in OS (HR=0.72). Assuming an exponential distribution of OS, this corresponds with an increase in median OS from 20 months to 27.8 months.

14.7 Analysis Populations

The safety analysis population will consist of all subjects who receive any study drug (talazoparib or protocol-specific physician's choice therapy).

The ITT population will consist of all randomized subjects.

The PK analysis population will consist of all subjects who receive at least 1 dose of talazoparib and provide evaluable PK assessments.

14.8 Statistical Criteria for Termination of the Study

There are no statistical criteria for the termination of the study.

14.9 Changes in the Conduct of the Study or Planned Analyses

Only the Sponsor may modify the protocol. Any change in study conduct considered necessary by the Investigator will be made only after consultation with the Sponsor, who will then issue a formal protocol amendment to implement the change. The only exception is when an Investigator considers that a subject's safety is compromised without immediate action. In these circumstances, immediate approval of the chairman of the IRB/EC/REB must be sought, and the Investigator should inform the Sponsor and the full IRB/EC/REB within 2 working days after the emergency occurs.

With the exception of minor administrative or typographical changes, the IRB/EC/REB must review and approve all protocol amendments. Protocol amendments that have an impact on subject risk or the study objectives, or require revision of the ICF, must receive approval from the IRB/EC/REB prior to their implementation.

When a protocol amendment substantially alters the study design or the potential risks or burden to subjects, the ICF will be amended and approved by the Sponsor and the IRB/EC/REB, and all active subjects must again provide informed consent.

Note: If discrepancies exist between the text of the statistical analysis as planned in the protocol, and the final SAP, a protocol amendment will not be issued and the SAP will prevail.

15 DATA MONITORING COMMITTEE

A Data Monitoring Committee (DMC) will be established to monitor the safety of the study on a regular basis. The committee will operate independently from the Sponsor and the clinical Investigators. The primary responsibilities of the DMC are to review the accumulating safety data on a regular and an ad hoc basis and to make recommendations to the Sponsor regarding the continued conduct of the study. Safety data will be provided at regular intervals to the DMC in the form of unblinded summary reports or data listings from an independent statistical center designated by the Sponsor. Details of the composition, role, operational considerations, and stopping guidelines will be provided in a separate DMC charter.

[redacted]

16 BLINDED CENTRAL INDEPENDENT RADIOLOGY FACILITY

An Independent Radiology Facility (IRF) will evaluate imaging data of trial subjects in a central, blinded, and independent fashion. Board-certified radiologists will determine radiographic response and/or progression following randomization by assessing CT, MRI, x-ray, and bone scans according to RECIST v.1.1 with modifications.

16.1 Confirmation of Progression

Subjects will continue to receive treatment until radiographic disease progression or other discontinuation criteria are met. Clinical deterioration or radiographic progression determined by the Investigator will not be considered progression events for the primary analysis; the analysis of PFS (conducted by the Sponsor or designee) will only include radiographic disease progression events as determined by the IRF. Radiographic progression must be verified centrally before removal of subject from the study drug. For each subject whom the site suspects has progressed, a confirmation of progression review will radiographically verify that a subject has progressed before discontinuing treatment. Sites will quickly be notified of the results. **Note:** The image review charter will contain further detail regarding the confirmation of progression review.

Details regarding IRF member qualification, training, methods, procedures, and other issues relevant to committee operations will be described in the IRF charter.

17 COMPENSATION, INSURANCE AND INDEMNITY

There will be no charge to study subjects to be in this study. The Sponsor will pay all costs of tests, procedures, and treatments that are part of this study unless otherwise covered by the subject’s health insurance company or other third party payer. In addition, after IRB/EC/REB approval, the Sponsor may reimburse the cost of travel for study-related visits. The Sponsor will not pay for any hospitalizations, tests, or treatments for medical problems of any sort, whether or not related to the study subject’s disease, that are not part of this study. Costs associated with hospitalizations, tests, and treatments should be billed and collected in the way that such costs are usually billed and collected.

The Investigator should contact the Sponsor immediately upon notification that a study subject has been injured by the IP or by procedures performed as part of the study. Any subject who experiences a study-related injury should be instructed by the Investigator to seek medical treatment at a pre-specified medical institution if possible, or at the closest medical treatment facility if necessary. The subject should be given the name of a person to contact to seek further information about, and assistance with, treatment for study-related injuries. The treating physician should bill the subject’s health insurance company or other third party payer for the cost of this medical treatment. If the subject has followed the Investigator’s instructions, the Sponsor will pay for reasonable and necessary medical services to treat the injuries caused by the IP or study procedures, if these costs are not covered by health insurance or another third party that usually pays these costs. In some jurisdictions, the Sponsor is obligated by law to pay for study-related injuries without prior recourse to third party payer billing. If this is the case, the Sponsor will comply with the law.

18 CASE REPORT FORMS AND SOURCE DOCUMENTS

Electronic case report forms will be provided for each subject. The Investigator must review and electronically sign the completed eCRF casebook to verify its accuracy before the data are locked.

Electronic case report forms must be completed using a validated web–based application. Study site personnel will be trained on the application and will enter the clinical data from source documentation. Unless explicitly allowed in the eCRF instructions, blank data fields are not acceptable.

In the event of an entry error, or if new information becomes available, the site personnel will correct the value by deselecting the erroneous response and then selecting or entering the factual response. In compliance with 21 CFR Part 11, the system will require the site personnel to enter a reason for changing the value. The documented audit trail will include the reason for the change, the original value, the new value, the time of the correction and the identity of the operator.

The study data on the eCRFs must be verifiable to the source data, which necessitates access to all original recordings, laboratory reports, and subject records. In addition, all source data should be attributable (signed and dated). The Investigator must therefore agree to allow direct access to all source data. Subjects (or their legally authorized representative) must also allow access to their medical records, and subjects will be informed of this and will confirm their agreement when giving informed consent.

A CRA designated by the Sponsor will compare the eCRFs with the original source documents at the study site and evaluate them for completeness and accuracy before designating them as “source data verified.” All eCRF data must be source data verified before the casebook is approved by the Investigator and locked. If an error is discovered at any time or a clarification is needed, the CRA or designee will create an electronic query on the associated field. Site personnel will then answer the query by either correcting the data or responding to the query. The CRA will then review the response and determine either to close the query or re–query the site if the response does not fully address the question. This process is repeated until all open queries have been answered and closed.

Upon completion of the clinical study report, an electronic copy of each site’s casebooks will be copied to a compact disk and sent to each site for retention with other study documents.

19 STUDY MONITORING AND AUDITING

Qualified individuals designated by the Sponsor will monitor all aspects of the study according to GCP and standard operating procedures for compliance with applicable government regulations. The Investigator agrees to allow these monitors direct access to the clinical supplies, dispensing, and storage areas and to the clinical files, including original medical records, of the study subjects, and, if requested, agrees to assist the monitors. During the review of these documents, the anonymity of the subject will be respected with strict adherence to professional standards of confidentiality. The Investigator and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by the Sponsor or its designees.

Members of the Sponsor’s Clinical Quality Assurance Department or designees may conduct an audit of a clinical site at any time before, during, or after completion of the study. The Investigator will be informed if an audit is to take place and advised as to the scope of the audit. Representatives of the FDA or other regulatory agencies may also conduct an audit of the study. If informed of such an inspection, the Investigator should notify the Sponsor immediately. The Investigator will ensure that the auditors have access to the clinical supplies, study site facilities, original source documentation, and all study files.

20 RETENTION OF RECORDS

The Investigator must retain all study records required by the Sponsor and by the applicable regulations in a secure and safe facility. A file for each subject must be maintained that includes the signed informed consent form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived. Subject identity information recorded will be maintained for at least 15 years on the subject confidentiality log or longer if required by local regulations.

The Investigator must consult a Sponsor representative before disposal of any study records, and must notify the Sponsor of any change in the location, disposition or custody of the study files. The Investigator/institution must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (eg, subject charts) as well as any original source documents that are electronic as required by applicable regulatory requirements.

All study records must be retained for at least 2 years after the last approval of a marketing application in the US or an ICH region and until (1) there are no pending or contemplated marketing applications in the U.S. or an ICH region or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 15 years. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by a Sponsor agreement. The Sponsor must be notified and will assist with retention should Investigator/institution be unable to continue maintenance of subject files for the full 15 years. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

21 USE OF INFORMATION AND PUBLICATION

The Sponsor recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and at seminars or conferences. Written approval from the Sponsor is required before disclosing any information related to this clinical trial, and no publications initiated by Investigators may be published until all protocol defined primary and secondary endpoints are published in a manuscript. Investigators in this study agree to have their name listed as an Investigator in any publication reporting results from this study, whether or not they are an author on the publication.

The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be described in the Clinical Trial Agreement between the Sponsor and the institution of the Investigator.

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23 SIGNATURE PAGE

Protocol Title: A Phase 3, Open-Label, Randomized, Parallel, 2-Arm, Multi-Center Study of Talazoparib (BMN 673) versus Physician's Choice in Germline BRCA Mutation Subjects with Locally Advanced and/or Metastatic Breast Cancer**,** Who Have Received Prior Chemotherapy Regimens for Metastatic Disease

Protocol Number: 673-301, Amendment 1

I have read the forgoing protocol and agree to conduct this study as outlined. I agree to conduct the study in compliance with all applicable regulations and guidelines, including ICH E6, as stated in the protocol, and other information supplied to me.

Investigator Signature Date

Printed name: ____

Accepted for the Sponsor:

On behalf of Medivation, Inc., I confirm that Medivation, Inc., as a Sponsor will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the Investigator is informed of all relevant information that becomes available during the conduct of this study.

Medical Monitor Signature Date

Printed name: ____

24 APPENDICES

24.1 ECOG Performance Status

0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework or office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

24.2 Common Terminology Criteria for Adverse Events

Please refer to: http://ctep.cancer.gov/reporting/ctc.html

24.3 Response Assessment using RECIST v.1.1 Criteria with Modifications

Tumor response will be assessed according to the revised Response Evaluation Criteria in Solid Tumor guideline (RECIST v.1.1) (Eisenhauer, Eur. J. Cancer. 2009). Modifications to the criteria, regarding progression by bone metastasis will be employed account for the enrollment of subjects with only bone lesions at study entry (documented in the table notes for Overall Visit Response). Another modification is a requirement for progression by imaging (omitting progression by digital photography or physical examination for superficial lesions), as described in Section 24.3.1. Computed tomography (CT), magnetic resonance imaging (MRI), X-ray, and nuclear medicine whole body bone scans will be reviewed at an independent review facility by radiologists trained in RECIST v.1.1 for this trial (Section 16), and blinded to subject demographics, treatment, and clinical status. Full details will be provided as a separate imaging charter.

24.3.1 Image Included in the Assessment

- CT is the preferred method of assessment. Intravenous contrast is required, unless the subject has an allergy to contrast that cannot be controlled with premedications. Anatomy scanned should include the chest (starting above the lung apices), abdomen, and pelvis (coverage to include the symphysis pubis). Slice thickness should be no greater than 5 mm, with no gaps. Details of the imaging protocols will be provided to sites in an imaging manual.
- If subjects are unable to receive iodinated CT contrast, the preferred imaging is non-contrast CT of the chest, and MRI of the abdomen and pelvis with contrast.
- For non-infiltrative and distinct skin nodules, CT or MRI remains the preferred method of assessment. Digital photography will not be acceptable as a method of radiographic assessment of skin lesions. Discrete skin nodules that are not visible using CT or MRI should be considered non-measurable, non-target lesions.
- For bone lesions, CT or MRI remains the preferred method of assessment. For lesions that cannot be quantified by CT or MRI, nuclear medicine bone scan may be used to assess metastases to bone. Whole body acquisition with planar spot views of areas of concern is acceptable. Single-photon emission computed tomography (SPECT) imaging, if acquired, is also acceptable.
- Chest X-ray is permitted by the RECIST v.1.1 guidelines to assess lung lesions, but CT of the chest is strongly preferred.

24.3.2 Overview of Assessment Process

The tumor burden will be documented at baseline. First, a reviewer will determine which lesions are appropriate for repeated quantitative assessment (measurable lesions). From the

measurable lesions, the reviewer will choose a set of lesions to be followed quantitatively throughout the trial (target lesions). Target lesions will be selected based on size, reproducibility of measurement, and whether the group of lesions represents the disease distribution. A value for the target tumor burden (sum of diameters) will be calculated. All tumor lesions that are not chosen for quantitative assessment will be documented and followed qualitatively as non-target lesions.

At each follow-up visit, the reviewer will assess the target lesions by making measurements that correspond to measurements made at baseline. The Reviewer will verify the calculated sum of diameters, and the comparison of that sum to the baseline value (for determining partial response) and to the nadir, the smallest value seen until that point (to look for progression). The Reviewer will assess the non-target lesions qualitatively, and will search for new lesions. Information about target, non-target, and new lesions will be combined to produce an overall visit response for the subject. After all visit assessments are completed, the Reviewer will verify each visit response, and the visit responses will be used to derive information relevant to the endpoints (such as the date of progression and the best overall response).

24.3.3 Measurable and Non-Measurable Disease

Eligibility of lesions for quantitative assessment will be determined at baseline, with target lesions selected from the measurable lesions identified. After baseline, target lesions will always be assessed quantitatively, and non-target lesions will be assessed qualitatively, with no further evaluation of measurability according to these definitions.

Measurable Disease

- A lesion is considered measurable if it has a diameter of ≥ 10 mm in the axial plane on CT or MRI, assuming that the slice thickness is 5 mm or less. If the slice thickness is greater than 5 mm, the minimum size increases to two times the slice thickness (slice thickness is the total distance between the tops of two adjacent slices, including any gap).
- Malignant lymph nodes are considered measurable if the short axis (greatest dimension perpendicular to the longest diameter) is ≥ 15 mm at baseline.
- If chest X-ray is used, a lesion is considered measurable if it is completely surrounded by aerated lung with clear boundaries, and has a diameter of 20 mm. In the unlikely event that a non-spiral CT scanner is used, the minimum size for measurability is 20 mm.

Non-Measurable Disease

- A lesion is considered evaluable, but not measurable, if it does not meet the measurability criteria described above, but which is a manifestation of malignancy that can be followed qualitatively as an indicator of disease progression or treatment response.
    - o By RECIST v.1.1 definitions, a lymph node that has a short axis diameter of 10-14 mm is considered evaluable, but not measurable. Nodes with a short axis diameter of <10 mm are considered normal.
    - o Palpable skin nodules that are not discernible using CT or MRI are considered evaluable but not measurable for this study
- Non-measurable lesions are those the reviewer strongly believes to be malignant, but which do not meet the definitions above.
    - o Bone lesions that are blastic are non-measurable by definition. Bone lesions that are lytic or mixed lytic-blastic, which have soft tissue components seen on CT or MRI, and which meet size criteria above, may be measurable.
    - o Simple cysts are considered benign by default. Cystic metastases may be considered measurable, but solid lesions are preferred for selection as target.
    - o Malignant ascites or pleural/pericardial effusions, lymphangitic infiltration of skin or lung, leptomeningeal disease, inflammatory breast disease, and infiltrative disease without clear borders are all examples of disease considered intrinsically non-measurable.
- Lesions seen on nuclear medicine bone scan, or modalities other than CT or MRI (plain X-ray [with the exception for lung lesions noted above], positron emission tomography [PET], etc.) cannot be measured. These modalities can be used only to determine whether a lesion is present or absent.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of previous treatment.

24.3.4 Baseline Lesion Selection and Documentation

- Target lesions will be chosen from among the measurable lesions. The lesions chosen should be the largest, most reproducible, and most representative of the overall disease distribution.
- All measurable lesions up to a maximum of 5 lesions total, and 2 lesions per organ, should be selected as target lesions. Paired organs (lungs, kidneys, adrenals, ovaries) are considered one organ. The lymph nodes collectively are considered one organ.

- Non-nodal target lesions are measured in the longest diameter in the axial plane (on CT or MR). Malignant lymph nodes are always measured in the short axis diameter (greatest dimension perpendicular to the longest diameter). The appropriate measurements for all target lesions chosen at baseline will be added to produce the recorded sum of diameters, which will be recorded.
- Other disease present at baseline should be recorded as 'Non-target lesions'. Multiple non-target lesions in a single organ can be recorded as one entry during assessment, as non-target lesions are assessed as a whole during follow-up.

24.3.5 Assessment of Response

The overall response for each visit is a combination of target lesion response, non-target lesion response, and the presence or absence of new lesions.

- **Target lesions measurements** should be performed in the same manner as at baseline. The sum of diameters of all target lesions must be calculated, and compared to the baseline value and to the nadir value (the smallest value previously seen during the trial, which may be the same as baseline). The following special rules apply to lesion measurements:
    - If two target lesions coalesce the longest diameter measurement of the coalesced mass is used. If a large target lesion splits, the longest diameter of each fragment is measured, and the sum is used.
    - Measurements for target lesions that become small should continue to be recorded, as long as the Reviewer is confident in the accuracy. If a target lesion is considered to have completely disappeared, 0 mm should be recorded. If it is too small to measure accurately, but is still present, a default value of 5 mm should be recorded.
    - When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.
- **Target lesion response** categories are defined as follows
    - **Complete response (CR):** Disappearance of all non-nodal target lesions. Target lymph nodes must reduce to < 10 mm in short axis
    - **Partial response (PR):** At least a 30% decrease in the sum of diameters of target lesions, compared to the sum at baseline.
    - **Progressive disease (PD):** At least a 20% increase in the sum of target lesion measurements, compared to the smallest sum on study (including baseline). Also, the absolute increase in the sum has to be at least 5 mm.

[redacted]

- **Stable disease (SD):** Neither PR nor PD criteria are met.
  - SD can follow PR only in rare cases, when the sum increases by less than 20% from the nadir, but enough that a previously seen 30% decrease from baseline no longer holds.
- **Non Evaluable (NE):** One or more target lesions cannot be assessed because assessment methods are not comparable to baseline (e.g., change of modality), lesion visibility is poor due to image quality or lesion features (except where the lesion is too small to measure), or one or more lesions that were excised or locally irradiated have not reappeared or increased; and the other lesions do not show sufficient growth to qualify for PD on their own.

- **Non-target lesion response** assessment is qualitative. Categories are defined as follows
  - **CR:** Disappearance of all non-nodal non-target lesions. Non-target lymph nodes must reduce to < 10 mm in short axis
  - **PD:** Unequivocal progression of non-target lesions, evaluated as a whole, such that it is clear that treatment has failed and disease is progressing, regardless of the status of the target lesions
  - **Non-CR/Non-PD:** Neither CR nor PD criteria are met.
  - **NE:** One or more non-target lesions cannot be assessed because assessment methods are not comparable to baseline (e.g., change of modality), lesion visibility is poor due to image quality or lesion features (except where the lesion is too small to measure), or one or more lesions that were excised or locally irradiated have not reappeared or increased; and the other lesions do not show sufficient growth to qualify for PD on their own.
- **New lesion response** is classified as present or not ("Yes" or "No"). The response is "Yes" if there is at least one lesion that the reviewer considers unequivocal new tumor.
  - Lesions that are equivocal (for example, due to small size) should not be considered new until they are confirmed by later scanning. Once confirmed, they can be retrospectively called new lesions at the time they were first seen.
  - A lesion identified in an area not previously scanned is considered a new lesion.
  - New lesions seen on nuclear medicine bone scans should be confirmed using anatomical imaging, whenever possible. If bone lesions are confirmed on later CT or MRI scan, progression should be assigned to the visit in which new lesion(s) were first seen on bone scan (in a manner similar to other equivocal new lesions). In the absence of structural confirmation, the pattern of lesions must clearly indicate metastasis, usually with at least two new lesions present.

- **Overall visit response** is determined by combining the target, non-target, and new lesion responses using a table.

For Subjects with Target Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Visit Response
CR	CR	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-CR/Non-PD or NE	No	PR
SD	Non-CR/Non-PD or NE	No	SD
PD	Any	Yes or No	PD
Any	PD†	Yes‡ or No	PD
Any	Any	Yes	PD

† Worsening of bone metastasis seen on bone scan alone, in the best judgment of the reader, must be such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

‡ Progression based on new bone scan lesions should be confirmed using CT or MRI whenever possible. If bone lesions are confirmed on later CT or MRI scan, progression should be assigned to the visit in which new lesion(s) were first seen on bone scan (in a manner similar to other equivocal new lesions). In the absence of structural confirmation, the pattern of lesions must clearly indicate metastasis, usually with at least two new lesions present.

For Subjects with Non-Target Disease ONLY

Non-Target Lesions	New Lesions	Overall Visit Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
NE	No	NE
Unequivocal PD†	Yes‡ or No	PD
Any	Yes	PD

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

† Worsening of bone metastasis seen on bone scan alone, in the best judgment of the reader, must be such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

‡ Progression based on new bone scan lesions should be confirmed using CT or MRI whenever possible. If bone lesions are confirmed on later CT or MRI scan, progression should be assigned to the visit in which new lesion(s) were first seen on bone scan (in a manner similar to other equivocal new lesions). In the absence of structural confirmation, the pattern of lesions must clearly indicate metastasis, usually with at least two new lesions present.

- After all visits have been evaluated, the sequence of overall visit responses is used to derive progression-free survival (PFS), best overall response (BOR), and duration of response (DOR).
  - PFS is defined as the time from randomization until the date of radiologic progressive disease (per RECIST v.1.1 with modifications) as determined by the IRF or death from any cause, whichever occurs first.
  - BOR is defined as the best visit response recorded from the start of the treatment until disease progression/recurrence.
    - RECIST v.1.1 states that confirmation of a BOR of PR or CR is required only for non-randomized trials in which response rate is the primary endpoint. Thus, confirmation is not required in this trial.
    - If SD is the best visit response seen on the trial, the SD must be maintained for at least 6 weeks from the start of treatment for SD to be the BOR.

- DOR is measured from the time of first radiographic documentation of CR or PR to disease progression by RECIST v.1.1 with modifications or death due to any cause, whichever occurs first
    - The duration of overall CR is measured from the time of first radiographic documentation of CR to disease progression by RECIST v.1.1 or death from any cause, whichever occurs first.

24.4 EORTC QLQ-C30/ EORTC QLQ-BR-23

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |__|__|__|__|

Your birthdate (Day, Month, Year): |__|__|__|__|__|__|__|__|

Today's date (Day, Month, Year): 31 |__|__|__|__|__|__|__|__|

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall <u>health</u> during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall <u>quality of life</u> during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31. Did you have a dry mouth?	1	2	3	4
32. Did food and drink taste different than usual?	1	2	3	4
33. Were your eyes painful, irritated or watery?	1	2	3	4
34. Have you lost any hair?	1	2	3	4
35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36. Did you feel ill or unwell?	1	2	3	4
37. Did you have hot flushes?	1	2	3	4
38. Did you have headaches?	1	2	3	4
39. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41. Did you find it difficult to look at yourself naked?	1	2	3	4
42. Have you been dissatisfied with your body?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4

During the past <u>four</u> weeks:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
44. To what extent were you interested in sex?	1	2	3	4
45. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Did you have any pain in your arm or shoulder?	1	2	3	4
48. Did you have a swollen arm or hand?	1	2	3	4
49. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50. Have you had any pain in the area of your affected breast?	1	2	3	4
51. Was the area of your affected breast swollen?	1	2	3	4
52. Was the area of your affected breast oversensitive?	1	2	3	4
53. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4