Protocol Amendment 8

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Intergroup Study (EORTC-1307-BCG) (BIG5-13) (TESARO PR-30-5010-C)

(EudraCT number 2013-000684-85)
(NCT01905592)
(IND number # 117580)

A phase III, randomized, open label, multicenter, controlled trial of niraparib versus physician's choice in previously-treated, HER2 negative, germline *BRCA* mutation-positive breast cancer patients.

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Title: A Phase III, randomized, open label, multicenter, controlled trial of niraparib versus physician's choice in previously – treated, HER2 negative, germline *BRCA* mutation-positive breast cancer patients.

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice.

Principal Investigator

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Protocol summary

Title of the Study	A phase III, randomized, open label, multicenter, controlled trial of niraparib versus physician's choice in previously-treated, HER2 negative, germline *BRCA* mutation-positive breast cancer patients.
Objective(s)	Primary objective: To compare progression-free survival (PFS) as assessed by blinded, central review between patients randomized to niraparib versus physician's choice. Key secondary objective: To compare overall survival between patients randomized to niraparib versus physician's choice. Secondary objectives: 1. Establish germline *BRCA* mutation status of screened patients using a centrally provided, validated test. Additional tests will be performed in order to determine concordance between tests for the purpose of developing a commercial companion diagnostic test. 2. To evaluate safety and tolerability as measured by all AEs 3. To compare PFS using investigator assessment of progression. 4. To evaluate time to treatment failure (discontinuation of treatment for any reason). 5. To compare response rate and duration of response. 6. To compare time to deterioration of health-related quality of life: QLQ-C30 and EQ-5D-5L. 7. To describe subsequent therapies and potential relationships with outcomes. 8. To assess genetic and non-genetic biomarkers relating to treatment efficacy. Germline and tumor mutations may be explored including somatic *BRCA*1 and 2 mutations, reversion mutations, loss of heterozygosity as well as genome landscape and transcriptional or functional measures of homologous recombination (HR) deficiency. 9. To assess outcomes by germline mutation *BRCA1* vs *BRCA2*. 10. Descriptive summary statistics will be used to summarize post-treatment data (.i.e subsequent anticancer therapies and any new malignancy)
Methodology	Phase III - superiority study. Randomization will be conducted with stratification for visceral disease (yes or no), histology (TNBC vs ER/PR positive) and number of lines of prior cytotoxic chemotherapy (not including hormonal therapy) for advanced/metastatic disease (0-1 or 2). No crossover to niraparib is permitted following discontinuation from physician's choice treatment.

Number of patients Number planed (Statistical design) Number analyzed	Randomization will be 2:1 (treatment: control). At least 306 patients with germline *BRCA* mutations, as confirmed by the central test, will need to be randomized. Patients can also be randomized on the basis of a local test. The intent-to-treat population, defined as all randomized patients with a central confirmation of germline *BRCA* mutation, is the primary analysis population for the efficacy analysis.
Diagnosis and main criteria for inclusion	1. Histologically or cytologically confirmed HER2-negative metastatic or locally advanced breast cancer that is not amenable to resection or radiation with curative intent. 2. Female and male patients age at least 18 years. 3. Patients with a deleterious or suspected deleterious germline *BRCA1* or *BRCA2* mutation may be enrolled into the study and randomized based on either local or central laboratory testing of *BRCA* status (Myriad Genetic Laboratories, Salt Lake City, UT, USA). On- study central confirmation of *BRCA* status will be performed for those patients who were enrolled based on either a previous Myriad test or a local test. If after inclusion, based on a local test result or a previously done Myriad test, a patient turns out not to have a germline *BRCA* mutation per central laboratory results (Myriad Genetic Laboratories, Salt Lake City, UT, USA) the patient can still continue on study based on his/her physician discretion and his/her own preference. 4. Measurable disease by RECIST v1.1 or non- measurable disease that is clinically evaluable (except sclerotic-only bone disease; bone-only disease that has a lytic component is allowed); there must evidence of disease progression within 3 months prior to enrollment without change of therapy. 5. Patients must not have symptomatic uncontrolled brain metastases. To be considered controlled, central nervous system (CNS) disease must have undergone treatment (whole brain radiation, radiosurgery or equivalent) at least 1 month previously and the patient has no new or progressive signs or symptoms related to the CNS disease, and are off steroid therapy two weeks. A post- treatment brain CT/MRI obtained at least 7 days off of steroids that shows no evidence of progression is needed. 6. Up to 2 prior cytotoxic regimens for advanced or metastatic breast cancer (not including adjuvant or neo-adjuvant therapy); patients with no prior cytotoxic regimens for advanced or metastatic disease will only be allowed if they relapsed during or within 12 months of (neo-) adjuvant cytotoxic therapy. 7. Prior therapy should have included a taxane and/ or anthracycline (unless contraindication to those) in the neoadjuvant, adjuvant, or advanced/metastatic setting. a. Hormone receptor positive patients must also have hormone resistant disease; either relapsed while on adjuvant endocrine treatment, or within one year of completing adjuvant endocrine treatment, or progression on at least one line of endocrine treatment for advanced cancer.

	8. Patients must not have received anticancer chemotherapy, radiotherapy (including palliative radiotherapy), hormonal therapy, biological therapy, or any other investigational therapy within 3 weeks prior to the start of study treatment. Patients with persistent toxicity (except alopecia) > grade 1 from prior cancer therapy will also be excluded. Bisphosphonate and denosumab is allowed. 9. No prior treatment with a known or putative PARP inhibitor (except iniparib). No other anticancer agent (chemotherapy, hormonal therapy, or other agent) is to be permitted during the course of the study for any patient. 10. Patients who have previously received platinum chemotherapy in the metastatic setting are allowed to enroll in the study as long as they did not progress while on or within 8 weeks from the day of the last platinum administration. Patients who received platinum in the (neo-) adjuvant setting are eligible, as long as they relapsed 12 months or more after the last dose of platinum. 11. ECOG performance status 0-2 (Appendix G). 12. Adequate organ function (assessed within 72 hours prior to the first dose): a. Absolute neutrophil count (ANC) ≥ 1,500 cells/µL b. Platelets ≥ 100,000 cells/µL c. Hemoglobin ≥ 9 g/dL d. Serum creatinine ≤ 1.5 × upper limit of normal (ULN) or ≥ 50mL/min using Cockcroft-Gault equation e. Total bilirubin ≤ 1.5 × ULN f. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 × ULN or < 5 × ULN with liver metastases 13. Patients able to swallow and retain oral tablets 14. Female patients must not be pregnant or breast feeding a. Female patient of childbearing potential must have a negative serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) within 72 hours prior to the first dose). 15. Patients of childbearing potential who are sexually active and their partners must agree to the use of a highly effective form of contraception throughout their participation during the study treatment and for 90 days after last dose of study treatment(s). These are: ♦ combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: ♦ oral route ♦ intravaginal route ♦ transdermal route

	♦ progestogen-only hormonal contraception associated with inhibition of ovulation ♦ oral ♦ injectable ♦ implantable ♦ intrauterine device (IUD) ♦ intrauterine hormone-releasing system (IUS) ♦ bilateral tubal occlusion ♦ Vasectomized partner ♦ sexual abstinence, if the preferred and usual lifestyle of the subject a Note: For patients with ER and/or PR positive tumors avoidance of hormonal methods is highly recommended 16. No known hypersensitivity to the components of niraparib or any of its analogs. 17. No major surgery within 2 weeks prior to registration. Patients must have recovered from earlier major surgery before registration. 18. No prior diagnosis of Stage IV ovarian cancer. Patients with history of Stage III ovarian cancer must have a 5-year disease-free interval Patients with Stage I or II ovarian cancer must have a disease-free interval of 2 years Patients with a prior history of ovarian cancer who have peritoneal disease should have a normal serum CA-125. For patients with a prior history of ovarian cancer who have peritoneal disease and elevated serum carcinoma antigen CA- 125, a biopsy of the peritoneal disease is required to prove the breast cancer origin of the metastasis. 19. No prior diagnosis, detection, or treatment of invasive cancer other than breast cancer within 2 years (except basal or squamous cell carcinoma of the skin that has been definitively treated) 20. Patients must not be considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, or active, uncontrolled infection. Examples include, but are not limited to uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent. 21. Absence of any psychological, familial, sociological or geographical condition potential hampering compliance with the study protocol and follow- up schedule; those conditions should be discussed with the patient before registration in the trial.

	22. No immunocompromised patients (e.g., patients who are known to be serologically positive for human immunodeficiency virus [HIV]). 23. No patients with known active Hepatitis B or C. 24. Patients should acknowledge that they are at an increased risk of infection with conventional chemotherapy drugs and since the effects with niraparib are unknown they must accept that live virus and bacterial vaccines should not be administered to them for the duration of the study and for 3 months after last dose of study medication. 25. If patients are blood donors they should accept not to donate blood during the study and for 3 months after the last dose of study drug. 26. Patients must have voluntarily agreed to participate by given informed consent. 27. If all of the comparator treatments are contraindicated the patient will not be included in the trial. 28. Patients must not have received a platelet transfusion within 4 weeks of the first dose of study treatment and must not have had any known, persistent (>4 weeks) ≥ grade 3 hematological toxicity or fatigue from last cancer therapy. 29. Patients must not have any known history of myelodysplastic syndrome (MDS). 30. Patients must agree to peripheral blood samples during screening and at the end of treatment for mutational profile testing (for mutations of selected myeloid related genes) that will be performed only if the patient develops MDS or acute myeloid leukemia (AML) during the study or the post-treatment follow-up (a third sample will be collected in this case).
Treatment Test product, dose and mode of administration Duration of treatment	Group 1: niraparib 300 mg (3x100 mg niraparib capsules) will be administered orally QD continuously in an open- label fashion. The consumption of water and food is permissible. Group 2: Physician's choice of chemotherapy [amongst one of the following four single agents: eribulin, gemcitabine (both administered intravenously) capecitabine (administered orally) or vinorelbine (administered orally or intravenously) will be administered in 3 week cycles. The physician's choice chemotherapy must be designated prior to randomization of each patient and the choice should be made according to the respective national available and approved treatment (Note: Gemcitabine will be administered as single agent as per NCCN guidelines. In France, gemcitabine is not allowed to be chosen as a treatment in the physician's choice arm). Patients will continue on study medication until disease progression as long as in the investigator's opinion they are benefiting from treatment and do not meet any other treatment discontinuation criteria.

Criteria for evaluation	The primary objective of this study is to determine the efficacy of niraparib compared to physician's choice amongst four single agent chemotherapy agents (eribulin, vinorelbine, gemcitabine or capecitabine) in treatment of patients with germline *BRCA* mutation with advanced/ metastatic HER2 negative breast cancer who have been treated with up to 2 prior lines of chemotherapy for advanced/ metastatic disease. This objective will be assessed by the primary endpoint of PFS as assessed by blinded, central review.
Efficacy	Key secondary endpoint is evaluation of overall survival.
Safety	Safety and tolerability will be described using frequency of AEs and AEs of CTCAE grade ≥3. Safety analyses will include all patients who have received at least one dose of study drug and will be evaluated descriptively.
Statistical methods	This is a phase III superiority trial of niraparib versus single agent chemotherapy (eribulin or vinorelbine or gemcitabine or capecitabine). The primary endpoint is PFS, which is defined as the time from the date of randomization to the date of first documentation of objective progression (by blinded central review) or death by any cause in the absence of documented objective progression whichever occurs first. The primary analysis population for efficacy constitutes all randomized patients who have a germline *BRCA* mutation per central laboratory (Myriad USA).The overall sample size for this study is based on the overall survival endpoint and is determined based on the alternative hypotheses that niraparib will result in an improvement in median survival of 9 to 13 months (corresponding to a hazard ratio = 0.69). For a true hazard ratio of 0.69, 265 deaths will provide 80% power (1-sided alpha = 0.025). Assuming 10 patients are enrolled per month in primary analysis population for efficacy, with 306 patients, 265 deaths are expected to occur approximately 54 months after the first patient enrolled. Assuming 40% of patients will be randomized on the basis of a local *BRCA* test and assuming that 15% of those patients will not be *BRCA* mutated per central test, it is estimated that an over-enrollment by 18 patients is needed to obtain the required 306 patients in the analysis population. The final PFS analysis is planned after 137 PFS events have occurred or end of recruitment, whichever occurs later. With 137 PFS events, there is 80 % power (1- sided alpha=0.025) to detect an HR 0.6 (equivalent to 3 to 5 months). A gate-keeping strategy (i.e. sequential testing procedure) will be used to test PFS and OS. OS will be tested at a 1-sided alpha of 0.025 only if the final test on PFS is significant at a 1-sided alpha of 0.025. The primary analysis of PFS and OS will be performed using a stratified log-rank test, stratifying by the randomization strata. Stratified Cox proportional hazards models will be used to estimate the treatment hazard ratio and its 95% confidence interval. PFS and OS will be descriptively summarized using Kaplan-Meier methodology. An interim analysis for futility is planned after 93 PFS events. If the results cross the pre-specified futility boundary, the IDMC may recommend stopping the study.

Translational research	1) A secondary endpoint of the trial is to establish germline *BRCA* mutation status of screened patients using a centrally provided, validated test. 2) Additional tests will be performed for the purpose of developing a commercial companion diagnostic test. Concordance of the candidate companion diagnostic test with the centralized *gBRCA* mutation test with respect to identifying patients with g*BRCA* mutations will be evaluated on a separate blood sample collected at the same time that the blood sample for central testing is taken. The sensitivity and specificity (along with the corresponding 95% confidence bounds) of the candidate companion diagnostic test will be benchmarked to the centralized, validated test performed as an inclusion criterion. 3) Archival tumor tissue (primary tumor or a metastatic lesion) will be collected with the intention to assessing markers of homologous recombination deficiency in the tumor genome landscape, (eg. HRD Score) assessment of LOH, somatic *BRCA*1 and *BRCA*2 mutations, reversion mutation analysis, methylation of alleles, transcriptional and protein expression profiles of DNA damage response (e.g. loss of 53BP1 expression in BRCA carriers). 4) Optional tumor biopsies (FFPE and snap frozen) will be collected at baseline and time of progression for assessment to validate markers of homologous recombination deficiency, HRD Score, assessment of LOH, mutation analysis, methylation of alleles, transcriptional and protein expression profiles of DNA damage response. The concordance between markers assessed on archival and optional baseline biopsy will be determined, and optional progression sample will be utilized to examine for mechanisms of acquired resistance to niraparib. 5) Plasma at baseline, 6- weeks and progression with intention to study circulating free DNA (e.g. reversion mutations) and humoral immune response biomarkers. 6) Blood sample at screening and treatment discontinuation will be collected to evaluate mutations for selected myeloid- associated genes if the patient develops MDS or acute myeloid leukemia during the study or the post- treatment follow- up (a third sample will be collected in this case). This test is a PCR- based next generation sequencing assay that screens DNA from leukocytes for the presence of mutations or insertions/deletion in commonly altered areas of 30 genes. Mutation profile before and after study treatment will be compared to determine whether any mutations were present prior to study treatment. These samples will be stored and analyzed if necessary for assessing niraparib related risk for MDS/AML development.

Quality of Life	Patient reported outcomes will be collected via questionnaires (EORTC QLQ-C30 and EQ-5D-5L). These must be completed within 4 weeks before randomization and subsequent questionnaires are filled in every 2 cycles (ie. 6 weeks) while on-treatment and every 3 months while in follow- up. Collection of HRQoL data is limited to the first 12 months after randomization. The primary HRQoL endpoint considered relevant for this study is time to HRQoL deterioration (TTQ). TTQ is defined as the time from randomization to death, progression or clinical relevant deterioration in pre-specified QLQ-C30 scales.
PK – PD	Blood samples for measurements of plasma levels of niraparib will be obtained in the experimental arm on cycle 1/ day 1 and on cycle 2/ day 1 at the following timepoints: 0 (predose within 30 minutes) and 2 hours post dose. In subsequent cycles, a blood sample for measurements of plasma levels of niraparib will be obtained on cycle 4/ day 1 predose (within 30 minutes) only.

Trial organization

This trial is an Intergroup Trial performed under the BIG umbrella, jointly conducted by several national/international cancer clinical research groups in different countries of European Union, North America and other countries.

TESARO is the Sponsor in all participating countries.

TESARO is responsible for the global management of the study set-up and execution.

BIG is responsible for the study governance set-up and management.

The EORTC centrally manages data collection and quality control of data and statistical analysis.

Publication is managed by EORTC and BIG.

TESARO (via PAREXEL) centrally manages the notification/submission of all necessary documents to the Competent Authorities and/or Ethics Committees and gets the confirmation of the review by IRB/IEC following applicable national laws. TESARO (via PAREXEL) also manages collection of essential documents, authorization of sites and sample logistics.

This protocol is to be followed by all participating groups and sites. All chapters are fully applicable to all participants.

The patient information sheet and informed consent templates are applicable for all participating groups and sites. Investigators will receive the translated and adapted Patient Information Sheet (PIS) & Informed Consents (ICs) directly from PAREXEL.

Investigators who are members of the clinical cancer research groups participating to the trial should select one of these groups for the framework of this trial and include all patients through this group. In some cases, because of the national legal framework the choice may be imposed. For EORTC members, all patients will be accounted for the membership independently from the group they choose to participate through (see EORTC Policy 10).

The investigational drug (niraparib) will be supplied by TESARO.

This trial is fully supported by TESARO.

1 Background and introduction

1.1 Advanced/metastatic breast cancer with g*BRCA* mutation

Breast malignancies typically arise from breast epithelium and are considered carcinomas, both non-invasive and invasive carcinomas occur (Ref. 1). The 2012 incidence of invasive breast cancer in the United States (US) was 230,000 with a mortality rate of 40,000 (National Cancer Institute, www.cancer.gov/cancertopics/types/breast). Using the TNM classification, breast cancer is staged from I-IV; patients with advanced (Stage III) and metastatic (Stage IV) breast cancers have a worse prognosis. Metastatic cancer is managed by various combinations of available treatments including surgery, radiation, chemotherapy, and targeted therapies. However, even with optimal treatment, 10-year survival rate is only about 10% (Ref. 2), and therefore a significant unmet medical need exists for new therapies to treat patients with advanced/metastatic breast cancer.

Current approaches to the management of metastatic breast cancer select patients for endocrine or human epidermal growth factor receptor 2 (HER2) targeted therapy based on the expression of cell surface markers on breast tumors influencing the choice of treatment. Patients with estrogen receptor (ER) or progesterone receptor (PR) positive tumors often respond to hormonal therapy, including selective estrogen receptors modulators (tamoxifen, toremifene), aromatase inhibitors (exemestane, anastrazole, letrozole), an ER antagonist (fulvestrant) or progestins (megestrol acetate). Multiple lines of hormonal therapy are often given upon progression of disease prior to initiating chemotherapy. Patients with HER2-positive disease are usually treated with HER2-targeting therapy (trastuzumab ± pertuzumab) along with chemotherapy. Upon progression, HER2-directed therapy (trastuzumab, lapatinib) may be continued along with different chemotherapy agents. Patients with ER-/PR-/HER2- triple negative breast cancer (TNBC) are usually treated with chemotherapy regimens involving either single agents or combinations. The most common single agents include: anthracyclines (doxorubicin, epirubicin, and pegylated liposomal doxorubicin), taxanes (paclitaxel, docetaxel, and albumin-paclitaxel), antimetabolites (capecitabine, gemcitabine) and antimitotics (vinorelbine, eribulin). The most common combinations include doxorubicin/epirubicin + cyclophosphamide (AC/EC), ±fluorouracil + AC (FAC/FEC), taxane + AC (anthracycline ± cyclophosphamide (AC/TAC), gemcitabine or capecitabine + taxane (GT or XT), and cyclophosphamide + methotrexate + F (CMF) (Ref. 3).

Germline mutations of *BRCA*1 and *BRCA*2 genes are found in the majority of patients with hereditary breast or ovarian cancer. Individuals with these germline mutations are at markedly increased risk to develop cancer, particularly breast and ovarian cancers. Nevertheless, *BRCA*1/2 associated cancers are rare representing less than 5% of all breast cancer cases. Data regarding the impact of *BRCA*1/2 mutational status on treatment of breast cancer are currently inconclusive and thus these genes do not currently affect the decision making process regarding the type of systemic therapy (Ref. 4, Ref. 5, Ref. 6, Ref. 7).

1.2 PARP and PARP inhibition

The Poly(ADP-ribose) polymerases (PARP) family of enzymes was first described over 40 years ago. PARP-1 and -2 are zinc-finger DNA-binding nuclear enzymes that play a crucial role in DNA repair. Upon formation of stalling DNA replication forks or single-strand DNA breaks, PARP binds DNA strands, a process which activates its enzymatic activity. Activated PARP catalyzes addition of long polymers of ADP-ribose on several proteins associated with chromatin, including histones and various DNA repair proteins including PARP itself. This results in chromatin relaxation, fast recruitment of DNA repair proteins and efficient repair of DNA breaks (Ref. 8).

Normal cells repair up to 10,000 DNA defects daily and single strand breaks are the most common form of DNA damage. Cells that are unable to repair this burden of DNA damage, such as those with defects in the base excision repair (BER) pathway, or those treated with PARP inhibitors, are at risk for accumulating

multiple lesions that will ultimately trigger apoptosis. They enter S phase (DNA replication) of the cell cycle with unrepaired single strand breaks. Pre-existing single strand breaks are converted to double strand breaks (DSB) as the replication machinery passes. Accumulated double strand breaks present during S phase are repaired by homologous recombination (HR). Homologous recombination is the preferred repair pathway because it is associated with a much lower error rate than other forms of repair. Cells unable to perform DNA repair via HR (e.g., due to inactivation of genes required for HR, such as *BRCA*1 and *BRCA*2 mutated cells), are at risk for accumulating multiple lesions that will ultimately trigger apoptosis. These cells accumulate stalled replication forks during S phase and are more likely to use the error-prone non-homologous end joining (NHEJ) pathway to repair double strand breaks in DNA. Accumulation of errors in DNA by NHEJ contributes to the mutation burden that promotes the development of cancer. Pre-clinical ex vivo and in vivo experiments suggested that PARP inhibitors are selectively cytotoxic for tumors with defects in the HR repair pathway, such as mutations in *BRCA*1 or *BRCA*2 genes. In normal or *BRCA* heterozygous cells, the lesion can be repaired and DNA replication and cell division continue. However in cells that lack functional DSB repair, loss of two DNA repair pathways causes 'synthetic lethality' and cell death (Ref. 9, Ref. 10).

Human cancers exhibit genomic instability and an increased mutation rate due to underlying defects in DNA repair. These deficiencies render cancer cells more dependent on the remaining DNA repair pathways and targeting these pathways is expected to have a much greater impact on the survival of the tumor cells than on normal cells. There are several PARP inhibitors in clinical development. Treatment with PARP-1 and -2 inhibitors represents a novel opportunity to selectively kill a subset of cancer cell types by exploiting their deficiencies in DNA repair. The publication in 2005 of paired pre- clinical papers in Nature demonstrating hypersensitivity of *BRCA*- deficient cancer cells to single- agent PARP inhibitors, opened the door to clinical research into these agents, and provided a clear demonstration of a class effect (Ref. 9, Ref. 11).

1.2.1 Niraparib: pre-clinical summary

Niraparib (formerly referred to as MK-4827) is a potent and selective PARP-1 and PARP-2 inhibitor with half maximal inhibitory concentration of control (IC50) of 3.8 and 2.1 nM, respectively, and is at least 100-fold selective over other PARP-family members. Niraparib inhibits PARP activity stimulated as a result of DNA damage caused by addition of hydrogen peroxide in various cell lines with an IC50 and a 90% inhibitory concentration of control (IC90) of about 4 and 50 nM, respectively (Ref. 12).

Niraparib demonstrates selective anti-proliferative activity for cancer cell lines that have been silenced for *BRCA*1 or *BRCA*2 or carry *BRCA*1 or *BRCA*2 mutations as compared to their wild type counterparts. Niraparib demonstrates weak activity on normal human cells.

Niraparib displayed strong antitumor activity in in vivo studies with *BRCA*1 mutant breast cancer (MDA-MB-436), *BRCA*2 mutant pancreatic cancer (CAPAN-1), ATM-mutant mantle cell lymphoma (GRANTA-519), serous ovarian cancer (OVCAR3), and colorectal cancer (HT29 and DLD-1) xenograft models and with patient-derived Ewing's sarcoma mice models.

Moreover, Murai et al demonstrated in 2012 that niraparib is the most potent amongst a series of 5 PARP inhibitors in trapping PARP (Ref. 13).

Non clinical testing of niraparib did not indicate any untoward effects that would prevent clinical investigation in the human setting.

Non clinical pharmacology studies with niraparib have generated sufficient data to support its clinical evaluation as a monotherapy for patients with advanced/metastatic breast cancer with *gBRCA* mutation.

Details of the non clinical studies conducted with niraparib can be found in the current Investigator's Brochure.

1.2.2 Niraparib: clinical summary

To date, niraparib has been evaluated in a series of Phase 1 clinical trials in patients with solid tumors. As of 01 February 2013, 144 patients have been treated with niraparib at doses up to 400 mg once daily (QD). The dose limiting toxicity at the 400 mg QD dose was thrombocytopenia. At ASCO 2013, Michie et al, reported the final results of a phase I trial of niraparib in 100 patients (69 women, 31 men) with various solid tumors (49 ovarian, 23 CRPC, 12 breast and 16 others) (Ref. 14). The drug was given in pill form once a day and the researchers established the maximum tolerated dose at 300 mg a day.

In these studies, niraparib was well tolerated, exhibited linear pharmacokinetics (PK), had evidence of target modulation, and had promising antitumor activity, especially in cancers with *BRCA* mutations.

Recently, the results of NOVA study (Niraparib in ovarian cancer) have shown that among patients with platinum- sensitive, recurrent ovarian cancer, the median duration of progression- free survival was significantly longer among those receiving niraparib than among those receiving placebo, regardless of the presence or absence of g*BRCA* mutations or HRD status, with moderate bone marrow toxicity (Ref. 41). The results of this study are summarized below:

1. *BRCA* mutated population: PFS (21 months niraparib vs 5.5 months placebo, HR= 0.27, P< 0.001)

2. Population with no *BRCA* mutation but Homologous Recombination deficient (HRD) tumors (12.9 months vs 3.8 months, HR= 0.38, P< 0.001)

3. Overall non-g*BRCA* mutated population (9.3 months vs 3.9 months, HR= 0.45, P< 0.001)

4. Non- *BRCA* mutated, Homologous Recombination Deficient negative population [exploratory] (6.9 months vs 3.9 months, HR= 0.58, P= 0.022)

Across these studies, the most commonly reported adverse events (AEs) during niraparib monotherapy (n=107) were nausea (57%), fatigue (55%), anemia (49%), vomiting (40%), constipation (39%), thrombocytopenia (34%), decreased appetite (33%), headache (24%), hyponatremia (24%), neutropenia (24%), cough (22%), diarrhea (22%), dyspnea (22%), and back pain (21%).

Pharmacodynamic analyses conducted in the Phase 1 Study PN001 confirmed PARP inhibition at doses ≥ 80 mg daily and antitumor activity was documented at doses ≥ 60 mg daily. Partial responses were observed in 7 (35%) of 20 ovarian cancer patients with *BRCA*1 and *BRCA*2 mutations receiving niraparib monotherapy. Two (50%) of 4 breast cancer patients with *BRCA*1 and *BRCA*2 mutations experienced partial responses.

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been observed in patients receiving treatment with olaparib, a PARP inhibitor; given the common mechanism of action, MDS and AML therefore represent a potential risk to patients receiving niraparib. Guidance on monitoring patients for new events of MDS/AML and the follow- up of patients with suspected MDS/AML is provided in section 5.5, section 6.2, section 12.3.4 and section 12.3.5.

Details of the clinical studies conducted with niraparib can be found in the current Investigator's Brochure.

1.2.3 Study rationale

This study is designed to compare the efficacy and safety of niraparib to current standard of care in the treatment of patients with HER2-negative germline *BRCA*1 or *BRCA*2 mutation (*gBRCA*^{mut}) breast cancer who have received no more than 2 prior chemotherapy regimens for advanced/metastatic disease, including prior taxane and/or prior anthracycline therapy and for whom one of the physician's choice treatments would be indicated as standard of care.

Individuals with g*BRCA*^{mut} have a markedly increased risk of developing breast cancer. About 5% of patients with breast cancer have mutations in *BRCA*1 or *BRCA*2 (Ref. 15); thus , based on the 2012 incidence of breast cancer in the US of 230,000, approximately 11,500 women develop breast cancer

annually in the US which harbor these mutations. Patients presenting with g*BRCA*^{mut} breast cancer tend to be younger, and have larger tumor size and higher tumor grade at diagnosis and based on this, have a worse prognosis. There is anticipated to be a significant internationally prevalent burden of breast cancer bearing a specific biological pathway perturbation that may be targeted by a synthetic lethal strategy with PARP inhibition with expectation of improvement in therapeutic ratio with improved efficacy and greater tolerability. The investigation of effect in comparison to standard of care requires an international collaboration involving centers with significant prevalence of *BRCA*1 and *BRCA*2 carriers with breast cancer.

Recent clinical studies have shown PARP inhibitors to be active in breast cancer. Clinical anticancer activity with PARP inhibitors has been seen in both patients with *gBRCA*^{mut} and patients without g*BRCA*^{mut}; however activity is more robust in patients with the germline mutation (Ref. 16, Ref. 17, Ref. 18, Ref. 19).

Niraparib is a potent and selective PARP-1 and PARP-2 inhibitor that is at least 100-fold selective over other PARP-family members. To date, 12 breast cancer patients have been treated with niraparib in the Phase 1 Study PN001, 2 of whom had objective responses, both in patients with *gBRCA*^{mut} (out of a total of 4 patients with known gBRCA^{mut}). PARP inhibitors such as niraparib selectively kill tumor cells with *gBRCA* mutations and provide a novel approach to potentially improve the treatment of patients with advanced/metastatic *gBRCA*^{mut} breast cancer (refer to investigator's brochure).

Although the majority of *BRCA*1 mutant breast cancers are associated with the triple negative subtype, 25-30% of *BRCA*1 mutant breast cancers are hormone-receptor positive. Furthermore, the majority of *BRCA*2 mutant breast cancers are hormone-receptor positive (Ref. 20, Ref. 21). Given the data observed with olaparib, another PARP inhibitor, showing objective responses in patients with *BRCA* mutant/hormone receptor positive disease (Ref. 17), for this study, both hormone receptor positive and hormone receptor negative advanced/metastatic breast cancer patients with *gBRCA*^{mut} will be enrolled. For patients with hormone-receptor positive disease, the disease must be hormone refractory (progression during at least one prior hormonal therapy) for which chemotherapy is indicated.

It is known that PARP inhibitor responsiveness and platinum sensitivity correlate with the *BRCA*ness phenotype in ovarian cancer (Ref. 22). This phenotype, which is similar to tumors with *BRCA* mutations, includes tumors with defects in the HR repair pathway caused by mutations in genes other than *BRCA*1 or *BRCA*2. Tumors with *BRCA*ness phenotype are characterized by homologous recombination repair deficiency (HRD). Non clinical ex vivo and in vivo experiments suggest that PARP inhibitors are selectively cytotoxic for tumors with *BRCA*ness. Furthermore, HRD correlates with platinum sensitivity and PARP inhibitor sensitivity (Ref. 23, Ref. 24). Clinical experience with olaparib in ovarian cancer also supports the correlation between platinum sensitivity and PARP inhibition responsiveness (Ref. 25). In the recent TNT study, advanced triple- negative breast cancer patients with germline *BRCA* mutations demonstrated significantly greater response and PFS when treated with carboplatin compared with docetaxel. Based on these data, the current study was amended to exclude advanced breast cancer patients with evidence of platinum resistance in the metastatic setting based on:

- Progression during platinum therapy
- Progression within 8 weeks from the end of platinum therapy (Ref. 26).

2 Objectives of the trial

2.1 Primary objective

The primary objective of this study is to compare progression-free survival (PFS), as assessed by blinded central review, of patients with advanced/metastatic HER2-negative *gBRCA*^{mut} breast cancer when treated with niraparib as compared to those treated with physician's choice single agent chemotherapy standards (eribulin, vinorelbine, gemcitabine or capecitabine).

2.2 Secondary objectives

2.2.1 Key secondary objective

To compare overall survival of patients with advanced/metastatic HER2-negative *gBRCA*^{mut} breast cancer when treated with niraparib as compared to those treated with physician's choice single agent chemotherapy standards (eribulin, vinorelbine, gemcitabine or capecitabine).

2.2.2 Other secondary objectives

1. To establish germline *BRCA* mutation status of screened patients using a centrally provided, validated test as well as future tests, and determine concordance between tests for the purpose of developing a commercial companion diagnostic test

2. To evaluate safety and tolerability as measured by all AEs.

3. To compare PFS using investigator assessment of progression

4. To evaluate time to treatment failure (discontinuation of treatment for any reason)

5. To compare response rate and duration of response

6. To compare time to deterioration of health-related quality of life (HRQoL): European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and EuroQol 5 Dimension 5 Level (EQ-5D-5L) (Appendices D, F, I)

7. To describe subsequent therapies and potential relationships with outcomes

8. To assess genetic and non-genetic biomarkers relating to treatment efficacy. Germline and tumor mutations may be explored including somatic *BRCA*1 and 2 mutations, reversion mutations, loss of heterozygosity as well as genome landscape and transcriptional or functional measures of homologous recombination (HR) deficiency.

9. To assess outcomes by germline mutation *BRCA*1 vs *BRCA*2.

10. Descriptive summary statistics will be used to summarize post- treatment data (i.e subsequent anticancer therapies and any new malignancy).

3 Patient selection criteria

Patient enrollment will follow a two-step procedure as illustrated in chapter 4 and chapter 15 (registration and randomization steps). Patients must meet all of the criteria described in section 3 to be eligible.

3.1 Registration step

All patients will be registered in the trial as soon as possible after written informed consent signature. After this point, material must be sent for central *BRCA* mutation analysis from all the patients irrespective of whether they had done it either locally or in Myriad. Material for companion diagnostic testing must be sent in as well.

1. Histologically or cytologically confirmed HER2-negative breast carcinoma with previously detected *gBRCA*^{mut} or patients that meet one of the criteria for further genetic assessment according NCCN guidelines (Appendix E).

2. Female and male patients age at least 18 years.

From registration to randomization a maximum of 90 days is permitted

3.2 Randomization step

1. Patients with a deleterious or suspected deleterious germline *BRCA1* or *BRCA2* mutation may be enrolled into the study and randomized based on either local or central laboratory testing of *BRCA* status (Myriad Genetic Laboratories, Salt Lake City, UT, USA). On- study central confirmation of *BRCA* status will be performed for those patients who were enrolled based on either a previous Myriad test or a local test. If after inclusion, based on a local test result or a previously done Myriad test, a patient turns out not to have a germline *BRCA* mutation per central laboratory results (Myriad Genetic Laboratories, Salt Lake City, UT, USA) the patient can still continue on study based on his/her physician discretion and his/her own preference .

2. Metastatic or locally advanced disease that is not amenable to resection or radiation with curative intent.

3. Measurable disease by RECIST v1.1 or non-measurable disease that is clinically evaluable (except sclerotic-only bone disease; bone-only disease that has a lytic component is allowed); there must be evidence of disease progression within 3 months prior to enrollment without change of therapy.

4. Patients must not have symptomatic uncontrolled brain metastases. To be considered controlled, central nervous system (CNS) disease must have undergone treatment (whole brain radiation, radiosurgery or equivalent) at least 1 month previously and the patient has no new or progressive signs or symptoms related to the CNS disease, and are off steroid therapy two weeks. A post-treatment brain CT/MRI obtained at least 7 days off of steroids that shows no evidence of progression is needed.

5. Up to 2 prior cytotoxic regimens for advanced or metastatic breast cancer (not including adjuvant or neo-adjuvant therapy); patients with no prior cytotoxic regimens for advanced or metastatic disease will only be allowed if they relapsed during or within 12 months of (neo-) adjuvant cytotoxic therapy.

6. Prior therapy should have included a taxane and/or anthracycline (unless contraindication to those) in the neoadjuvant, adjuvant, or advanced/metastatic setting.

   a. Hormone receptor positive patients must also have hormone resistant disease; either relapsed while on adjuvant endocrine treatment or within one year of completing adjuvant endocrine treatment, or progression on at least one line of endocrine treatment for advanced cancer.

7. Patients must not have received anticancer chemotherapy, radiotherapy (including palliative radiotherapy), hormonal therapy, biological therapy, or any other investigational therapy within 3 weeks prior to the start of study treatment. Patients with persistent toxicity (except alopecia) > grade 1 from prior cancer therapy will also be excluded. Bisphosphonate and denosumab are allowed.

8. No prior treatment with a known or putative PARP inhibitor (except iniparib). No other anticancer agent (chemotherapy, hormonal therapy, or other agent) is to be permitted during the course of the study for any patient.

9. Patients who have previously received platinum chemotherapy in the metastatic setting are allowed to enroll in the study as long as they did not progress while on or within 8 weeks from the day of the last platinum administration. Patients who received platinum in the (neo-) adjuvant setting are eligible, as long as they relapsed 12 months or more after the last dose of platinum.

10. ECOG performance status 0-2 (Appendix G)

11. Adequate organ function (assessed within 72 hours prior to first dose):

a. Absolute neutrophil count (ANC) ≥ 1,500 cells/µL

b. Platelets ≥ 100,000 cells/µL

c. Hemoglobin ≥ 9 g/dL

d. Serum creatinine ≤ 1.5 × upper limit of normal (ULN) or ≥ 50 mL/min using Cockcroft-Gault equation

e. Total bilirubin ≤ 1.5 × ULN

f. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 × ULN or < 5 × ULN with liver metastases

12. Patients able to swallow and retain oral tablets

13. Female patients must not be pregnant or breast feeding

a. Female patient of childbearing potential must have a negative serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) within 72 hours prior to first dose).

14. Patients of childbearing potential who are sexually active and their partners must agree to the use of a highly effective form of contraception throughout their participation during the study treatment and for 90 days after last dose of study treatment(s). These are:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral route
  - intravaginal route
  - transdermal route
- progestogen-only hormonal contraception associated with inhibition of ovulation
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- Vasectomized partner
- sexual abstinence, if the preferred and usual lifestyle of the subject

Note: For patients with ER and/or PR positive tumors avoidance of hormonal methods is highly recommended

15. No known hypersensitivity to the components of niraparib or any of its analogs.

16. No major surgery within 2 weeks prior to registration. Patients must have recovered from earlier major surgery before registration.

17. No prior diagnosis of Stage IV ovarian cancer.

Patients with history of Stage III ovarian cancer must have a 5-year disease-free interval

Patients with Stage I or II ovarian cancer must have a disease-free interval of 2 years

Patients with a prior history of ovarian cancer who have a peritoneal disease should have normal serum carcinoma antigen CA-125.

For patients with a prior history of ovarian cancer who have peritoneal disease and elevated serum carcinoma antigen CA- 125, a biopsy of the peritoneal disease is required to prove the breast cancer origin of the metastasis.

18. No prior diagnosis, detection, or treatment of invasive cancer other than breast cancer within 2 years (except basal or squamous cell carcinoma of the skin that has been definitively treated)

19. Patients must not be considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.

20. Absence of any psychological, familial, sociological or geographical condition potential hampering compliance with the study protocol and follow- up schedule; those conditions should be discussed with the patient before registration in the trial.

21. No immunocompromised patients (e.g., patients who are known to be serologically positive for human immunodeficiency virus [HIV]).

22. No patients with known active Hepatitis B or C.

23. Patients should acknowledge that they are at an increased risk of infection with conventional chemotherapy drugs and since the effects with niraparib are unknown they must accept that live virus and bacterial vaccines should not be administered to them for the duration of the study and for 3 months after last dose of study medication.

24. If patients are blood donors, they should accept not to donate blood during the study and for 3 months after the last dose of study drug.

25. Patients must have voluntarily agreed to participate by given informed consent.

26. If all of the comparator treatments are contraindicated the patient will not be included in the trial.

27. Patients must not have received a platelet transfusion within 4 weeks of the first dose of study treatment and must not have had any known, persistent (>4 weeks) ≥ grade 3 hematological toxicity or fatigue from last cancer therapy.

28. Patients must not have any known history of myelodysplastic syndrome (MDS).

29. Patients must agree to peripheral blood samples during screening and at the end of treatment for mutational profile testing (for mutations of selected myeloid associated genes) that will be performed only if the patient develops MDS or acute myeloid leukemia (AML) during the study or the post- treatment follow-up (a third sample will be collected in this case).

4 Trial design

4.1 Overall study design

This study is a randomized, open-label, multicenter, controlled trial to compare niraparib versus physician's choice, amongst one of the following four single agents: eribulin, vinorelbine, gemcitabine or capecitabine, in patients with HER2-negative *gBRCA*^{mut} breast cancer. Patients will be centrally registered at the EORTC Headquarters prior to the start of treatment, and after verification of the eligibility criteria, eligible patients will be randomized 2:1 to receive niraparib orally at a dose of 300 mg QD on a continuous dosing regimen or physician's choice amongst one of the following four single agents (eribulin, vinorelbine, gemcitabine or capecitabine) according to the national available and approved treatment (Gemcitabine will be administered as single agent as per NCCN guidelines. In France, gemcitabine is not allowed to be chosen as a treatment in the physician's choice arm.).

A schematic of the study design is provided in the following scheme. Screening assessments to determine patient eligibility for the study and to assess baseline disease status will be conducted within 28 days prior to the first dose (cycle 1/day 1). Clinic visits will be conducted at the beginning of every cycle (i.e., every 3 weeks ± 3 days). Contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI) if CT is not feasible will be required at screening and every 2 cycles (6 weeks ± 7 days) for the first 12 months, then every 3 cycles (9 weeks ± 7 days) until disease progression. Patients will continue on their assigned treatment until disease progression (determined by Response Evaluation Criteria in Solid Tumors [RECIST] v.1.1), unacceptable toxicity, death, withdrawal of consent, or they are lost to follow-up (please refer to chapter 5.3 and 5.4).

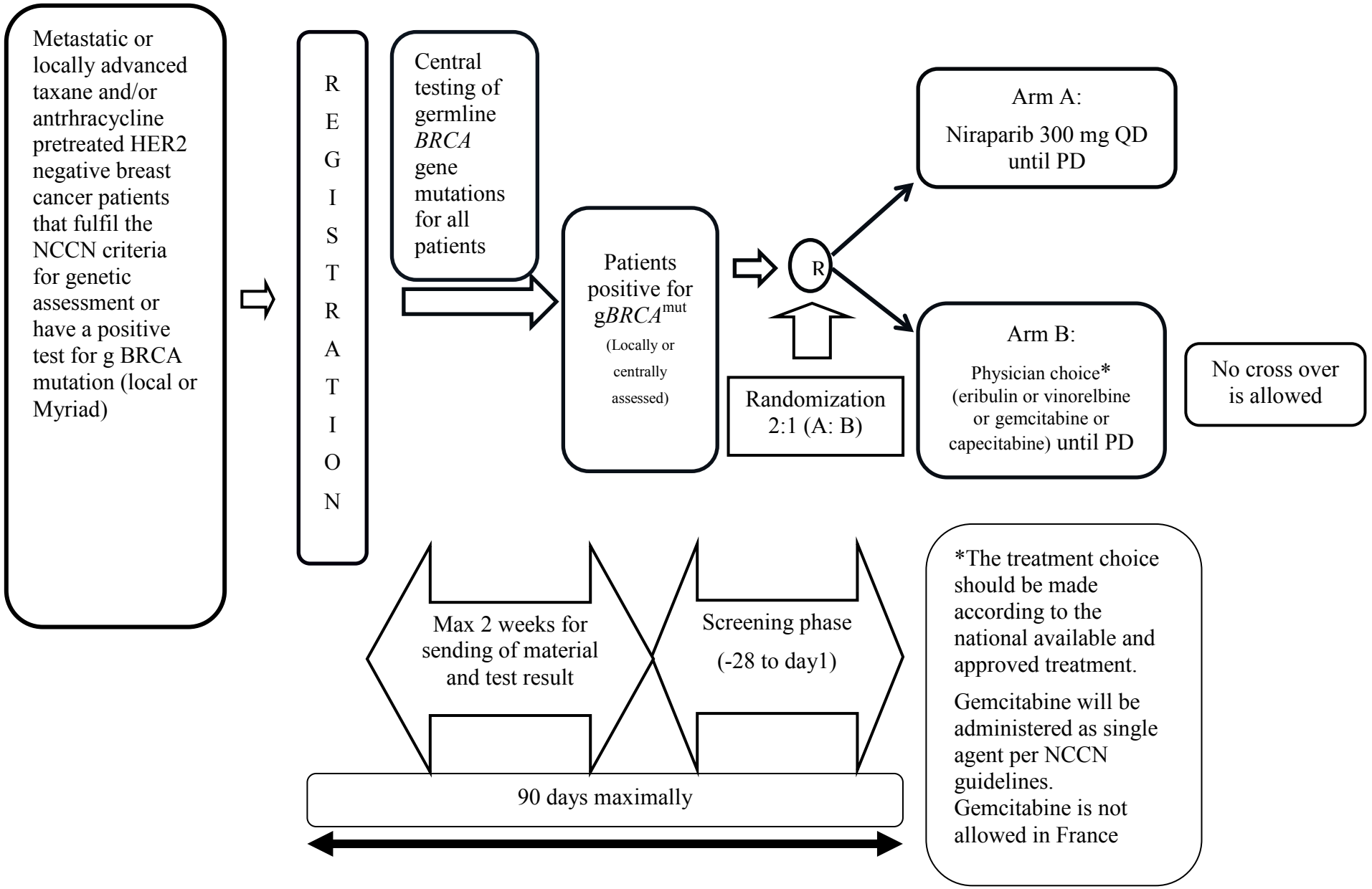
Evaluation of CT scans and MRI, including determination of response to treatment and date of progression based on RECIST v.1.1, will be conducted by a central blinded review committee comprised of 2 radiologists, with an arbiter as necessary. Results of the central blinded assessment will be used to determine the primary efficacy endpoint of PFS and will be conducted retrospectively. The study investigators also will assess response to treatment and date of progression based on RECIST v.1.1 during the conduct of the study.

Patient reported outcomes (PROs) will be evaluated at screening, during the treatment period and after treatment discontinuation for a maximum period of up to 12 months after randomization. All patients randomized to niraparib will also undergo sparse blood sampling (predose and 2 hours postdose except for C4D1 that will be done only predose) at specified study visits for measurement of plasma levels of niraparib and translational protocol specified analyses.

Safety will be evaluated throughout the study by AE monitoring and clinical laboratory assessments, (hematology, chemistry), vital signs, electrocardiograms (ECGs), physical examinations, and use of concomitant medications.

After treatment discontinuation, information on subsequent anticancer therapy and survival (including new malignancy information) will be collected. If the patient discontinues prior to disease progression, tumor imaging, and assessment of PROs, will continue during the post-treatment phase at specified time intervals until disease progression or until the patient starts his/her subsequent anticancer therapy. No crossover to niraparib is permitted following discontinuation from physician's choice treatment.

Figure 1: Study schema



An independent data monitoring committee (IDMC) will be established to provide independent review and assessment of the efficacy and safety data in a systematic manner and to safeguard the interest and safety of the participating patients in the study. The membership, key responsibilities of the IDMC, and the corresponding procedures will be defined in an IDMC charter.

4.2 Justification of study design and choice of endpoints

The key design features of the study include randomization and the use of an active control. Random assignment of patients avoids bias and helps ensure that both known and unknown risk factors are distributed evenly between treatment groups. Randomization is being conducted on a 2:1 basis to expose more subjects to niraparib allowing for the evaluation of safety of the compound in approximately 200 patients. Randomization is being stratified by factors known to be prognostic for response, including presence or absence of visceral disease, histologic subtype, and number of lines of prior therapy.

Due to the nature of the treatment regimens, specifically daily oral administration of niraparib versus various oral or intravenous regimens employed for the physician's choice treatment arm, blinding is not possible. The primary evaluation of efficacy will be conducted by a central blinded review.

Niraparib is to be administered orally at a dose of 300 mg daily. This dose was chosen based on the efficacy, pharmacokinetic / pharmacodynamics, safety and tolerability profiles of niraparib in early clinical testing.

The comparator agents used in the trial – eribulin, vinorelbine, gemcitabine, or capecitabine – are widely available and approved for use or commonly used as single agents in the treatment of metastatic breast cancer. Regimens for all 4 agents conform to the 21-day cycle regimen should be planned for this protocol (Notes: 1. Gemcitabine will be administered as single agent as per NCCN guidelines. In France gemcitabine is not allowed to be chosen as a treatment in the physician's choice arm 2. A 28- day cycle regimen may apply to the intravenous administration of physician's choice vinorelbine).

The primary endpoint in this trial – PFS – is a standard measure to assess the efficacy of treatment in cancer trials that is not confounded by subsequent therapy (Guidance for Industry: Clinical Trial Endpoints for the approval of Cancer Drugs and Biologics). Evaluation of this endpoint, including the assessment of tumor burden, response to treatment, and progression are based on established criteria in patients with solid tumors, specifically RECIST. The assessments will be conducted by an independent review committee based on RECIST who will be blinded to study medication. This central review will provide for standardization in the assessment of radiographs across all patients in this multicenter, multinational trial by radiologists with expertise in the evaluation of patients with solid tumors, including breast cancer.

The key secondary endpoint of the trial is overall survival, which is an accepted direct measure of benefit. The study design includes long-term follow-up to capture subsequent anticancer therapy – including response to that therapy, as well as survival. New malignancy information will also be collected as part of this assessment.

The patient population for this study, specifically patients with histologically or cytologically confirmed HER2-negative *gBRCA*^{mut} metastatic or locally advanced breast cancer who have received up to 2 prior cytotoxic regimens, have very limited treatment options.

5 Therapeutic regimens, expected toxicity, dose modifications

5.1 Drug information

5.1.1 General information

Niraparib ([3S]-3-[4-(7-(aminocarbonyl)-2H-indazol-2-yl) phenyl] piperidine [tosylate monohydrate salt]) is an orally available, potent, highly selective PARP-1 and -2 inhibitor. The crystalline tosylate monohydrate salt of niraparib is being developed as a monotherapy agent for tumors with defects in the HR DNA repair pathway and as a sensitizing agent in combination with cytotoxic agents and radiotherapy. This salt form is non-hygroscopic and comprised of agglomerated bundles of rod-like or columnar primary particles. Niraparib has an aqueous solubility of 0.77 mg/mL. Its molecular formula is C26H30N4O5S and its molecular weight is 510.617 daltons. It is formulated as a dry blend of niraparib and lactose lubricated with magnesium stearate. The active potency is 100 mg in size 0 gelatin capsules.

Physician's choice study medication will be eribulin, vinorelbine, gemcitabine, or capecitabine. All compounds are currently approved for the treatment of patients with breast cancer. However the choice should be made according to the national available and approved treatment.

Important note: Gemcitabine will be administered as single agent as per NCCN guidelines. In France, gemcitabine is not allowed to be chosen as a treatment in the physician's choice arm.

Study Medication	Dosage Form	Route
Niraparib	Capsule, 100 mg strength	Oral
Physician's choice: ♦ i.v eribulin, ♦ i.v or oral vinorelbine ♦ i.v gemcitabine ♦ oral capecitabine	Various	IV or oral

5.1.2 Drug supply

Niraparib will be provided free of charge by Tesaro. Practicalities for drug supply and re-supply will be detailed in separate guidelines.

5.1.3 Packaging, dispensing and storage

Niraparib 100 mg capsules will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each dosing container will contain sufficient capsules for one cycle of treatment plus overage. Niraparib will be dispensed to patients on day 1 of every cycle (21 days) thereafter until the patient completes the study, withdraws from the study, or closure of the study.

All niraparib study medication must be stored in accordance with the manufacturer's instructions. Until dispensed to the patients, niraparib study medication will be stored in a suitable container at storage conditions specified by the Sponsor in a securely locked area, accessible to authorized personnel only. The pharmacist will dispense study drug for each patient according to the protocol and pharmacy manual, if applicable.

Physician's choice treatments will be obtained from commercial supplies. Physician's choice treatments will be administered (dose, route, regimen) according to their respective product package insert or local practice. Gemcitabine as single agent will be administered per NCCN guidelines. In France gemcitabine is not allowed to be chosen as a treatment in physician's choice arm.

5.1.4 Drug reconciliation procedures

Accountability of the investigational study drugs is under the responsibility of the investigator and can be delegated to an appropriately qualified person.

Study drug accountability should be maintained by each site based on capsules dispensed versus returned to the clinic at each visit and the number days since last visit.

Accountability records should include receipt date, lot numbers, expiry dates, patient number, use by subject, dispensing dates, quantities (lowest unit) and stock balance. Product returned to the pharmacy or site will be stored under the same conditions as products not yet dispensed but will be marked as 'returned' and kept separate from the products not yet dispensed.

In addition to internal accountability documentation on site, study-specific accountability and drug destruction forms will be supplied for this purpose by TESARO (via PAREXEL), if site-specific forms are deemed not sufficiently detailed or do not provide enough information, according to PAREXEL quality assurance criteria.

The drug accountability and destruction forms will be verified during monitoring visits. The study monitor will reconcile the drug accountability log with products stored in the pharmacy.

At the end of study, when all patients have stopped protocol treatment, complete drug reconciliation per batch should be available at the site for verification by PAREXEL in order to allow drug destruction or return procedure. All dispensing and accountability records will be available for Sponsor review. After receiving Sponsor approval in writing, the investigational site is responsible for destruction of study drug according to local regulations. If a site does not have the capability for on- site destruction, Sponsor will provide a return for destruction service to a third party.

Both the unused and expired study medication must be destroyed, upon authorization of the sponsor, according to local regulations and procedures, and a copy of the destruction form must be returned to PAREXEL.

The medication provided for this trial is to be used only as indicated in this protocol and only for the patients entered in this study.

5.2 Initial dose and schedule

Niraparib 300 mg (3 x 100 mg niraparib capsules) will be administered orally QD continuously in an open-label fashion. Based on the results from the food effect study (Sub study of a phase 3 randomized double-blind trial of maintenance with niraparib versus placebo in patients with platinum Sensitive Ovarian Cancer), patients are not required to fast before and after each daily dose of niraparib (refer to updated investigator's brochure). Patients will be instructed to take their dose at the same time each day, preferably in the morning. Patients must swallow and not chew all capsules. The consumption of water is permissible. The first dose will be administered at the site as well as on day 1 of cycles 2 and 4 (PK sub-study). All dose interruptions and reductions (including any missed doses), and the reasons for the reductions/interruptions, are to be recorded in the electronic case report forms (eCRF).

Once the dose of study medication has been reduced, any re-escalation is not allowed.

Administration of the drugs on the arm of physician's choice and the medical supervision will be managed according to the guidance provided by the holder of the marketing authorization for the licensed compounds and according to the national available and approved treatment (Note: gemcitabine will be

administered as a single agent as per NCCN guidelines. In France gemcitabine is not allowed to be chosen as a treatment in the physician's choice arm).

5.3 Treatment duration

Treatment should be administered until documented disease progression, unacceptable toxicity, or patient refusal. Patients will continue on study medication until disease progression and as long as, in the Investigator's opinion, they are benefiting from treatment and do not meet any other treatment discontinuation criteria.

5.4 Withdrawal criteria

Whatever the disease status, the treatment will always be discontinued in case of:

- Unacceptable toxicity, as judged by the local investigator, despite appropriate dose reduction and / or toxicity management. See section 5.5 for guidance on dose reductions.
- Disease progression according to RECIST v.1.1
- Risk to patients as judged by the Investigator
- Risk to patients as judged by the Sponsor
- Severe non-compliance with the protocol as judged by the Investigator
- Severe non-compliance with the protocol as judged by the Sponsor
- Patient request
- The patient becomes pregnant
- Withdrawal of consent for any reasons
- Physician's recommendation
- Occurrence of a second malignancy

The reason for withdrawal from study treatment must be documented in the electronic case report forms.

Patients who discontinue from treatment will continue to receive follow-up assessments (treatment outcome with next therapy and overall survival including new malignancy information) as part of the study unless they are discontinued from the study by one of the following events:

- Withdrawal of consent by the patient, who is at any time free to discontinue their participation in the study, without prejudice to further treatment
- Patient lost to follow-up
- Death from any cause

Patients discontinuing therapy in the absence of progression should not receive any other cancer treatment before their disease progresses, unless this is clearly not in the interest of the patient.

After progression, the treatment will be left to the discretion of the treating physician.

Any anti-cancer therapy other than the study drug given as single agent will not be considered as part of the protocol treatment.

Patients may be discontinued from treatment or from the study at any time. Patients who discontinue from the study will not be replaced.

5.5 Dose and schedule modifications

A three week interval of dosing will be considered as a "treatment period "or cycle of therapy. All adverse events caused by the drugs in the physician's choice treatment arm will be managed according to the guidance provided by the holder of the marketing authorization for the licensed compounds.

5.5.1 Niraparib- related dose modification for toxicity (hematologic and non- hematologic)

Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the patient. In addition, the following are protocol defined criteria for dose modification.

Treatment must be interrupted for any treatment- related non-hematologic Common Terminology Criteria for Adverse Events v 4.0 (CTCAE), (Appendix C) grade 3 or 4 AE or serious AE (SAE) which the Investigator considers to be related to administration of niraparib. If the toxicity is resolved to baseline or ≤ grade 1 for non-hematological toxicities or above the lower limits defined in table 2 for hematologic toxicities (Hgb ≤ 9 g/dl, PLTs ≤ 100,000/µl, Neut≤1,500/ µl) within 28 days, the patient may restart treatment with niraparib, but with a dose level reduction unless prophylaxis is considered feasible (table 1). If the toxicity requiring dose interruption has not resolved completely or to NCI- CTCAE grade ≤ 1 for non- hematological toxicities or above the lower limit as defined in table 2 for hematologic toxicities (Hgb ≤ 9 gr/ dl, PLTs ≤100, 000 / µl, Neutr≤ 1,500/ µl), during a maximum of 4 week (28 days) dose interruption period, and/ or the patient has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the patient must permanently discontinue treatment with niraparib. At the investigator's discretion, following dose interruption (no longer than 28 days), patients may be considered for dose reductions, providing they have not already undergone the maximum number of 2 dose reductions allowed(no more than 2 dose reductions will be permitted). If upon re- challenging with the study treatment at the lowest allowable dose , any CTCAE Grade 3 or 4 adverse events (AEs) requiring dose interruption recur, the patient must be discontinued. Once niraparib dose has been reduced for a patient, all subsequent cycles must be administered at that dose, unless further dose reduction is required. For major surgery, up to 28 days of drug interruption is allowed.

In case of dose interruptions, the next cycle will follow patient's original calendar schedule. Cycle timing will not be delayed for treatment interruptions and tumor assessment should occur according to this schedule regardless of whether study treatment is interrupted. Additional laboratory work-up prior to next treatment initiation should also be performed at the physician's discretion. Missed doses of niraparib (i.e. any dose that is not administered within the protocol defined administration window) will not be taken at a later date.

Table 1 Niraparib dose reductions for non-hematologic toxicities

Event	Dose[1]
Initial dose	300 mg QD
1st dose reduction for treatment-related CTCAE Grade 3 or 4 AE or SAE where prophylaxis is not considered feasible	200 mg QD
2nd dose reduction for treatment-related CTCAE Grade 3 or 4 AE or SAE where prophylaxis is not considered feasible	100 mg QD
Continued treatment-related CTCAE Grade 3 or 4 AE or SAE ≥ 28 days	Discontinue study medication

[1] Dose not to be decreased below 100 mg daily

Management of hematologic toxicities is described in Tables 2. For grade 3 or 4 neutropenia, thrombocytopenia, or anemia, treatment with niraparib must be interrupted with weekly blood counts monitored until recovery to ≤ grade 1. Niraparib should be resumed with a dose level reduction at that time. Cytokines (granulocyte colony stimulating factor [GCSF] may be administered as clinically indicated to manage febrile neutropenia according to local standard of care. Secondary prophylaxis should not be used for the niraparib arm but is allowed for the physician's choice arm.

Thrombocytopenia is an expected event associated with the use of niraparib and is described in Version 1 of the Investigator's Brochure. Thrombocytopenia associated with the use of niraparib resolved upon treatment interruption and/or dose reduction. The occurrence of thrombocytopenia during cycle 1 requires additional patient monitoring in order to identify hematologic changes early and prevent higher grade thrombocytopenic events. A weekly monitoring of the complete blood count (CBC) during the first month is considered mandatory.

If a patient completes the first cycle with no incidence of hematologic toxicity requiring dose interruption or modification, then CBC monitoring will proceed according to protocol every 3 weeks, thereafter. If dose interruption or modification is required at any point on study, weekly CBC will be required for another 4 weeks after the adverse event has been resolved, to ensure safety of the new dose, after which monitoring every 3 weeks may resume.

Any patient requiring transfusion of platelets or red blood cells (on two different occasions) or hematopoietic growth factor support must undergo a niraparib dose reduction upon recovery if study treatment is resumed.

It is strongly recommended to refer the patient to the hematologist for further evaluation (1) if transfusions are required on more than two occasions in the absence of non- treatment related causes or (2) if the treatment- related hematologic toxicities have not recovered to allow retreatment with niraparib after 4 weeks. If a diagnosis of MDS/AML is confirmed by a hematologist, the patient must permanently discontinue study treatment.

Table 2 Management of hematologic toxicities

Platelet count 75,000-99,999 µL/	Study medications must be interrupted until platelet counts are equal to or greater than 100,000/µL with weekly blood counts for CBC monitored until recovery. Study medication may then be resumed at same dose or reduced dose based on clinical judgment
Further occurrence of platelet count 75,000-99,999 µL	Study medications must be interrupted until platelet counts are equal to or greater than 100,000/µL with weekly blood counts for CBC monitored until recovery. Study medication may then be resumed at the same dose or reduced dose based on clinical judgment. Dose reduction should be made in case that new treatment interruption is needed in less than 3 weeks after resume of treatment.
Platelet count <75,000* µL	Study medications must be interrupted until platelet counts are equal to or greater than 100,000/ µL with weekly blood counts for CBC monitored until recovery. Study medication may then be resumed at the reduced dose.
Neutrophil < 1,000/µL	Study medications must be interrupted until neutrophil counts are equal to or greater than 1,500/µL with weekly blood counts for CBC monitored until recovery. Study medication may then be resumed at the reduced dose.
Hemoglobin < 8g/dL	Study medications must be interrupted until Hb is equal to or greater than 9 g/dL with weekly blood counts for CBC monitored until recovery. Study medication may then be resumed at the reduced dose

Note: If the hematologic toxicity has not recovered to the specified levels within 4 weeks of dose interruption and/or the patient has already undergone a maximum of 2 dose reductions then, the patient should be discontinued from study therapy. Specifically for thrombocytopenia, patients with a platelet count < 100,000/ µL (as AE of thrombocytopenia) must have the study medication interrupted and have weekly blood counts monitored until recovery ≥ 100,000 / µL. If the thrombocytopenia has not reverted to platelet count of ≥ 100,000 / µL within 4 weeks (28 days), the patient should be discontinued.

*For patients with platelet count ≤ 10,000/µL prophylactic platelet transfusion per guidelines may be considered (Ref. 27, Ref. 28). Any patient requiring transfusion of platelets or red blood cells (on two different occasions) or hematopoietic growth factor support must undergo a niraparib dose reduction upon recovery if study treatment is resumed. The patient must be referred to a hematologist for further evaluation (1) if transfusions are required in more than 2 occasions in the absence of non- treatment related causes or (2) if the treatment- related hematologic toxicities have not recovered to allow re- treatment with niraparib after 4 weeks. For patients taking anticoagulation or antiplatelet drugs, consider the risk/benefit of interrupting these drugs and/or prophylactic transfusion at an alternate threshold, such as ≤ 20,000/µL.

5.5.2 Physician's choice dose modification

Dose modifications for physician's choice drugs will be according to the respective product package insert or local practice. Treatment interruptions longer than 28 days are not allowed.

In case of dose interruptions, tumor assessment should occur according to the patient's original calendar schedule regardless of whether study treatment is interrupted. Additional laboratory work-up prior to next treatment initiation should also be performed at the physician's discretion.

Important Note: Any patient requiring transfusion of platelets or red blood cells (on two different occasions) or hematopoietic growth factor support must undergo a study drug (physician's choice) dose reduction upon recovery if study treatment is resumed.

It is strongly recommended to refer the patient to the hematologist for further evaluation (1) if transfusions are required in more than two occasions in the absence of non- treatment related causes or (2) if the treatment- related hematologic toxicities have not recovered to allow re- treatment with the study drug (physician's choice) after 4 weeks. If a diagnosis of MDS/AML is confirmed by a hematologist, the patient must permanently discontinue study treatment.

5.6 Concomitant treatments

5.6.1 Supportive care in case of toxicity

Primary cytokine prophylaxis is not allowed. For patients on Physician's choice chemotherapy, secondary prophylactic treatment with cytokine (granulocyte colony- stimulating factor [GCSF] may be administered as clinically indicated according to local standard of care. For patients on niraparib GCSF prophylaxis is not considered appropriate and is not allowed. For patients on either niraparib or physician's choice chemotherapy GCSF may be administered as clinically indicated for the treatment of febrile neutropenia according to the local standard of care. Patients requiring hematopoietic growth factor support must undergo a niraparib dose reduction upon recovery if treatment is resumed.

5.6.2 Other concomitant therapies

At screening, patients will be asked what medications they have taken during the last 30 days. At each subsequent study visit, patients will be asked what concomitant medications they are currently taking.

Any medication the patient takes other than the study medication, including herbal and other alternative/ complementary remedies are considered concomitant medication. All concomitant medications must be recorded in the eCRF; information to be recorded for each concomitant medication includes generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRFs.

Niraparib has potential to induce cytochrome P1A2 (CYP1A2) and its substrates. Therefore, caution should be used when drugs metabolized by CYP1A2 are administered concomitantly (Appendix H).

Niraparib is a substrate for P-glycoprotein (P-gp); therefore, use caution with drugs that are inhibitors or substrates of P-gp (Appendix J).

The niraparib safety profile includes risk for thrombocytopenia; therefore, patients should be advised to use caution with anticoagulation and antiplatelet drugs.

For physician's choice treatment, the product package insert will guide the use of concomitant medications.

6 Clinical evaluation, laboratory tests and follow-up

6.1 Before Treatment

6.1.1 Registration

Registration must be done directly after specific for registration informed consent signature by the patient.

Blood sample for centralized *gBRCA* mutation testing (can be done at any time prior to randomization). Patients that already have a positive test for g *BRCA* mutation previously done by Myriad or local laboratory at any time can proceed to the screening phase before the central result is available; however a new blood sample has to be drawn in the frame of this study.

Additional blood sample to evaluate the concordance of a candidate companion diagnostic test with the centralized *gBRCA* mutation test with respect to identifying *gBRCA* mutated patients.

The period between registration and randomization is defined for up to 90 days. In case that a patient is not randomized in this timeframe, randomization can be done at a period exceeding this time frame, after screening is repeated (The patient will be re- registered and a new Seq ID will be assigned).

6.1.2 Screening (day -28 to day 1)

- At screening, the following procedures/tests will be performed:
- Written main informed consent
- Demographics (age, height, weight, race, ethnicity, sex)
- Medical (including details of any prior invasive malignancy), surgical, medication history and breast cancer disease history which will include: Date of first diagnosis, tumor type, stage at time of initial diagnosis, histology and grade of disease at diagnosis and most recent biopsy if additional biopsy performed, date of start of first treatment, agents in first treatment, date of last dose of first treatment, dates of start of all subsequent treatments, agents in all subsequent treatments, dates of last dose of all subsequent treatments, best response for each prior treatment and date of recurrence for each treatment.
- Formalin fixed paraffin embedded archival tumor sample(s) (primary or metastatic site) tumor block (preferred) or 20 slides of 5 micron thickness (they can be collected/sent during screening or after randomization [during Cycle 1]).
- Optional tumor biopsy (FFPE and snap frozen cores) – a fresh tumor biopsy may be obtained using separate informed consent.
- Sample collection (whole blood) for mutational profile testing (for mutations of selected myeloid associated genes) #.
- Blood samples for plasma biomarker analysis and humoral immune response monitoring
- Serum pregnancy test – required being negative within 72 hours prior to first dose of study drug for females of childbearing potential.
- Physical examination
- Vital signs (blood pressure, pulse, temperature)
- ECOG performance status (Appendix G)
- SAE monitoring from registration
- Assessment of all adverse events according to CTCAE v4.0

- Collection of prior history (up to 1 year prior to enrollment) of myelosuppression (i.e. anemia, neutropenia, thrombocytopenia or leukopenia)
- Cancer signs and symptoms
- Concomitant medications
- Hematology* (within 72 hours prior to first dose) (will include hemoglobin, platelets, mean corpuscular volume, white blood cells, differential white cell count, activated partial thromboplastin time and international normalized ratio)
- Chemistry (within 72 hours prior to first dose) (will include sodium, potassium, calcium, magnesium, chloride, glucose, creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate transaminase, alanine transaminase, urea or blood urea nitrogen, total protein, albumin, lactic dehydrogenase, and amylase)
- For patients with peritoneal disease and a prior ovarian cancer: Serum CA-125
  - In case CA-125 is elevated: biopsy of the peritoneal disease
- Urinalysis (within 72 hours prior to first dose): Specific gravity, leukocyte esterase, nitrite, blood, protein, glucose, ketones, urobilinogen, bilirubin.
- 12-lead ECG
- RECIST tumor assessment (chest, abdomen and pelvis CT or MRI scans)
- HRQoL: QLQ-C30 and EQ-5D-5L to be completed within 4 weeks prior to randomization (chapter 10)
- Randomization (within 72 hours prior to first dose). Note that physician's choice treatment must be designated prior to randomization

Tumor assessments (chest, abdomen and pelvis CT or MRI scans) that were done as part of standard of care due to progression of disease prior to receiving Myriad test results, do not need to be repeated but can be used for screening, provided that they were performed within 28- day screening timeframe.

- *Samples for mutational profile testing (mutations of selected myeloid associated genes) will be stored but they will be analyzed if necessary for assessing niraparib related risk for MDS/ AML development (e.g the patient develops MDS/ AMS during treatment or post- treatment follow-up).*
- *Activated partial thromboplastin time (a PTT) and international normalized ratio (INR) will be done only at screening.*

6.2 During treatment

Visits should occur within ± 3 days of the scheduled visit, unless otherwise specified as outlined in Table 6.3). All times should be recorded using the 24 hour clock (e.g., 23:20, not 11:20 PM).

For a highly clinically suspected MDS/AML case reported while a patient is receiving treatment with the study drug, the patient should be referred to the local hematologist to confirm the diagnosis of MDS/AML. Testing with bone marrow aspirate and biopsy is strongly recommended in these cases. The study site must receive a copy of the hematologist's report of aspirate-biopsy findings which must include a classification according to World Health Organization (WHO) (Ref. 40). A whole blood sample will be also collected for mutational profile testing (mutations of selected myeloid- associated genes) for any highly clinically suspected MDS/AML case reported while a patient is receiving treatment.

6.2.1 Cycle 1, day 1

- On the day of the first dose of study medication, the following procedures will be performed (predose, unless otherwise specified):
- Physical examination*
- Vital signs (blood pressure, pulse, temperature, and weight)
- ECOG performance status (Appendix G)*
- Concomitant medications*
- Hematology/chemistry*. The same tests as in screening phase will be performed (except activated partial thromboplastin time [a PTT] and international normalized ratio [INR]).
- Niraparib arm only: 12-lead ECG predose and 2 hours postdose; the ECGs should be performed prior to blood draws for PK assessment.
- Niraparib arm only: Blood samples for determination of niraparib levels predose (within 30 minutes) and 2 hours postdose.
- First dose to be administered at the site

**It does not need to be repeated if it was assessed at screening and within 72 hours of the cycle 1/day 1 dose. Hematology tests (only CBCs esp. for platelet counts) need to be done weekly for the 1 month of treatment for patients receiving treatment in both arms. That means for the first cycle at D1#, D8# and D15# (Blood draw for CBC will also need to be done in D1 and D8 of the second cycle). Thereafter it is left at the discretion of the treating physician if he/she prefers to repeat hematology evaluation more often than what is described in the current protocol. The test can be performed at the most convenient laboratory (in accordance with local regulations) or the study site for the patient and the site must be informed of the result and keep a copy of it in the file of the patient. This data will be captured in the database.*

 # It is strongly advised that these dates are followed.

6.2.2 Cycle 2, day 1

- On cycle 2/day 1, the following procedures will be performed (predose, unless otherwise specified):
- Physical examination
- Vital signs (blood pressure, pulse, temperature, and weight)
- ECOG performance status (Appendix G)
- Assessment of all adverse events according CTCAE v 4.0 that have occurred since the previous visit
- Concomitant medications
- Hematology/chemistry (same tests as in screening phase except activated partial thromboplastin time [a PTT] and international normalized ratio [INR])*.
- Niraparib arm only: 12-lead ECG, conducted predose and 2 hours postdose; the ECGs should be performed prior to blood draws for PK assessment.
- Niraparib arm only: Plasma samples for determination of niraparib levels predose (within 30 minutes) and 2 hours postdose.

* *A blood draw only for CBC needs to be repeated at D8 of the second cycle to complete the first month of mandatory weekly hematological evaluation.*

6.2.3 Day 1, subsequent cycles

- Cycle 3/day 1 only: blood samples for plasma biomarker analysis and humoral immune response monitoring
- On day 1 of each subsequent cycle, the following procedures will be performed (predose, unless otherwise specified):
- Physical examination
- Vital signs (blood pressure, pulse, temperature, and weight)
- ECOG performance status (Appendix G)
- Assessment of all adverse events according CTCAE v 4.0 that have occurred since the previous visit
- Concomitant medications
- Hematology /chemistry (same tests as in screening phase except activated partial thromboplastin time [a PTT] and international normalized ratio [INR]).
- 12-lead ECG to be conducted as clinically indicated
- Cycle 4/Day 1 only: plasma samples for determination of niraparib levels predose (within 30 minutes).
- RECIST tumor assessment (chest, abdomen, pelvis CTs or MRIs and CT or MRI scans of known sites of disease) conducted every 2 cycles (every 6 weeks ± 7 days) for the first 12 months and then every 3 cycles (9 weeks ± 7 days) until disease progression
- HRQoL: QLQ-C30 and EQ-5D-5L completed every 2 cycles (every 6 weeks ± 7 days) during the first 12 months after randomization (chapter 10).

Pregnancy testing will occur per site specific processes: please refer to the niraparib Investigator's Brochure for guidance.

If patient is seen by local hematologists at any time during the conduct of the study, results of any additional tests performed to evaluate the bone marrow capacity should be reported accordingly in the e-CRF.

6.2.4 Study medication termination visit (within 28 days following the start of the last cycle)

The following procedures should be conducted within 28 days following the start of the last cycle:

- Physical examination
- Vital signs (blood pressure, pulse, temperature, and weight)
- ECOG performance status (Appendix G)
- Assessment of all adverse events according CTCAE v 4.0 that have occurred since the previous visit
- Concomitant medications
- Hematology/ chemistry (same tests as in screening phase except activated partial thromboplastin time [a PTT] and international normalized ratio [INR]).
- 12-lead ECG
- Optional tumor biopsy (FFPE and snap frozen cores) at the point of treatment discontinuation for progression – a fresh tumor biopsy may be obtained using separate informed consent.

- Sample collection (whole blood) for mutational profile testing (mutations of selected myeloid-associated genes). *These samples will be stored and analyzed if necessary for assessing niraparib related risk for MDS/AML development (for e.g the patient develops MDS/AML during treatment or post- treatment follow-up).*
- Blood samples for plasma biomarker analysis and humoral immune response monitoring (at termination due to progression or due to any other cause)
- RECIST tumor assessment (chest, abdomen, pelvis CT or MRI and CT or MRI scans of known sites of disease, CT or MRI scans of known sites of disease) will continue on the study-specified schedule until disease progression or until the patient starts his/her subsequent anti- cancer therapy for patients terminating study for reasons other than PD.
- Collect any unused study medication.

  *If patient is seen by a local hematologist, results of any additional tests performed to evaluate the bone marrow capacity should be reported in the e- CRF [e.g bone marrow aspirate/ biopsy findings which must include a classification according to World Health Organization (WHO) (*Ref. 40*)].*

6.2.5 Follow-up Visit

All patients will be followed through 30 days post-treatment for assessment of adverse events.

6.2.6 For those patients who discontinue treatment in the absence of progression

Patients who discontinue treatment without disease progression will undergo tumor assessments per the planned schedule: every 6 weeks ± 7 days during the first 12 months after randomization, and then every 9 weeks ± 7 days until disease progression or until the start of subsequent anti-cancer therapy). New malignancy information will also be collected as part of this assessment. HRQoL (QLQ-C30 and EQ-5D-5L) will be collected every 3 months during the first 12 months after randomization (chapter 10).

6.2.7 After progression, survival follow-up visits

Once patients discontinue from study medication they will enter the survival follow-up phase for assessment of subsequent anticancer therapies and overall survival. Assessments will occur every 3 months (± 7 days). HRQoL (QLQ-C30 and EQ-5D-5L) will be collected every 3 months during the first 12 months after randomization (chapter 10). New malignancy information will also be collected as part of this assessment. For subsequent anticancer therapies, the following information will be collected: name and/or class, start date, dose- limiting toxicities, best response (CR, PR, SD, PD) and progression date. For a highly clinically suspected MDS/AML case reported while a patient is followed for post- treatment assessments, the patient should be referred to the local hematologist to confirm the diagnosis of MDS/AML. Testing with bone marrow aspirate and biopsy is strongly recommended in these cases. The study site must receive a copy of the hematologist's report of aspirate/ biopsy findings which must include a classification according to World Health Organization (WHO) (Ref. 40). A whole blood sample will be also collected for mutational profile testing (mutations of selected myeloid- associated genes) for any highly clinically suspected MDS/AML case reported during survival follow-up visits.

6.3 Summary table

Cycle[1]	Registration	Screen	C1			C2		Subse-quent cycles[2]	Study Medication Termination (to occur within 28 days of start of Last cycle)	Post- treatment follow-up		
										30-Day Follow-up	Every 6 weeks ± 7 days for the first 12 months and then every 9 weeks ± 7 days until PD or subsequent treatment	Follow-up every 3 months
Day	At any time prior to screening	-28 to day 1	D1	D8	D15	D1	D8	Cycle n, Day 1				
Informed Consents	X	X										
Demographics		X										
Medical, surgical, cancer, medication history		X										
Blood sample for g*BRCA* mutation analysis[3]	X											
Blood sample for companion diagnostic test[4]	X											
Archival tumor samples[5]		X	X									
Optional tumor biopsy[6]		X							X[6]		X[6]	
Pregnancy test[7]		X[7]										
Randomization		X[8]										

Cycle[1]	Registration	Screen	C1			C2		Subse-quent cycles[2]	Study Medication Termination (to occur within 28 days of start of Last cycle)	Post- treatment follow-up		
										30-Day Follow-up	Every 6 weeks ± 7 days for the first 12 months and then every 9 weeks ± 7 days until PD or subsequent treatment	Follow-up every 3 months
Day	At any time prior to screening	-28 to day 1	D1	D8	D15	D1	D8	Cycle n, Day 1				
Physical examination		X	X			X		X	X			
Vital signs, height[9], weight		X	X			X		X	X			
ECOG performance status		X	X			X		X	X			
Adverse event monitoring	X[23]	X	X			X		X	X	X		
Collection of prior history of myelosuppression (i.e. anemia, neutropenia, leukopenia and thrombocytopenia)		X										
Serious adverse event monitoring	X[23]	X	X			X		X	X	X		
Concomitant medications		X	X			X		X	X			
Hematology (CBC only)		X	X[10]	X	X	X	X	X	X			

Cycle[1]	Registration	Screen	C1			C2		Subse-quent cycles[2]	Study Medication Termination (to occur within 28 days of start of Last cycle)	Post- treatment follow-up		
										30-Day Follow-up	Every 6 weeks ± 7 days for the first 12 months and then every 9 weeks ± 7 days until PD or subsequent treatment	Follow-up every 3 months
Day	At any time prior to screening	-28 to day 1	D1	D8	D15	D1	D8	Cycle n, Day 1				
INR/aPTT		X[10]										
Serum Chemistry		X	X[10]			X		X	X			
Urinalysis		X										
12-lead ECG		X	X[11]			X[11]		X[12]	X			
Blood sample for biomarkers[13]		X						X[13]	X			
Blood sample for pharmacokinetic analysis			X[14]			X[14]		X[15]				
Tumor Assessment (RECIST v1.1) Chest, abdomen, pelvis CTs or MRIs.[16]		X						X[16]	X[16]		X[16]	X[16]
CA-125 measurement in case of peritoneal disease and previously diagnosed ovarian cancer		X										

Cycle[1]	Registration	Screen	C1			C2		Subse-quent cycles[2]	Study Medication Termination (to occur within 28 days of start of Last cycle)	Post- treatment follow-up		
										30-Day Follow-up	Every 6 weeks ± 7 days for the first 12 months and then every 9 weeks ± 7 days until PD or subsequent treatment	Follow-up every 3 months
Day	At any time prior to screening	-28 to day 1	D1	D8	D15	D1	D8	Cycle n, Day 1				
HRQoL[17]		X						X[17]			X[17]	X[17]
Niraparib capsules dispensed/collected or Physician's choice treatment[19]			X			X		X	X[19]			
Sample collection (whole blood) for mutational profile testing[20]		X[20]							X[20]			
Additional tests to confirm the diagnosis of MDS/AML[21]									X[21]			X[21]
Anti-cancer therapies assessment												X[22]
Survival Assessment												X[22]

1 Treatment cycles are 21 days (3 weeks) long, visits on Day 1 of each cycle, unless otherwise specified (A 28-day cycle regimen may apply to the intravenous administration of physician's choice vinorelbine)

2 Visits continue every 3 weeks until study medication termination visit.

3 Centralized germline *BRCA* mutation (*gBRCA*^{mut}) testing of DNA. Patient blood sample may be drawn and performed at any time prior to randomization. Enrollment will be based on either central or local positive for germline *BRCA* mutation result.

4 A second blood sample will be archived for test bridging.

5 Formalin-fixed, paraffin-embedded tumor samples (primary or metastatic site; tumor blocks or 20 slides of 5 micron thickness). Genetic and non-genetic markers relating to DNA repair will be tested (alternatively can be done after randomization or during cycle 1).

6 A fresh tumor biopsy (FFPE and snap frozen cores) may be performed at screening and one time at progression using separate informed consent. Genetic and non-genetic markers relating to DNA repair and/or markers that predict efficacy and safety of PARP inhibitors will be tested.

7 Negative serum pregnancy test required within 72 hours prior to the first dose of study medication for females of childbearing potential. *Pregnancy test will occur per site processes; please refer to the niraparib Investigator's Brochure for guidance.*

8 Randomization should occur within 72 hours prior to first dose (Cycle 1, Day 1). Note that physician’s choice treatment must be designated prior to randomization.

9 Height obtained at screening only.

10 If screening laboratory testing [hematology (CBC plus INR and aPTT), chemistry] was performed within 72 hours of Cycle 1, Day 1, repeat testing not required. Please note that during the first month of study treatment, it is mandatory to perform weekly blood draws for CBC for both treatment arms. INR and a PTT will be done only at screening.

Also in case of a dose modification due to hematologic toxicity , weekly blood draws for CBC will be required for an additional 4 weeks after the adverse event has been resolved to baseline or grade 1, after which monitoring every 3 weeks may resume.

11 For the niraparib arm only :12-lead ECG conducted, Cycle 1, Day 1 (predose and 2 hours post dose), Cycle 2, Day 1 (predose and 2 hours postdose), and cycle 1 and Cycle 2 Day 1 assessments should be conducted prior to blood draws for PK assessments.

12 12-lead ECG as clinically indicated in subsequent cycles.

13 Blood samples will be taken at screening, at 6 weeks (Cycle 3/Day1) and at treatment termination (due to progression or due to any other cause). Analysis of circulating genetic and non-genetic markers relating to DNA repair and/or markers that predict efficacy and safety of PARP inhibitors will be tested.

14 Blood samples for measurement of plasma levels of niraparib collected on Cycle 1, Day 1 and Cycle 2, Day 1 predose (within 30 minutes) and 2 hours post dose.

15 Additional blood samples for plasma levels of niraparib collected on Cycle 4, Day 1 predose (within 30 minutes).

16 Chest, abdomen and pelvis CT or MRI as well as CTs or MRIs scans of any other known sites of the disease are required at screening; thereafter every 6 weeks ±7 days (i.e. every 2 cycles) for the first 12 months, then every 9 weeks ±7 days (i.e. every 3 cycles)until disease progression. Tumor assessments must continue on schedule if patients have dose delays.

If the patient discontinues prior to disease progression, tumor imaging will continue at specified time intervals (every 6 weeks ± 7 days during the first 12 months after randomization, and then every 9 weeks ± 7 days weeks) until progression or until the start of subsequent anti-cancer therapy.

Patients without measurable disease at baseline are not excluded from this study. These patients should be followed with the same assessment schedule as those with measurable disease at baseline and throughout the study.

17 Questionnaires include EORTC QLQ-C30 and EQ-5D-5L (Appendix F and Appendix I). The time schedule is detailed in 10.4.1. The questionnaires must be filled within 4 weeks before randomization and subsequent questionnaires are filled in every 2 cycles (i.e., every 6 weeks ±7 days) for the first 12 months while on-treatment and every 3 months after study medication discontinuation. HRQoL forms will be collected regardless of progression status and will be limited to the first 12 months after randomization.

18 Physician's choice chemotherapy (eribulin, vinorelbine, gemcitabine, or capecitabine) to be administered according to product package insert or local standard of care. Gemcitabine will be administered as single agent as per NCCN guidelines. In France gemcitabine is not allowed to be chosen as a treatment in the physician's choice arm.

19 No new study medication dispensed.

20 Blood samples collected at screening and EOT (due to any cause including development of new MDS/AML)will be stored for evaluation if necessary for assessing niraparib-related risk for MDS/AML development (e.g if the patient develops MDS/AML during treatment or post- treatment follow- up). Mutation profile before and after study treatment will be compared to determine whether any mutations were present prior to study treatment. Additional details on sample collection and analysis can be found in Section 12.3.5.

21 For a highly clinically suspected MDS/AML case reported while a patient is receiving treatment with the study drug or being followed for post- treatment assessments; the patient should be referred to the local hematologist to confirm the diagnosis of MDS/AML. Results of any additional tests performed by the hematologist should be reported as well in the e-CRF. Testing with bone marrow aspirate and biopsy is strongly recommended in these cases. The study site must receive a copy of the hematologist's report of aspirate/ biopsy findings which must include a classification according to World Health Organization (WHO) (Ref. 40). A whole blood sample will be also collected for mutational profile testing for any highly clinically suspected MDS/AML case reported during treatment.

22 Assessments to occur every 3 months following study medication discontinuation. . In addition to survival, this assessment includes outcomes for subsequent anticancer therapies including any new malignancy information.

23 From registration. Registration must be done directly after informed consent signature by the patient

7 Criteria of evaluation

7.1 Evaluation of efficacy

Objective tumor response and progression free survival will be measured according to the RECIST criteria (version 1.1) (Ref. 30).

Response criteria are essentially based on a set of measurable lesions identified at baseline as target lesions, and – together with other lesions that are denoted as non-target lesions – followed until disease progression.

The following paragraphs are a quick reference to the RECIST criteria (version 1.1). The complete criteria are included in the published RECIST document (Ref. 30) also available at http://www.eortc.be/RECIST).

7.1.1 Measurability of tumor lesions at baseline

7.1.1.1 Definitions

- **Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- **Measurable lesions** - *tumor lesions* that can be accurately measured in at least one dimension (longest diameter to be recorded as ≥ 10 mm with CT scan or clinical examination [using calipers]. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component > 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters) by use of a ruler or calipers. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.
- **Non-measurable lesions** - All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Nodes that have a short axis <10 mm at baseline are considered non-pathological and should not be recorded or followed.
- **Target Lesions**. When more than one measurable tumor lesion or malignant lymph node is present at baseline all lesions up to *a maximum of 5 lesions total* (and a maximum of 2 *lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be calculated and recorded.

- **Non-target Lesions**. All non-measurable lesions (or sites of disease) including pathological nodes (those with short axis ≥ 10 mm but < 15 mm), plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

7.1.1.2 Methods of measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, which may be treatment arm dependent. While on study, all target lesions recorded at baseline should have their actual measurements recorded on the CRF at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

- **Clinical Lesions**. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.
- **Chest X-ray**. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. **CT, MRI**. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). While PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).
- **Ultrasound**. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT should be obtained.
- **Endoscopy, Laparoscopy**. The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.
- **Tumor Markers**. Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.

- **Cytology, Histology**. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

7.1.2 Tumor response evaluation

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of all *target* and *non-target* lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures < 10 mm (Note: continue to record the measurement even if < 10 mm and considered CR). Tumor markers must have normalized. Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated before CR can be accepted.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment, for example where the tumor burden appears to have increased by at least 73% in volume (which is the increase in volume when all dimensions of a single lesion increase by 20%). Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but on further documentation, the earlier date must be used.

Table 5: Integration of target, non-target and new lesions into response assessment:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this category also requires
Patients with Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of tumor markers, tumor nodes < 10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	Documented at least once ≥ 4 wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Patients with Non target lesions ONLY				
No Target	CR	No	CR	Normalization of tumor markers, all tumor nodes < 10 mm
No Target	Non-CR/non-PD	No	Non-CR/ non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression [or evidence of unequivocal disease progression] at that time should be reported as "*symptomatic deterioration*". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.				

In this trial where response is not the primary endpoint, complete or partial responses do not need confirmation to lead to best response.

7.1.2.1 Frequency of tumor re-evaluation

Subsequent tumor assessments of known sites of disease via CT or MRI scan will be required at the end of every 2 cycles (every 6 weeks ± 7 days) for the first 12 months and then every 3 cycles (9 weeks ± 7 days) until disease progression. In case of dose interruptions, the next cycle will follow patient's original calendar schedule. Cycle timing will not be delayed for treatment interruptions and tumor assessment should occur according to this schedule regardless of whether study treatment is interrupted. If the patient discontinues prior to disease radiological progression, tumor imaging will continue at the specified time intervals until progression or until the start of subsequent anti-cancer therapy. Disease progression assessments outside of the stated windows will not be disregarded for the purpose of establishing progression status.

Patients without measurable disease at baseline are not excluded from this study. These patients should be followed with the same assessment schedule as those with measurable disease at baseline and throughout the study. Patients without measurable disease will be assessed for progression according to RECIST criteria based on non-target and/or new lesions.

Radiological examinations performed in the conduct of this study will be submitted for blinded centralized review. The central review committee, who will determine response to treatment and date of progression of disease, will be comprised of 2 radiologists and an arbiter, if necessary. A separate charter and imaging manual will be provided that details the central blinded review and the procedures for submitting images to the central laboratory. Investigators will also assess response and date of progression. The date of progression as assessed by central review will be used for determination of PFS in the primary efficacy analysis; Investigator assessment for PFS is a secondary endpoint in this trial.

The central review process is described in the independent review charter.

7.1.2.2 Date of progression

This is defined as the first day when the RECIST (version 1.1) criteria for PD are met. **Refer to section 7.1 for further information on what constitutes early progression, assessment of progression of non-target disease and new lesions.**

Further criteria to evaluate disease progression will be stated in the radiology charter.

7.1.3 Reporting of tumor response

All patients must be assessed for response to treatment, even if there is a major protocol treatment deviation or if they are ineligible, or not followed/re-evaluated. Each patient will be assigned one of the following categories: complete response, partial response, stable disease, progressive disease, early death or not evaluable.

Early death will be defined as death occurring within 90 days from randomization. Patients who die on treatment (= up to 30 days post treatment) will be reported in separate detail for safety.

Patients' response will be classified as "not evaluable" if insufficient data were collected to allow evaluation per these criteria.

Refer to the table 5 in section 7.1.

7.1.4 Response duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented. Patients without subsequent recurrence/progression will be censored at the same time as for the PFS endpoint.

7.1.5 Time to treatment failure

Time to treatment failure is defined from the date of randomization to progression or discontinuation of treatment for any reason, including but not restricted to disease progression, treatment toxicity, and death. If progressive disease occurred earlier than treatment discontinuation, the date of progressive disease will be the date of treatment failure. **At the time of analysis, patients who are continuing to receive treatment will be censored on the date of last contact.**

7.1.6 Progression Free Survival (PFS)

Primary endpoint: PFS per central review.

Progression Free Survival (PFS) is calculated as the time from randomization to either the date of disease progression or the date of death. The date of first documented disease progression (as per central review) will be used as the date of event. Patients who die without prior documented disease progression will have a date of event on their death date. For the primary analysis, PFS will be censored according to FDA guidance on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, appendix table A. The application of the guidance will be further detailed in the study Statistical Analysis Plan.

Secondary endpoint: PFS per investigator.

The definition is the same as for PFS per central review, using investigator reported PD dates instead of centrally reviewed PD dates.

7.1.7 Overall Survival (OS)

Overall Survival (OS) is calculated as the time from randomization to the date of death (any cause). Patients still alive at the time of analysis are censored at the last time they are known to be alive. Early death will be defined as death occurring within 90 days from randomization. Patients who die on treatment (= up to 30 days post treatment) will be reported in separate detail for safety.

7.2 Evaluation of safety

7.2.1 Adverse events

All AEs, including intercurrent illnesses, occurring from registration ICF signature until 30 days after last dose administration (or up to initiation of new anticancer therapy, whichever is earlier) will be documented in the eCRF. All adverse events must be followed until resolution or stabilization. Serious adverse events will be collected from registration till 30 days after last dose administration (or up to initiation of new anticancer therapy, whichever is earlier). Thereafter, only SAEs that are considered to be at least likely related to the protocol treatment will be collected. Survival follow-up visits will take place every three months following study medication discontinuation. New malignancy information will also be collected as part of this assessment.

Deaths occurring 30 days beyond last dose administration will not be collected unless considered related to study treatment. Concomitant illnesses, which existed before entry into the study, will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page.

All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, ECG, reported by patient), must be documented and recorded; the investigator will assess whether those events are drug related and this assessment will be recorded in the database for all adverse events.

The AE should be recorded individually in patient's own words (verbatim) unless, in the opinion of the investigator, the AE constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual symptom. All AEs will be coded using the CTCAE and recoded by the Sponsor in the Medical Dictionary for Regulatory Activities (MedDRA). The collection period of these AEs will start from registration.

All adverse events must be followed until resolution or stabilization.

7.2.2 General evaluation of adverse events

This study will use the International Common Terminology Criteria for Adverse Events (CTCAE) (Appendix C), version 4.0, for adverse event reporting. A copy of the CTCAE can be accessed from the EORTC home page www.eortc.org\investigators-area\ctc.

The highest CTCAE grading per cycle and per patient will be computed at the EORTC HQ for analysis.

Planned safety analysis and tabulations are described in the statistics section.

The event of disease progression is an efficacy criterion and is therefore not considered an AE. If AEs/SAEs occur in relation to disease progression, the AEs/SAEs must be reported per AE/SAE reporting requirements described in Section 7.2.1 and Section 7.2.3.

7.2.3 Serious adverse events

Serious adverse events are defined by the Good Clinical Practice Guideline.

Serious adverse events should be immediately reported according to the procedure detailed in this PROTOCOL (see chapter on Reporting Serious Adverse Events)

7.2.4 Toxic deaths

Toxic death is defined as death due to toxicity (defined as adverse events that are not confirmed as unrelated). The cause of death must be reported as "toxicity". The evaluation of toxic deaths is independent of the evaluation of response (patients can die from toxicity after a complete assessment of the response to therapy).

7.2.5 Evaluability for safety

All patients who have started the treatment will be included in overall safety analyses.

For hematological events, the medical review team may decide that blood counts have not been performed and/or reported according to the protocol and are therefore inadequate for the evaluation of one/several hematological parameters in some patients.

Patients who have discontinued treatment because of toxicity will always be included in the safety analyses.

8 Statistical considerations

The statistical analysis described below will be further detailed in a dedicated Statistical Analysis Plan (SAP). This plan will also further specify calculation of endpoints (as described in Chapter 7).

A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol (i.e. definition or analysis of primary or key secondary endpoint). Any changes to the methods described in the plan will be described and justified in the final clinical study report.

8.1 Statistical design

8.1.1 Sample size

At least 306 g*BRCA*^{mut} patients, confirmed by the centralized test, will need to be randomized as described in Section 12.1.

The primary analysis population for efficacy (incl. primary PFS and OS analyses) constitutes all randomized patients who have a germline *BRCA* mutation per central laboratory results (Myriad USA)

The overall sample size for this study is based on the overall survival endpoint and is determined based on the assumption that niraparib will result in an improvement of 4 months in median overall survival from 9 to 13 months (corresponding to a hazard ratio= 0.69). For a true hazard ratio of 0.69, 265 deaths will provide 80% power at a 1-sided alpha of 0.025. Assuming 10 patients eligible for the primary analysis population for efficacy are enrolled per month, with 306 such patients, 265 deaths are expected to occur approximately 54 months after the first patient enrolled. At the time of the final analysis of PFS (primary endpoint) an interim analysis will be performed on OS, using an O'Brien-Fleming alpha spending function (see 8.3).

Assuming 40% of patients will be randomized on the basis of a local *BRCA* test and assuming that 15% of those patients will be *BRCA* negative by the central test, it is estimated that we will need to randomize a total of 324 patients in order to obtain the required 306 patients in the analysis population. If the average enrollment rate is greater than 11 patients per month during the second year of enrollment, the sample size to achieve the required 265 events may be increased to up to 350 *gBRCA*^{mut} patients in the primary analysis population for efficacy.

PFS analysis in the original design of the BRAVO study was planned when 232 PFS events occur. Assuming the median PFS time is 3 months for physician choice and 6 months for niraparib (corresponding to a hazard ratio=0.50), with 232 PFS events, there would be 99.6% power (1-sided alpha=0.025) to detect a difference from 3 to 6 months in median PFS. Assuming a true PFS treatment hazard ratio of 0.64 (median PFS time of 3 months for physician's choice and 4.68 months for niraparib), the study would have approximately 80% power to detect a difference (1-sided alpha=0.025).

The clinical relevance of the maximum significant HR of 0.759 that could be detected by 232 events was re-evaluated in the current treatment landscape. The assumptions needed to be revised in a way that the statistically significant HR observed in the study is also clinically relevant. Thus, PFS analysis is redesigned to give 80% power to detect an HR 0.6 (equivalent to 3 to 5 months) with a one-sided alpha of 0.025, which will require approximately 137 PFS events to perform the final analysis.

All patients should be recruited before the final PFS analysis is conducted, and therefore the final PFS analysis is to be conducted at approximately 137 events or end of recruitment, whichever occurs later. Patients should be continued to be followed until death even after the final analysis of PFS to assess long-term effects of niraparib.

A gate-keeping strategy (i.e. sequential testing procedure) will be used to test PFS and OS. OS will be tested at a 1-sided alpha of 0.025 only if the final test on PFS is significant at a 1-sided alpha of 0.025. This is motivated by the fact that OS is defined as a key secondary endpoint and such approach allows control of the overall Type I error rate. Note that, as a result of the gatekeeping strategy, the power of the overall analysis of the trial, i.e to detect a HR = 0.6 for PFS and a HR = 0.69 for OS, will be lower than 80%.

One futility interim analysis on the primary endpoint of PFS is planned. This futility analysis will be performed after approximately 93 (68%) of the minimum required total number of PFS events have been recorded. A gamma family beta spending function with a non-binding gamma ($\gamma = -5$) stopping boundary will be used for the futility analysis.

Overall survival (accounting for interim analysis performed at the time of final PFS analysis) and PFS (including futility analysis) sample size calculations were performed using PROC SEQDESIGN in SAS and confirmed with East software.

8.1.2 Randomization and stratifications

Patients will be centrally randomized (for practical details, see chapter on registration / randomization procedure) in a 2:1 ratio (treatment: physician choice). Permuted block randomization will be used for random treatment allocation stratifying by visceral disease (yes vs no), histology (TNBC vs ER/PR positive) and number of lines of prior cytotoxic chemotherapy (not including hormonal therapy) for advanced/metastatic disease (0-1 or 2).

8.2 Statistical analysis plan

8.2.1 Primary and secondary endpoints

Primary endpoint: progression-free survival (PFS) per central review. Refer to Chapter 7 for definition.

Secondary endpoints:

- Overall survival (key secondary efficacy endpoint).
- Determine concordance between g*BRCA*^{mut} tests for the purpose of developing a commercial companion diagnostic test.
- Safety and tolerability, as documented by AEs and laboratory values
- PFS using investigator assessment of progression
- Time to treatment failure
- Response rate and duration of response
- Health-related quality of life: QLQ-C30 and EQ-5D-5L (see chapter 10).
- Subsequent therapies and potential relationships with outcomes
- To assess outcomes by germline mutation *BRCA*1 vs *BRCA*2

8.2.2 Analysis populations

- Intention-to-treat population: All randomized patients with centrally confirmed g*BRCA*^{mut} will be analyzed in the arm they were allocated by randomization.
- Per protocol population (PP): All patients with centrally confirmed g*BRCA*^{mut} , who are eligible, have started their allocated treatment (at least one dose of the study drug(s) in chemotherapy trials) and who do not have protocol deviations that are believed a-priori to significantly impact the interpretation of efficacy results. The PP population will be further described in the SAP.
- Safety population: All patients who have started their allocated treatment (at least one dose of the study medication received)

A patient will be considered to be eligible if he/she did not have any deviation from the patient entry criteria listed in chapter 3 of the protocol. Potential eligibility problems will be assessed by the Clinical Research Physician at time of medical review.

The ITT population is the primary analysis population for all efficacy analyses. For this analysis, patients will be analyzed as randomized.

Efficacy will also be analyzed using the PP population.

The safety population will be the primary analysis population for the safety analyses. Patients will be analyzed as treated, not necessarily by allocated treatment.

8.2.3 Statistical methods

Descriptive statistics will be used to summarize demographics and baseline characteristics.

Medical history, medications used prior to treatment and concomitant medications will be summarized by treatment group.

Analyses of efficacy endpoints are described below. Further details will be provided in the SAP including any sensitivity analyses that may be performed. Primary efficacy analyses will be performed comparing the niraparib arm against the pooled physician's choice arm. Descriptive statistics will also be presented for the individual single-agent therapies (eribulin, vinorelbine, gemcitabine or capecitabine) comprising the physician choice arm.

Unless otherwise stated, statistical tests will be performed at the 1-sided 0.025 significance level. For estimation purposes, 2-sided 95% confidence intervals will be provided in final analyses.

The primary PFS analysis will be performed using a stratified log-rank test for the difference in the distribution of PFS between the niraparib group and the control group (one-sided α-level of 0.025). Randomization factors will be used as the strata in the stratified log-rank test. The following hypothesis will be tested:

H0: $PFS(t)_{physician\ choice} = PFS(t)_{niraparib}$

Ha: $PFS(t)_{physician\ choice} < PFS(t)_{niraparib}$

where PFS(t) represents the progression-free survivorship function at any time t.

Kaplan-Meier estimates for median PFS and OS with the corresponding 2-sided (1-alpha) % confidence intervals will be presented. A non-stratified log-rank test will also be performed to assess the robustness of the primary result. The standard error of the Kaplan-Meier estimates will be computed using the Greenwood formula. Medians - if reached - will be presented with a 2-sided (1-alpha) % confidence interval based on the non-parametric method (Ref. 29).

In addition, Cox proportional hazards model with a term for treatment group will be used to estimate the treatment hazard ratio and its 2-sided (1- alpha) % confidence interval. The settings (covariates, levels of

covariates, and method of covariate selection) of this Cox model will be further described in the dedicated SAP.

8.2.3.1 Key Secondary Endpoint Analyses – Overall Survival

The primary analysis of overall survival will be performed using a stratified log-rank test, stratifying for the factors used for randomization. Kaplan-Meier estimates for median overall survival with the corresponding 95% confidence intervals will be presented. A non-stratified log-rank test will also be performed to assess the robustness of the primary result.

In addition, Cox proportional hazards model with a term for treatment group will be used to estimate the treatment hazard ratio and its 2-sided 95% confidence interval.

8.2.3.2 Secondary Endpoints Analyses

If it is determined that analytic validation alone is not sufficient for bridging between the central and proposed companion diagnostic test (i.e., in the example where the proposed companion diagnostic test is not the companion diagnostic test version of the centralized test), the following analyses will be performed. Concordance of the candidate companion diagnostic test with the centralized *gBRCA* mutation test with respect to identifying $gBRCA^{mut}$ patients will be evaluated using archived study samples. The sensitivity and specificity of the test compared to the centralized test with respect to *gBRCA* status will be determined along with the corresponding 2-sided 95% confidence interval.

The best response (CR, PR, SD or PD) for each patient will be summarized by treatment arm. The overall response rate (ORR = CR+PR) will be summarized by treatment arm along with the corresponding exact 2-sided 95% confidence interval. A chi-square test will be used to compare ORR between the treatment arms. Duration of response will be summarized for the subgroup of patients that obtained objective response (CR or PR) using the Kaplan-Meier method and be displayed graphically where appropriate. The median duration and 2-sided 95% confidence interval for the median will be provided for each treatment arm.

Analyses of investigator-assessed PFS and time to treatment failure will be performed using the primary analysis methodology described above. Censoring rules will be further described in the SAP.

The QLQ-C30 and the EQ-5D-5L will be utilized in this study. The analyses of these endpoints are detailed in chapter 10.

Clinical laboratory parameters, vital signs, and ECGs will be summarized by treatment group and by study visits. Descriptive summary statistics in observed values as well as changes from baseline will be presented. In addition, thresholds of marked abnormalities will be predefined for specific safety parameters. Incidence of marked abnormalities and shift tables will be presented.

8.2.4 Pre-planned sensitivity or exploratory analyses

Supportive analyses including additional sensitivity analyses of the primary endpoint (PFS) will be performed, the details of which will be provided in the SAP.

Subgroups will also be explored for the primary efficacy endpoint based on: age, race, geographic region, ECOG performance status, visceral disease, histology, number of lines of prior cytotoxic chemotherapy (not including hormonal therapy) for advanced/metastatic disease, prior platinum treatment and germline mutation (*BRCA*1 vs *BRCA*2).

8.2.5 Prognostic factor analyses

Cox models will be constructed for PFS and OS, using a backward stepwise method, with a two-sided 0.10 cutoff for selection, and forcing treatment arm to stay in the model.

Evaluation of the prognostic value of biomarkers will initially be performed using univariate Cox proportional hazards and Kaplan-Meier analyses, followed by multivariate Cox proportional hazard models. Additional exploratory analyses may be performed.

8.2.6 Post-treatment analyses

Descriptive summary statistics will be used to summarize post- treatment data (i.e subsequent anticancer therapies and any new malignancy).

8.2.7 Data recoding and display

Frequency tables will be tabulated (by treatment group or otherwise) for all categorical variables by the levels of the variables as they appear on the CRF (with %). Categories with a text field specification will be tabulated as categories and then supplemented by a listing with the following information for the patients fulfilling the condition for the specification (patient id, institution, treatment group, value of the item and text field contents).

Dates relating to events prior to entry will be presented as the delay in days (or weeks, months, or years) between the past event and the date of entry (date of randomization – date of past event + 1) and presented using the median and range. For example, on the randomization checklist, the date of last administration of prior treatment (or the date of first diagnosis of the cancer) will be presented as the time elapsed (in days, weeks, months or years, as appropriate) since the day of the last administration and the date of entry on study (date of randomization – last administration/diagnosis +1).

Other delays (eg. re-treatment delays) are presented as continuous variables using the median and range.

Continuous variables for which a coding system exists (such as for laboratory data) will be recoded into categories (for adverse events, the grading scale specified in the protocol will be used). Whenever no specific scale exists, lab data will be categorized based on the normal range: for example, below the lower normal limit (when appropriate), within the normal range, above the upper normal limit (ULN) and the degree to which it is above the ULN (for example > 2.5 x ULN, > 5 x ULN, > 10 x ULN). For laboratory data, the nadir is generally displayed. The nadir in a given cycle is the lowest laboratory value in that cycle; the overall nadir for a patient is the lowest laboratory value among all cycles.

Other continuous variables (for example age, dose …) will be presented using the median and range (minimum, maximum).

Dose intensity calculations will be performed according to specification in the dedicated SAP.

If appropriate, continuous data may also be presented in categories (for example, age may also be grouped in decades)

8.3 Interim analysis

As outlined in Section 8.1.1, one interim futility analysis is planned for the PFS endpoint. The purpose of this interim analysis is to allow early stopping of the study for futility based on PFS data and to assess the safety of the niraparib regimen. The interim analysis is planned after 93 PFS events (68%) have been documented. It is anticipated that at this time, approximately 164 patients will have been randomized.

A gamma family beta-spending function with a non-binding gamma (γ=-5) stopping boundary based on the actual number of PFS events at the time of interim analysis data cutoff will be used for the interim futility analysis of PFS. Non-binding for futility implies that the futility boundary is constructed in such a

way that it can be overruled without inflating the Type I error. There is no intention of stopping early for efficacy at these interim analyses therefore no alpha spending is incorporated.

An interim analysis of overall survival is planned at the time of the final PFS analysis. The interim analysis will utilize O'Brien-Fleming type boundaries derived from the Lan DeMets alpha spending function based on the actual number of deaths observed at the time of the interim analysis.

8.4 End of study

End of study occurs when all of the following criteria have been satisfied:

1. Thirty days after all patients have stopped protocol treatment
2. The trial is mature for the analysis of overall survival as defined in the protocol
3. The database has been fully cleaned and frozen for this analysis

9 Data Monitoring

Safety data are reviewed within the EORTC Headquarters on a regular basis as part of the Medical Review process. Problems which are identified will be discussed with the Study Coordinators and the Sponsor who will take appropriate measures. Safety information will also be included in trial status reports which serve as a basis of discussion during Group meetings. These reports will be made available to investigators participating in the study.

An independent data monitoring committee (IDMC) will be established to provide independent review and assessment of the efficacy and safety data in a systematic manner and to safeguard the interest and safety of the participating patients in the study. The IDMC will be comprised of at least 3 independent individuals, including one biostatistician and 2 physicians. The IDMC is tasked with making a recommendation to the Sponsor based on their assessment of efficacy and safety information to continue or stop the trial. A futility analysis is planned after 93 PFS events (see Section 8.3). If the results cross the prespecified futility boundary, the IDMC may recommend stopping the study. The membership, key responsibilities of the IDMC, and the corresponding procedures will be defined in an IDMC charter.

The Independent Data Monitoring Committee (IDMC) will review all safety problems identified by the EORTC Headquarters for which an advice is sought. In principle, no access to outcome data is necessary for safety reviews. However, the IDMC will also provide recommendations as an initial step in phase III trials to advise if a full review of all study data and endpoints is needed.

No efficacy results will be presented at EORTC/BIG Group meetings or elsewhere before the trial is closed to recruitment and the data are mature for the analysis of the primary endpoint, unless recommended otherwise by the IDMC.

10 Quality of life assessment

10.1 Rationale

Health related quality of life (HRQoL) is a multidimensional construct, which can be defined as a state of general well-being reflecting physical, psychological, and social well-being and the impact of the disease and/or treatment related symptoms on daily-life functioning. The patient's subjective perspective is an inherent component of HRQoL and is therefore best assessed via self-administration.

Reducing mortality and morbidity is still the most important factor in cancer clinical research. Nevertheless, issues such as reducing side effects, symptom relief and improving patients' satisfaction have also become relevant parameters in the evaluation of medical strategies. Cancer treatments may

produce adverse effects and diminish a patient's quality of life even when survival is extended. Progress in the acceptance of new cancer therapies is sometimes critically dependent on their HRQoL consequences.

Given the poor overall prognosis of the study population, improvement of the well-being during the remaining (progression-free) survival is an important factor for the patient.

10.2 Objective

In the present study, HRQoL is a secondary endpoint. The hypothesis is that Niraparib will result in improved progression-free survival and overall survival compared to the standard arm which may result in a beneficial effect on HRQoL.

It is expected that deterioration in HRQoL (both symptoms and functioning) is inevitable in almost all patients eventually due to the metastatic disease. The primary working hypothesis is that Niraparib will cause a later occurrence of the deterioration. Therefore the endpoint will be to compare the time to HRQoL deterioration between the both arms.

The specific HRQoL domains of interest for HRQoL deterioration are:

- Specific symptoms: fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation and diarrhea.
- Specific functionality: physical functioning, role functioning, social functioning and emotional functioning.
- General health.

Time to HRQoL deterioration defined in section 10.5 will be compared between the two treatment arms.

Secondary HRQoL hypotheses of interest are:

- Niraparib will lead to less severe side effects.
- Niraparib will lead to less patients experiencing a clinical relevant HRQoL deterioration.

10.3 HRQoL instrument

HRQoL will be assessed with various instruments to capture the various HRQoL domains as specified above.

General quality of life domains will be assessed via the EORTC Quality of Life Questionnaire (QLQ-C30) version 3. This instrument is composed of multi-item and single-item scales. These include five functional scales (physical, role, emotional, social, and cognitive), three symptom (fatigue, nausea and vomiting and pain) and a global health status/QoL scale and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). All scales and single items meet the standards for reliability. The reliability and validity of the questionnaire is highly consistent across different language-cultural groups (Ref. 31). The average time to complete the questionnaire is approximately 10 minutes.

The EORTC QLQ-C30 version 3 has been translated in over 50 languages according to a standardized translation procedure.

The domains of interest as specified in the previous paragraph are covered by the QLQ-C30.

A breast cancer specific module (BR23) to complement the QLQ-C30 exists. It is meant for use among breast cancer patients varying in disease stage and treatment modality (i.e. surgery, chemotherapy, radiotherapy and hormonal treatment). However, as the module relates mainly to symptoms and functionality related to surgery and hormonal treatment, it does not fit the study objectives and is therefore not included (Ref. 32).

English versions of the HRQoL Instrument(s) and the EORTC "Guidelines for administration of questionnaires" are included in Appendix D, Appendix F and Appendix I.

10.4 Study design

HRQoL questionnaires must be filled out at the hospital when patients come for a scheduled visit according to the EORTC "Guidelines for administration of questionnaires" (see Appendix D). The pre-treatment questionnaires must be filled within 4 weeks before randomization. Subsequent questionnaires are filled in every 2 cycles (i.e., every 6 weeks ± 7 days) for the first 12 months while on-treatment and every 3 months while off-treatment. The on-treatment schedule coincides with the imaging schedule. Collection of HRQoL data will be limited to the first 12 months after randomization. Beyond that time, the absolute number of patients available is expected to be too low to allow reliable analyses and therefore data collection is no longer justified.

Master copies of the HRQoL questionnaires will be sent to the institutions. Additional copies or translations can be provided upon request via the EORTC contact person. The clinical report forms will include a question whether the HRQoL forms have been filled in, and if not, the reason why. The questionnaire will be handed out to the patients by the investigator or a study nurse prior to seeing the doctor for clinical evaluations. The patient should complete the questionnaires by her/himself in her/his own language during the visit to the outpatient clinic as completely and accurately as possible. It is recommended that a key person (e.g. research nurse) at each center should be responsible for questionnaire data collection in order to optimize the compliance of the patient and to ensure the completeness of the data.

During the study, compliance with completing questionnaires will be investigated at each time point. The compliance of the HRQoL assessments will also be reviewed twice a year and will be part of the descriptive report.

10.4.1 HRQoL schedule

The time windows for eligible HRQoL assessments will be as follows:

Assessment	Time window
Baseline	Can be completed before or on the day of randomization itself but no earlier than 4 weeks before.
On protocol treatment: every 2 cycles (i.e., every 6 weeks).	To be completed every 2 cycles (i.e., every 6 weeks ± 7 days from randomization) while on protocol treatment irrespective of treatment delays. Eligible time window is up to 1 week before or 1 week after the target assessment date.
Off protocol treatment: every three months	To be completed every 3 months after end of protocol treatment. Eligible time window is up to 1 month before or 1 month after the target assessment date.

⚠ **Important note: HRQoL forms will be collected regardless of progression status. HRQoL data collection will be limited to the first 12 months after randomization.**

10.5 Statistical considerations

Data from the EORTC QLQ-C30 will be scored according to the algorithm described in the EORTC scoring manual. All scales and single items are scored on categorical scales and linearly converted to 0-100 scales.

The primary HRQoL endpoint considered relevant for this study is time to HRQoL deterioration (TTQ). TTQ is defined as the time from randomization to the first observed of the following events:

- Death
- Progression
- Deterioration in any of the following QLQ-C30 scales: fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, physical functioning, role functioning, social functioning and emotional functioning or global health/QoL scale. Patients are considered to have deteriorated for a given scale if a worsening of 10 points at any time point after baseline is observed. A change of 10 points or more is considered to be clinically relevant (Ref. 33).

Patients who have not experienced an event at the time of analysis will be censored at the time of the last completed HRQoL assessment. All patients who have a baseline and at least one follow- up HRQoL assessment will be included in the TTQ analysis.

TTQ will be calculated using Kaplan–Meier method and compared using the two-sided log-rank test across the randomized arms. TTQ will be described using medians and hazard ratio with 95% confidence intervals (CIs).

In order to assess the robustness of the results the following sensitivity variants to the TTQ endpoint will be investigated:

- TTQ1 – time from randomization to death, treatment discontinuation or deterioration in any of the selected QLQ-C30 scores. (treatment discontinuation instead of progression)
- TTQ2 – time from randomization to death or deterioration in any of the selected QLQ-C30 scores. (excluding progression as event)
- TTQ3 – time from randomization to deterioration in any of the selected QLQ-C30 scores. (excluding both death and progression)
- TTQ4 – time from randomization to death, progression or deterioration in any of the following QLQ-C30 scores: fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea. (limit only to symptom deterioration).

These alternative formulations serve only to investigate the robustness of the main results. They do not replace the primary endpoint. In case a significant difference is found in TTQ, the endpoint will be split up in its various events (death, progression and the selected scales) in order to investigate the treatment effect on each of these components.

In addition the following summary statistics per patient will be calculated for the secondary objectives as sensitivity analyses and to complement the interpretation of the time-to-event model:

- average change from baseline during the on protocol treatment period.
- average change from baseline during the off protocol treatment period.
- 10 point worsening from baseline during the on protocol treatment period (y/n).
- 10 point worsening from baseline during the off protocol treatment period (y/n).

These statistics will be compared between the two groups using non-parametric Wilcoxon rank test (for the summary statistics based on average change) or Fisher exact test (for the summary statistics based on 10

point worsening). Results will be summarized by the appropriate statistic estimation and corresponding 95% CI interval. For the two binary summary statistics, missing data due to attrition will be imputed as worsening for sensitivity purposes.

All available scales from the QLQ-C30 will be summarized per treatment arm on an exploratory basis.

10.5.1 Missing data

Missing data is a potential major source of bias in HRQoL assessment.

In order to check the potential impact in the study, the compliance mechanism will be investigated prior to initiating the HRQoL analysis. HRQoL compliance at a certain assessment time T_i will be defined as the ratio of the number of valid forms received over the number of forms expected at that time:

$$Compliance(T_i) = \frac{valid\ QoL\ forms\ within\left[L_i\ , U_i\right]}{QoL\ expected\ at\ T_i}$$

where L_i and U_i are the lower and upper bound of the time windows associated with T_i. HRQoL forms will be considered as invalid if no validated completion date was provided, the completion date falls outside of the time windows, mulitple HRQoL forms were received during the time window (the form closest to the assessment date will be kept), a wrong version or wrong translation of questionnaire was used or the form was filled out by an unauthorized person. QoL forms are expected at T_i for each patient that was within the QoL assessment schedule; ie. alive at time T_i. Reasons for non-completion if an assessment was missed will be collected via the CRFs. Characteristics of patients with and without valid HRQoL data will be compared and trends over time per dropout pattern will be investigated. Model building will be used in order to investigate whether the compliance mechanism is linked to selected prognostic variables.

Once the main analysis is completed, sensitivity analyses will be undertaken to verify the robustness of the results vis-à-vis the missing data.

In case overall compliance is deemed too low (< 50%), only an exploratory analysis will be performed in lieu of the main analysis.

10.6 Health Economics

In addition, the EQ-5D-5L will be administered at same times as the HRQoL instruments. The EQ-5D-5L is a general health status and health utility measure (Ref. 34). It measures 5 dimensions of health state: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression each assessed by a single question on a five-point ordinal scale. It also includes a visual analogue scale (VAS) to measure health state. The EQ-5D-5L will be included in this study for the purpose of the computation of utilities that can be used in health economic studies. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability (Ref. 35). In addition, validated translations for this instrument are available for a number of countries and languages.

The outcomes of the EQ-5D-5L will be used to define distinct health states with corresponding utilities for use in economic modeling evaluations.

11 Pharmacokinetics

5 ml blood samples into EDTA tube for measurements of plasma levels of niraparib will be obtained on cycle 1/day 1 and on cycle 2/day 1 at the following time points: 0 (predose within 30 minutes) and 2 hours post dose. In subsequent cycles, a blood sample for measurements of plasma levels of niraparib will be obtained on cycle 4/day 1 predose (within 30 minutes) only.

The time of last dose prior to PK blood draw should be recorded.

Model predicted AUCs will be derived. Parameters of interest include AUC, Cmin, Cmax, CL/F, Vz/F, AUCss, Cminss, Cmaxss.

Complete instructions for collection, processing, shipping, and handling are detailed in the Laboratory Manual, which will be provided to the sites prior to authorization.

12 Translational research

12.1 *BRCA* 1/2 mutation analysis for patient enrolment

12.1.1 Objective

Before randomization, patients will be screened centrally for germline *BRCA* mutation status. Patients with *BRCA*1 or *BRCA*2 mutation that is considered deleterious or suspected deleterious (include those mutations or translocations termed "deleterious" or "suspected deleterious" according to Myriad reporting) by analysis at an either local or central laboratory will be deemed eligible to enter the trial. On study central confirmation of *BRCA* status will be performed for those patients who were enrolled based on either a previous Myriad test or a local test.

12.1.2 Material and methods

7 mL of whole blood will be collected in EDTA tube.

Central testing under the context of this protocol may be performed **at any time prior to randomization**.

BRCA DNA mutation analysis will be performed centrally by certified Myriad Genetic Laboratories (Myriad Genetic Laboratories, Salt Lake City, UT, USA) by using the validated, sequencing-based, BRAC*Analysis*® test. Patients who have a prior test done by Myriad or any other local test may enroll in the study but on study central confirmation of BRCA status will be performed at Myriad Genetic Laboratories , Salt Lake City, UT, USA .

Further details on the test, including definition of "deleterious" or "suspected deleterious" mutations, analytical specificity and sensitivity, can be found in the publicly available "BRAC*Analysis*® Technical Specifications" and will be included in the final statistical analysis plan.

12.2 Concordance of the companion diagnostic test for determination of germline *BRCA* 1/2 mutations

12.2.1 Objective

Additional mutation analysis testing will be performed for the purpose of developing a commercial companion diagnostic test.

The concordance of the candidate companion diagnostic test with the centralized *gBRCA* mutation test with respect to identifying *gBRCA* mutated patients will be evaluated using a separate blood sample.

The sensitivity and specificity of the companion diagnostic test to the centralized validated test with respect to g*BRCA* status will be determined along with the corresponding 95% confidence intervals. Assuming the true sensitivity is 95%, with 306 samples, there is 99% probability that the width of the 95% confidence interval is within 5%. Assuming the true specificity is 95%, with at least 125 samples, there is 90% probability that the width of the 95% confidence interval is within 5%.

In addition, the effect of treatment on PFS will be evaluated by cohort (as identified by the candidate companion diagnostic test) using the analysis methodology described for the primary PFS analysis. If a companion diagnostic is not needed or it is determined that analytic validation is sufficient for bridging the

centralized test to the candidate companion diagnostic test, the above mentioned sensitivity, specificity and PFS analyses may not be performed.

12.2.2 Material and methods

7 mL of whole blood will be collected in EDTA tube at the same time that the blood sample for central testing is taken.

Further analytical and methodological details will be included in the final statistical analysis plan.

12.3 Evaluation of predictive biomarkers related to efficacy and safety of niraparib

The overall aim is to explore molecular mechanisms mediating response and resistance to niraparib. Such an approach will be through the analysis of DNA and mRNA alterations.

12.3.1 Tumor biomarkers

12.3.1.1 Objective

Mutation of germline *BRCA* leads to malignancies deficient in *BRCA* and homologous recombination capabilities, and appears to be a predictive marker for responsiveness to niraparib and other PARP inhibitors. Changes independent of *BRCA* mutation within malignancies are known to cause phenotype of homologous recombination deficiency. This study will look at somatic markers of DNA repair. Other biomarkers that are postulated to be related to efficacy of niraparib will also be evaluated in the context of this trial.

12.3.1.2 Material and methods

- **1 Formalin-fixed, paraffin-embedded (FFPE) tumor block** (preferred) or 20 slides of 5 micron thickness from **archival** primary tumor or a metastatic lesion will be collected at the screening visit prior to enrollment or after randomization (during cycle1).
- **Optional**: for patients with accessible metastatic lesions, repeat biopsies at baseline and at progression are requested as an option.
- The following material shall be submitted:
  - 1-2 FFPE cores
  - Frozen tumor tissue: 2-4 snap frozen cores embedded in optimal temperature cutting (OCT) compound

A minimum of 1-2 frozen and 1-2 FFPE cores using a 14-gauge or smaller diameter spring-loaded biopsy needle will be taken. Two biopsies are the minimum number with at least one frozen and one FFPE and then the next priority should be a frozen sample.

For new tumor tissue biopsies and archival samples (primary tumor and metastatic lesions), evaluation of genome landscape scoring measures of homologous recombination deficiency such as homologous recombination deficiency (HRD) score, assessment of loss of heterozygosity (LOH), reversion mutation analysis, methylation of alleles, transcriptional and protein expression profiles of DNA damage response (e.g. loss of 53BP1 expression in *BRCA*1 carriers) will be studied.

Tumor samples (both primary and metastatic) may be deep sequenced to look at clonal evolution, co-existent mutations and mutation profiles using next generation sequencing technologies.

Serial biopsies will be assayed for the changes that occur during progression and resistance to the niraparib. These will be also compared with the primary tumor or prior sample collected.

If enough RNA can also be extracted, gene expression of these tumors may be evaluated using a genome-wide, deep sequencing technology or by alternative methods.

Significant alterations identified with these technologies can also evaluated using circulating plasma DNA.

Further analytical and methodological details will be included in the final statistical analysis plan.

12.3.2 Assessment of circulating plasma DNA

12.3.2.1 Objective

Plasma of cancer patients sometimes contains cell-free tumor DNA that can carry information on tumor mutations and tumor burden. This information may be useful as a minimally-invasive way of monitoring advanced disease using cancer genetic alterations (mutations, rearrangements) that are specific to the individual's tumor. This information may allow us to track and monitor tumor dynamics during the disease course as well emergence of new clones (ie resistance mechanisms). The aim of the correlative deep sequencing is to understand the molecular landscape (mutations, rearrangements and copy number changes) associated with *BRCA* mutant tumors as well as response or resistance to the study therapy.

12.3.2.2 Material and methods

10 mL whole blood will be collected in an EDTA tube for plasma preparation **at baseline, 6-weeks** (cycle 3/day 1) **and at study termination (due to progression or any other reason)**.

Individual mutations may be assessed using technologies such as Sequenom Mass Spectrometry or deep sequencing.

Further analytical and methodological details will be included in the final statistical analysis plan.

12.3.3 Humoral immune response monitoring

12.3.3.1 Objective

There is significant evidence of increase in both humoral and cell mediated immune response and circulating tumor antigen expression in highly genome unstable triple negative (Ref. 36) and *BRCA* mutation (Ref. 37) associated breast cancer, in particular where the immune infiltrated medullary and atypical medullary variants of breast cancer are enriched (Ref. 38). There is also evidence reviewed in that immunogenic cell death can be responsible for a significant proportion of the therapeutic effect of agents that impact the DNA damage response in breast cancer (Ref. 39).

The objective is to understand the drivers of immunogenic cell death in a disease with significant evidence of cancer antigen and immune cell up-regulation and how this might affect the response to PARP inhibitor.

12.3.3.2 Material and methods

Aliquots of serial plasma samples collected at baseline, 6-weeks and at study termination (due to progression or any other reason) (see section 12.3.2.2) will be assessed for humoral immune markers.

Further analytical and methodological details will be included in the final statistical analysis plan.

12.3.4 Mutation profile screening test for selected myeloid- associated genes

At Screening and treatment discontinuation as well as for any suspected MDS/AML case, blood samples (5 ml EDTA) will be collected to evaluate mutations for selected myeloid- associated genes. This test is a PCR- based next generation sequencing assay that screens DNA from leukocytes for the presence of mutations or insertion/deletion in commonly altered areas of 30 genes. The panel includes genes that are associated with AML, MDS or myeloproliferative neoplasias, including ASXL1, CEBPA, DMNT3A FLT3, IDH1, IDH2, NPM1, RUNX1, TET2 and TP53. These samples for mutation screening test will be stored for evaluation (of the selected myeloid- associated genes mutations) if necessary for assessing niraparib- related risk for MDS/AML (e.g the patient develops MDS/ AML). Mutation profile before and after study treatment will be compared to determine whether any mutations were present prior to study treatment.

Details on blood sample collection can be found in the Laboratory Manual.

12.3.5 Summary of sample collection

Type of sample	Local storage conditions	Amount of sample	Collection time points	Purpose
Mandatory				
Blood	Room temperature	7mL	Any time prior to randomization	Central *BRCA* 1/2 mutation analysis
Blood	Room temperature	7mL	Any time prior to randomization	Concordance of companion diagnostic test
FFPE tumor tissue	Room temperature	Archival block or 20 unstained slides	Screening	Predictive biomarkers
Blood	Room temperature	5 ml	Any time prior to randomization, end of treatment and for any highly clinically suspected MDS/AML case during treatment or follow- up period.	Mutations of selected myeloid- associated genes.
Blood	Frozen at -80°C(or store short term at -20°C for max. 3 months prior to transfer to -80°C for long term)	10mL	Screening, 6 weeks and at study termination (due to progression or any other reason).	Circulating plasma DNA and humoral immune response
Optional				
FFPE tumor tissue	Room temperature	1-2 core needle biopsies	Screening and at progression	Predictive biomarkers
Snap frozen tumor tissue embedded in OCT	Frozen at -80°C	2-4 core needle biopsies	Screening and at progression	Predictive biomarkers

12.4 Routing and banking of human biological material

Blood samples taken for the central testing will be sent to Myriad Genetic Laboratories (USA) prior to randomization.

Blood samples taken for myeloid neoplasm mutational screening will be shipped to and stored at QUEST Laboratories (USA).

Other samples will be shipped to central repositories (based in USA for US sites and in Europe for European sites) as promptly as feasible on day of draw or 6-monthly.

From here, samples will be redistributed to other laboratories performing the research described above (see chapter 12.5 on General Principles for HBM collection).

If tumor blocks are provided, they will be promptly and diligently returned after sections are cut (assuming sufficient remaining tissue in block) to the originating pathology department upon request.

Complete instructions for collection, processing, shipping, and handling are detailed in the Laboratory Manual.

12.5 General principles for human biological material (HBM) collection

Human biological material (HBM) collection involves the collection and storage of biological material, residual biological material or derivatives in compliance with ethical and technical requirements.

Biobanking refers to the chain of procedures that encompass the life cycle of the biological material, e.g. from collection, shipping to long term storage and use, and may also be subject to local regulation and/or national/international legislation.

In this study, biological material will be centralized and stored in central repositories (based in USA for US sites and in Europe for European sites). From here, the biological material will be used or distributed to the other research laboratories involved in the translational research (TR) projects specified in this protocol or defined in the future.

Collection, storage and access to HBM for use in research shall be in accordance with the specific policy and charter developed for the study.

Translational research proposals not outlined in this protocol will be assessed by the study steering committee (as defined in the related study charter) for merit and feasibility. Academic and sponsor proposals to access the data to explore hypotheses will also be considered by the study steering committee.

12.6 Data storage, transfer and development of statistical analysis plan

The translational projects will be the result of the work of TESARO, the collaborating groups and central laboratories. Statistical analysis plan will be written before starting any analysis of samples and will specify the analytical and methodological details. Clinical and patient-reported outcome data will be collected and stored in the EORTC clinical database and biological investigational data will remain with each party conducting the research. Transfer of data will be realized according to applicable study policy and charter for access to study data and biological material.

13 Publication policy

Publications and oral presentations of any results from the study shall be in accordance with accepted scientific practice, academic standards and customs and in accordance with the specific dedicated policy developed for the study. This policy will be made available to all investigators/sites and groups participating in the study.

The final publication of the main trial results will be written by the Study Coordinators on the basis of the final analysis performed at the EORTC Headquarters and published in a major scientific journal.

14 Investigator authorization procedure

Investigators will be authorized to register and/or randomize patients in this trial only once they have returned the required documents to PAREXEL. Documents might include, but are not limited to the following:

- The updated signed and dated Curriculum Vitae of the Principal Investigator
- The (updated) list of the normal ranges, for their own institution signed and dated by the head of the laboratory. Please make sure normal ranges are provided also for those tests required by the protocol but not routinely done at the investigator's institution.
- A Study Agreement between the sponsor and Principal Investigator, stating that the investigator will fully comply with the protocol and including a statement on any conflict of interest that may arise due to trial participation. This may include an estimate of yearly accrual.
- A copy of the favorable opinion of the local or national (whichever is applicable) ethics committee mentioning the documents that were reviewed (including the version numbers and version dates of all documents). A list of all members of the ethics committee is also requested.
- A copy of the translated and adapted (according to all national requirements) Patient Information / Informed Consent sheet. Version numbers and dates must be clearly stated on each page.
- The signature log-list of the staff members with a sample of each authorized signature and the indication of the level of delegations.
- The full name, address, phone numbers and e-mail address of the local pharmacist who will be responsible for the trial medication.
- An accreditation, a certification, an established quality control / external quality assessment or another validation should be provided for the own laboratory.

The center specific applicable list of required documents will be included in the protocol activation package, with proper instructions as required by this protocol, your group and / or the applicable national law.

The new investigator will be added to the "authorization list", and will be allowed to register/randomize patients in the trial as soon as

- All the applicable documents are available at PAREXEL.
- All applicable national legal and regulatory requirements are fulfilled.

Patient registration/randomization from centers not (yet) included on the authorization list will not be accepted.

15 Patient randomization procedure

Patient randomization will only be accepted from authorized investigators (see chapter on “investigator authorization procedure").

A patient can only be randomized after verification of eligibility. Both the eligibility check and randomization must be done before the start of the protocol treatment.

Patients should be registered directly on the **EORTC online randomization system** (ORTA = online randomized trials access), accessible 24 hours a day, 7 days a week, through the internet. To access the interactive randomization program, the investigator needs a username and a password (which can be requested at http://orta.eortc.be/).

In case of problems investigators can phone the EORTC Headquarters from 9.00 am to 5.00 pm (Belgian local time) from Monday through Friday to randomize patients via the EORTC call center. Randomization via the phone is not available on Belgian holidays. A list of these holidays is available on the EORTC web site (http://orta.eortc.be/) and it is updated annually.

Through Internet:	http://orta.eortc.be/
In case of problems randomization by phone:	PPD

15.1 Registration procedure for screening (step 1)

STANDARD INFORMATION REQUESTED:

- EORTC institution number
- EORTC protocol number
- step number: 1
- name of the responsible investigator
- patient's code (*maximum 4 alphanumerics*)
- patient's birth date (*day/month/year*)

PROTOCOL SPECIFIC QUESTIONS:

- confirmed HER2-negative breast carcinoma
- date of written informed consent (*day/month/year*)

At the end of the procedure, a patient sequential identification (SeqID) number will be assigned. This number will allow the identification of the patients in the VISTA/Remote Data Capture system (VISTA/RDC) that will be used to complete the Case Report Forms.

15.2 Eligibility checklist (step 2)

Patient randomization will only be accepted after patient has been registered (step 1).

A patient can only be randomized after verification of eligibility. Randomization must be done before the start of the protocol treatment.

An exhaustive list of questions to be answered during the randomization procedure is included in the eligibility checklist, which is part of the case report forms.

STANDARD INFORMATION REQUESTED:

- EORTC institution number
- EORTC protocol number
- step number: 2
- name of the responsible investigator
- patient's code (maximum 4 alphanumerics)
- patient's birth date (day/month/year)

PROTOCOL SPECIFIC QUESTIONS:

- all eligibility criteria will be checked
- stratification factors
- physician's choice of intended treatment for control arm
- date foreseen for protocol treatment start

Once eligibility has been verified, the treatment arm will be randomly (2:1) allocated to the patient.

16 Forms and procedures for collecting data

16.1 Case report forms and schedule for completion

Data will be reported on the **electronic CRFs specifically designed by the EORTC Headquarters for this study**, with the exception of the Quality of Life form (EORTC QLQ-C30), Health questionnaire form (EQ-5D-5L), the SAE form and the Pregnancy notification form which are paper CRFs.

Copies of the Quality of Life and Health questionnaire forms should be sent directly to the EORTC Headquarters by one of the following means:

- By regular post to the EORTC Headquarters:

Breast Group Data Manager
EORTC Headquarters
Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique

SERIOUS ADVERSE EVENTS AND PREGNANCY NOTIFICATION FORMS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL (see chapter on Reporting Serious Adverse Events).

A. Before the treatment starts:

- The patient must be registered and randomized through your data center.
- The electronic CRFs, to be completed for a patient, are available on the VISTA/RDC website one day after the registration on http://rdc.eortc.be/ or on http://www.eortc.org in the section for investigators.

The paper CRF(s) will be made available to the institution at the time the institution is authorized.

B. During/after treatment

The list of forms to be completed for this study and their submission schedule are available on the VISTA/RDC website and are also described in the "guidelines for completion of case report forms" that are provided to each participating investigator.

ALL Forms must be electronically approved and sent by the responsible investigator or one of his/her authorized staff members with the exception of the paper Quality of Life and Health questionnaire form (no signature needed).

16.2 Data flow

The case report forms must be completed electronically, with the exception of the paper forms (the Quality of Life forms, Health questionnaire, SAE form and pregnancy notification form if applicable), dated and signed by the investigator or one of his/her authorized staff members as soon as the requested information is available.

The list of staff members authorized to sign case report forms (with a sample of their signature) must be sent to the EORTC Headquarters by the responsible investigator before the start of the study. To enter the RDC system, the investigator or authorized staff member needs to use the same username and password that are used to access the interactive randomization program (ORTA).

In all cases, it remains the responsibility of the principal investigator to check that data are entered as soon as possible and that the (electronic) forms are filled out completely and correctly. The EORTC data manager will subsequently apply the corrections into the database.

The EORTC Headquarters will perform extensive consistency checks on the CRFs and issue queries in case of inconsistent data. The queries for the electronic forms will appear in the VISTA/RDC system and must be answered there directly.

If an investigator (or an authorized staff member) needs to modify a CRF after the form has been electronically sent to the EORTC Headquarters, he/she should create a request for data correction in the VISTA/RDC system.

The data corrections will appear in the VISTA/RDC system and the EORTC data manager will subsequently apply the corrections into the database.

When satellite institutions are involved all contacts are done exclusively with the primary institution, for purposes of data collection and all other study related issues.

More details on the data flow and related monitoring activities can be found in the Guidelines for completion of Case Report Forms.

17 Reporting of Serious Adverse Events

ICH GCP and the EU Directive 2001/20/EC require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

17.1 Definitions

These definitions reflect the minimal regulatory obligations; specific protocol requirements might apply in addition.

AE: An **Adverse Event** is defined as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment”. An adverse event can therefore be any unfavorable and unintended

signs (such as rash or enlarged liver), symptoms (such as nausea or chest pain), an abnormal laboratory finding (including results of blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment, whether or not considered related to the investigational medicinal product.

AR: An **Adverse reaction of an investigational medicinal product** is defined as "any noxious and unintended response to a medicinal product related to any dose administered".

All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

UAR: An **Unexpected Adverse Reaction** is "any adverse reaction, the nature, or severity of which is not consistent with the applicable product information" (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for a marketed product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

Severity: The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe, or as described in CTC grades); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

SAE: A **Serious Adverse Event** is defined as any untoward medical occurrence or effect in a patient, whether or not considered related to the protocol treatment, that at any dose:

- results in death
- is life-threatening (i.e. an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- requires inpatient hospitalization or prolongation of existing patient hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is a medically important event or reaction (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above). NOTE: Any new malignancy will be monitored and must be reported as serious adverse event regardless of the treatment arm the subject is in. This includes any new malignancy occurring at any time for the duration of the study. Documentation on the diagnosis of the new malignancy must be provided at the time of reporting as a serious adverse event (e.g., any confirmatory histology or cytology results, X-rays, CT scans, radiology reports with the conclusions summary in English, etc.). Additionally, new malignancy should also be reported on the eCRF.
- Medical and scientific judgment should be exercised in deciding whether other situations should be considered. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

SAR: A **Serious Adverse Reaction** is defined as any SAE which is considered related to the protocol treatment.

SUSAR: Suspected Unexpected Serious Adverse Reaction.

SUSARs occurring in clinical investigations qualify for expedited reporting to the appropriate Regulatory Authorities within the following timeframes:

- Fatal or life-threatening SUSARs within 7 calendar days
- Non-fatal or non-life-threatening SUSARs within 15 calendar days

Inpatient hospitalization: a hospital stay equal to, or greater than, 24 hours.

Second primary malignancy is one unrelated to the treatment of a previous malignancy (and is NOT a metastasis from the previous malignancy).

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

17.2 Exceptions

The following situations do not need to be reported as SAEs:

- Elective hospitalization for pre-existing conditions that have not been exacerbated by trial treatment.
- A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated.
- A hospitalization planned for protocol related treatment or protocol related procedure as per institutional standard timelines.
- Social and/or convenience admission to a hospital.
- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an (S)AE .
- Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation, overdose without occurrence of an adverse event).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

By EORTC convention, clinical events related to the primary cancer being studied or to the primary cancer progression are not to be reported as SAEs, even if they meet any of the seriousness criteria from the standard SAE definition, **unless** the event is more severe than expected and therefore the investigator considers that their clinical significance deserves reporting.

17.3 Severity assessment

The severity of all AEs (serious and non-serious) in this trial should be graded using CTCAE v4.0 www.eortc.org\investigators-area\ctc

17.4 Causality assessment

The Investigator will assess the causality/relationship between the study drug and the AE. One of the following categories should be selected based on medical judgment, considering the definitions and all contributing factors:

- Related: A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration, and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment should be clinically plausible.

- Likely related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other drugs or chemicals.
- Unlikely to be related: A clinical event, including laboratory test abnormality, with a temporal relationship to treatment administration which makes a causal relationship improbable, or in which other drugs, chemicals or underlying disease provide likely explanations.
- Unrelated: A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. Typically explained by extraneous factors (e.g., concomitant disease, environmental factors or other drugs or chemicals).

The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the protocol treatment will be considered and investigated.

The decision will be recorded on the SAE form and if necessary the reason for the decision will also be recorded.

17.5 Expectedness assessment

The expectedness assessment is the responsibility of the sponsor of the study. The expectedness assessment will be performed against the following reference documents:

- Niraparib: Investigator's Brochure.
- Eribulin: Summary of Product Characteristics
- Vinorelbine: Summary of Product Characteristics
- Gemcitabine: Summary of Product Characteristics
- Capecitabine: Summary of Product Characteristics

17.6 Reporting procedure for investigators

This procedure applies to all Serious Adverse Events (SAEs) occurring from the time a subject is registered until 30 days after last protocol treatment administration (or up to initiation of new anticancer therapy, whichever is earlier) and to any SAE that occurs outside of the SAE detection period (after the 30-days period/initiation of new anticancer therapy), if it is considered to be at least likely related to the protocol treatment or study participation.

Registration till 30 days after last protocol treatment administration(or up to initiation of new anticancer therapy, whichever is earlier):	All SAEs
From day 31 after last protocol treatment administration/initiation of new anticancer therapy, (whichever is earlier):	Only related SAEs

Any new malignancy should also be reported in expedited way on a SAE form with the appropriate seriousness criteria!

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (e.g., hospital reports, consultant reports, autopsy reports etc.), with the patient's personal identifiers removed. All relevant information obtained by the Investigator through review of these documents will be recorded and faxed within 24 hours of receipt of the information.

In order to be compliant with regulatory reporting requirements, all initial SAE reports should always include the following minimal information:

- Name of person sending the report (i.e., name, address of Investigator)
- Patient identification (screening/randomization number, initials, NOT patient name)
- Protocol number
- Description of SAE
- Causality assessment, if possible

All points on the SAE form should be covered in the initial report. In addition, all events must be documented in the AE eCRF.

All reporting must be done by the principal investigator or authorized staff member (i.e. on the signature list) to confirm the accuracy of the report.

All SAE data must be collected on the study-specific SAE form.

All SAEs must be reported immediately and no later than 24 hours from the time the investigator or staff became aware of the event.

All SAE-related information needs to be provided in English.

All additional documents in local language must be accompanied by a translation in English, or the relevant information must be summarized in a follow-up SAE report form.

Investigators must fax or e-mail (scan) all SAE-related information to:

EORTC Pharmacovigilance Unit:

Fax No. PPD
Email: PPD

Complete information requested on the SAE form of any reported serious adverse event must be returned within 7 calendar days of the initial report. If the completed form is not received within this deadline, the EORTC Pharmacovigilance Unit will make a written request to the investigator.

Queries sent out by the EORTC Pharmacovigilance Unit need to be answered within 7 calendar days.

All forms need to be dated and signed by the principal investigator or any authorized staff member (i.e. on the signature list).

17.7 Reporting responsibilities of the Sponsor

The EORTC Pharmacovigilance Unit will forward all SAE reports to the appropriate persons within the EORTC Headquarters and to the pharmacovigilance contact at the pharmaceutical company.

After receipt of the initial report, the sponsor will review the information and, if necessary, contact the Investigator, to obtain further information for assessment of the event. The Sponsor will evaluate the seriousness and the causal relationship of the event to study medication. In addition, the Sponsor will evaluate the expectedness according to the reference documents (see above). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.

The EORTC Pharmacovigilance Unit and the Company have outlined the reporting of SUSARs in a pharmacovigilance agreement.

The EORTC Pharmacovigilance Unit will provide a six-monthly summary which will be added in the Trial Status Report and which will be accessible to all participating investigators.

17.8 Pregnancy reporting

Pregnancy occurring during a patient's participation in this trial, although not considered an SAE, must be notified to the EORTC Pharmacovigilance Unit within the same timelines as an SAE (within 24 hours) on a Pregnancy Notification Form. The outcome of a pregnancy should be followed up carefully and any adverse outcome to the mother or the child should be reported. This also applies to pregnancies in female partners of a male patient participating in this trial.

- Any pregnancy in a female subject or in a female partner of a male subject diagnosed during the treatment period or within 30 days after last protocol treatment administration must be reported to the EORTC Pharmacovigilance Unit
- This must be reported within 24 hours of first becoming aware of the event by fax or e-mail (scan), to the Pharmacovigilance Unit on a Pregnancy Notification Form
- All outcomes of pregnancy must be reported on the same form within 30 days after he/she has gained knowledge of the normal delivery or elective abortion.
- Any SAE that occurs during pregnancy must be recorded on the SAE report form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (see above).

18 Quality assurance

18.1 Control of data consistency

Data forms will be electronically sent to the EORTC Headquarters database by the VISTA/RDC (Remote Data Capture) system. Computerized and manual consistency checks will be performed on newly received forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the data manager. Inconsistent forms will be kept "pending" until resolution of inconsistencies.

18.2 On-site quality control

PAREXEL will perform on-site monitoring visits according to the monitoring plan.

The aim of these site visits will be:

- to verify that the site facilities remain adequate for performing the trial
- to verify that the principal investigator and site staff involved in the trial are working in compliance with GCP and protocol requirements
- to assess the consistency of data reported on the case report forms with the source data
- to check that Serious Adverse Events have been properly reported and that follow-up information or queries are correctly fulfilled
- to assist the site in resolving any outstanding queries
- to control the drug accountability process

The retention of archived study documentation is determined by the national regulatory requirements and will be defined by contractual agreement(s) between the study site(s) and the Sponsor (or Sponsor's delegate).

18.3 Audits

The EORTC Quality Assurance and Control Unit (QA&C), BIG, TESARO or TESARO's designee will conduct audits of institutions participating in this protocol. Audits will be coordinated such that PAREXEL will have primary responsibility for routine audits of the sites (according to audit plan), while EORTC, BIG, TESARO or TESARO's designee will perform additional audits whenever needed. These audits are performed to provide assurance that the rights, safety and wellbeing of subjects are properly protected, to assess compliance with the protocol and IMP handling, processes and agreements, ICH GCP standards and applicable regulatory requirements, and to assess the quality of data.

The investigator, by accepting to participate in this protocol, agrees that EORTC, TESARO, BIG, any third party (e.g. a CRO) acting on behalf of them, or any domestic or foreign regulatory agency, may come at any time to audit or inspect their site and all subsites, if applicable.

This audit consists of interviews with the principal investigator and study team, review of documentation and practices, review of facilities, equipment, IMP storage and source data verification.

The investigator will grant direct access to all paper and/or electronic documentation pertaining to the clinical study (e.g. CRFs, source documents such as hospital patient charts and investigator study files) and for inspection of the IMP, to these authorized individuals. All site facilities related to the study conduct could be visited during an audit (e.g. pharmacy, laboratory, archives, etc). The investigator agrees to co-operate and provide assistance at reasonable times and places with respect to any auditing activity, including timely follow-up to observations noted and corrective and preventive actions that may be required to address such observations.

If a regulatory authority inspection is announced, the investigator must inform the EORTC Headquarters QA&C Unit, BIG and TESARO immediately (contact at: PPD

In this way EORTC and BIG can provide support in preparing and/or facilitating the inspection in their institution. EORTC representatives/delegates may also attend the inspection.

18.4 External review of responses

In accordance with the recommendations of the RECIST v.1.1 criteria, all responses will be reviewed by an expert or experts independent of the study.

18.4.1 Tumor assessments

Radiological examinations performed during the conduct of this study will be submitted for blinded central review. The central review committee, who will determine response to treatment and date of progression of disease, will be comprised of 2 radiologists and an arbiter, if necessary. A separate charter and imaging manual will be provided that details the central blinded review and the procedures for submitting images to the central laboratory. Investigators will also assess response and date of progression. The date of progression as assessed by central review will be used for determination of PFS in the primary efficacy analysis; Investigator assessment for PFS is a secondary endpoint in this trial.

Best response to treatment (CR, PR, SD, and PD) also will be determined based on RECIST v.1.1 by both central blinded review and site Investigator review as secondary endpoints.

The central review process will be conducted as follows:

- When the patient discontinues treatment and/or the Investigator determines that the patient has progressed, all imaging data will be submitted for central review.
- The scans will undergo central radiology review based on RECIST v.1.1.

19 Ethical considerations

19.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf).

The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation.

19.2 Subject identification

The name of the patient will neither be asked for nor recorded at the EORTC Headquarters. A sequential identification number will be automatically allocated to each patient registered in the trial. This number will identify the patient and will be included on all case report forms. In order to avoid identification errors, the patient's code (maximum of 4 alphanumerics) and date of birth will also be reported on the case report forms.

19.3 Informed consent

All patients will be informed about

- the aims of the study
- the possible adverse events
- the procedures and possible hazards to which the patient will be exposed
- the mechanism of treatment allocation
- strict confidentiality of any patient data
- medical records possibly being reviewed for trial purposes by authorized individuals other than their treating physician

The template of the patient's informed consent statement is given as a separate document dated and version controlled to this protocol.

An adapted translation of the PIS/PIC will be provided by EORTC Headquarters and it is the responsibility of the Coordinating investigators for this trial (sometimes called National Coordinators) to adapt it to national/local requirements where necessary.

The translated informed consent documents are to be submitted to ethics committees for approval. The competent ethics committee for each institution must approve the informed consent documents before the center can join the study. It is the responsibility of the competent ethics committee to ensure that the translated informed documents comply with ICH-GCP guidelines and all applicable national legislation.

It is emphasized in the patient information sheet that participation is voluntary and that the patient is free to refuse further participation in the protocol whenever he/she wants to. This will not have any impact on the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered and/or randomized at the EORTC Headquarters. The written informed

consent form must be signed and personally dated by the patient or by the patient's legally acceptable representative.

All of the above must be done in accordance with the applicable national legislation and local regulatory requirements.

20 Administrative responsibilities

20.1 The study coordinator

The Study Coordinators (in cooperation with the EORTC Headquarters) will be responsible for writing the protocol, contributing to the medical review, discussing the contents of the reports with the Data Manager and the Statistician, and for publishing the study results. He will assist the Clinical Research Physician for answering some clinical questions concerning eligibility, treatment, and the medical review of the patients.

Study coordinator:

PPD
PPD
United Kingdom
Phone: PPD
e-mail: PPD

Study co-coordinators:

PPD
PPD
PPD
United Kingdom
Phone: PPD
Fax: PPD
e-mail: PPD

PPD
Tufts University School of Medicine
800 Washington St,
South 7 Room 7127
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Phone: PPD
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PPD
Vall Hebron Institute of Oncology (VHIO)
Passeig Vall d'Hebron 119-129
Barcelona 08035
Spain
Phone: PPD ext PPD
Fax PPD
e-mail: PPD

20.2 The EORTC Headquarters

The EORTC Headquarters will be responsible for writing the protocol and PIS/IC, reviewing the protocol, setting up the trial, collecting case report forms, controlling the quality of the reported data, organizing the medical review and generating reports and analyses in cooperation with the Study Coordinator. All methodological questions should be addressed to the EORTC Headquarters.

EORTC HEADQUARTERS

Avenue E. Mounier 83/11
1200 Brussels
Belgium
Fax: PPD

20.3 The BIG Headquarters

The BIG Headquarters will be responsible for the global management of the study set-up, the study governance set-up and management, reviewing the protocol and PIS/IC, and the site management (together with the sponsor of the study).

BIG HEADQUARTERS

Breast International Group (BIG)-aisbl
Institut Jules Bordet / 121 Blvd de Waterloo, 7th floor
B-1000 Brussels, Belgium
Phone: PPD
Fax: PPD
e-mail: PPD
www.breastinternationalgroup.org

20.4 The EORTC group

BREAST EORTC group

Chairman:

PPD
PPD
Portugal
Phone: PPD
Fax: PPD
e-mail: PPD

Vice-chair:

PPD
France
Phone: PPD
Fax: PPD
e-mail: PPD

21 Trial sponsorship and financing

TESARO is the Sponsor in all participating countries and is fully supporting the study.

Sponsor contact details:

PPD

Medical Director
TESARO
1000 Winter Street North #3300
Waltham
MA 02451
United States of America
Phone: PPD
Fax: PPD
E-mail: PPD

22 Trial insurance

A clinical trial insurance has been taken out according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

Clinical trial insurance is only valid in centers authorized by TESARO (via PAREXEL). For details please refer to the chapter on investigator authorization.

Appendix A: References

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Appendix B: Abbreviations

ADL	Activities of Daily Living
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AML	Acute Myeloid Leukemia
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate transaminase
β-HCG	β-human chorionic gonadotropin
BER	Base excision repair
BOR	Best overall response
*BRCA*1, *BRCA*2	Breast cancer 1, 2 gene
BUN	Blood urea nitrogen
CA125	Carcinoma antigen 125
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CNS	Central nervous system
CR	Complete response
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP1A2	Cytochrome P1A2
DNA	Deoxyribonucleic acid
DSB	Double strand break
ECG	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EE	Ethinyl estradiol
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer quality of life questionnaire – Core 30
EQ-5D-5L	EuroQoL 5 Dimension 5 Level
ER	Estrogen receptor

FISH	Fluorescent in- situ hybridization
g*BRCA*^{mut}	Germline *BRCA* mutation
GCP	Good Clinical Practice
GCSF	Granulocyte colony-stimulating factor
GGT	Gamma glutamyltransferase
HDPE	High-density polyethylene
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HR	Homologous recombination
HRD	Homologous recombination repair deficiency
IC50	Half maximal inhibitory concentration of control
IC90	90% inhibitory concentration of control
ICF	Informed consent form
ICH	International Conference on Harmonization
DMC	data monitoring committee
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional review board
ITT	Intent-to-treat
IUD	Intrauterine device
IWRS	Interactive web response system
LDH	Lactic dehydrogenase
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NE	Non evaluable
NHEJ	Non-homologous end joining
ORR	Overall response rate
PARP	Poly(ADP-ribose) polymerase
PD	Progressive disease
PFS	Progression-free survival

P-gp	P-glycoprotein
PK	Pharmacokinetics
PP	Per-protocol
PR	Progesterone receptor; partial response
PRO	Patient reported outcome
QD	Once daily
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TNBC	Triple negative breast cancer
ULN	Upper limit of normal
US	United States
WBC	White blood cells

Appendix C: Common Terminology Criteria for Adverse Events

In the present study, adverse events and/or adverse drug reactions will be recorded according to the

Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address: http://ctep.cancer.gov/reporting/ctc.html.

The EORTC Headquarters web site www.eortc.org\investigators-area\ctc provides a link to the appropriate CTC web site. This link will be updated if the CTC address is changed.

Appendix D: EORTC Quality of Life evaluation: guidelines for administration of questionnaires

EORTC Quality of Life evaluation: guidelines for administration of questionnaires

The instructions given below are intended to provide some general guidelines for collecting quality of life (QOL) data in EORTC studies. These instructions apply for all types of questionnaires.

1. Who is the responsible person (RP) for QOL data collection?

In each institution, the principal investigator is the responsible for the local organization of QoL data collection. This can be delegated to a physician, data manager, (research) nurse or a psychologist. Such a person should have the full protocol at his/her disposal as well as the questionnaire(s). This person would also be the intermediate contact point in case of any necessary clarification asked by the EORTC Headquarters.

2. Who should fill out the questionnaire?

In principle it is the patient who has to complete the QOL forms and preferably without help from others. In the case where a patient is too sick to fill out the questionnaire by him/herself or if the patient is not able to complete the questionnaire for such reasons as forgetting his/her glasses, another person could read the questions without making any suggestions and report the answers on the forms. It is not allowed for another person to fill in the questionnaire as if (s)he was the patient (proxy assessment) unless specifically allowed by the protocol.

3. What instructions should be given to the patient?

At entry in a study, the RP should give the patient an explanation of the objective of the study and instructions for completing the questionnaires.

The patient should be informed that participation in the QOL protocol is voluntary and that the information provided is confidential (identification is only for administrative purposes and includes date of birth and today's date (completion date)).

The following issues should be explained to the patient:

- The schedule of assessments.
- The questionnaire is a self administered questionnaire that should be completed by the patient him(her)self. The patient can ask for aid in reading or writing but should not let another person provide the answers.
- The patient should circle the choice that best corresponds to his/her situation.
- There is no right or wrong answer to any of these questions. The answers will not influence any medical decision making.
- All questions should be answered.
- The patient will be given a questionnaire in the default language(s) of the hospital. If desired, the patient may request another language. The RP will then contact the EORTC Headquarters for the appropriate translation.

The RP should make sure that the patient understands the instructions.

At each subsequent assessment as defined by the protocol, the patient should receive the questionnaire from the RP or from other appropriate staff if the RP is unavailable.

4. Where should the patient complete the questionnaire?

The patient should complete the questionnaire at the clinic, and, ideally in a quiet, private room. If this is not possible, the waiting room is an acceptable alternative. In general it does not take long to complete the questionnaire, but patients should be given the time they need to answer all questions.

5. When should they complete the questionnaire?

The timing of the planned QoL assessments is detailed in the protocol. When a QOL assessment is planned, the questionnaire should be given to the patient preferably before the meeting with the physician, ensuring that the patient has enough time to complete the questionnaire. If the patient is to receive a therapy, the questionnaire should be filled out before administration of the treatment (unless indicated otherwise in the protocol). The questionnaire should not be taken home and/or mailed (unless indicated otherwise in the protocol).

6. Review of the completed questionnaire

After the patient has completed the questionnaire, the person handling the questionnaire should:

- Complete the "Hospital Staff" specific data box.
- Check that the completion date is correctly filled in by the patient.
- Screen the questionnaire for omissions.

If this is the case:

- Please ask the patient the reason for omissions. It may be that patient forgot to flip a page or did not understand a question. The patient should not be forced to provide an answer if (s)he does not wish to do so.
- Additional explanation may be provided, but the questions should not be rephrased.

7. Missing forms

If for some reason the patient is unable or does not wish to complete a quality of life questionnaire the reason and the date of visit should be documented on the corresponding CRF (case report form).

8. Mailing to EORTC Headquarters

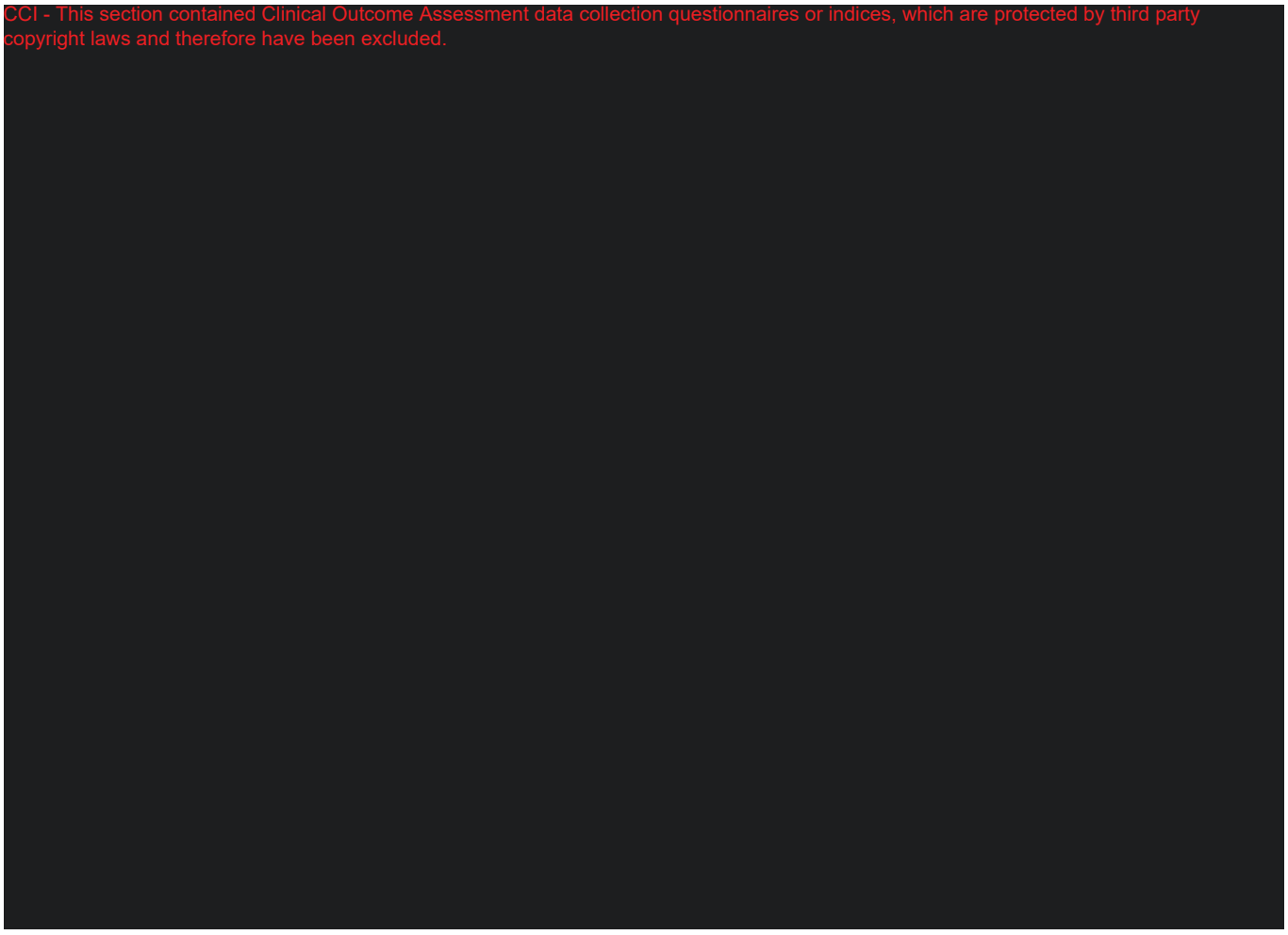
A copy of the questionnaires should be sent to EORTC Headquarters as soon as possible, while the original source document should be kept on site. As it is impossible to retrospectively collect missing quality of life data, please make sure the patient completes the questionnaire at the time-point when he/she is supposed to complete it.

Copies of the Quality of Life and Health questionnaire forms should be sent directly to the EORTC Headquarters by one of the following means:

- By fax, to the attention of Breast Group Data Manager: PPD
- By scanning and e-mailing the forms (see CRF guidelines)
- By post to the EORTC Headquarters:

Breast Group Data Manager
EORTC Headquarters
Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique

Appendix E: NCCN guidelines version 1.2015 breast and/or ovarian cancer genetic assessment



Appendix F: European Quality of Life scale, 5-dimension 5 level (EQ-5D-5L)

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

Appendix G: Eastern Cooperative Oncology Group (ECOG) performance status

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

Appendix H: Drugs known to inhibit or induce CYP1A2

Inhibitors of CYP1A2

Strong	Moderate	Weak
≥5-fold increase in AUC or >80% decrease in CL	≥2 but <5-fold increase in AUC or 50-80% decrease in CL	≥1.25 but <2-fold increase in AUC or 20-50% decrease in CL
Ciprofloxacin, enoxacin, fluvoxamine	Methoxsalen, mexiletine, oral contraceptives, phenylpropanolamine, thiabendazole, vemurafenib, zileuton	Acyclovir, allopurinol, caffeine, cimetidine, Daidzein, disulfiram, Echinacea, famotidine, norfloxacin, propafenone, propranolol, terbinafine, ticlopidine, verapamil

Inducers of CY1A2

Strong	Moderate	Weak
80% decrease in AUC	50-80% decrease in AUC	20-50% decrease in AUC
	Montelukast, phenytoin, smokers versus non-smokers	Moricizine, omeprazole, phenobarbital

Substrates of CYP1A2

Sensitive substratesa	Substrates with narrow therapeutic rangeb
Alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine	Theophylline, tizanidine, Warfarin

Guidance for Industry, Drug Interaction Studies, February 2012

Sensitive CYP substrates refers to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor or AUC ratio in poor metabolizers vs. extensive metabolizers is greater than 5-fold.

CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

Appendix I: EORTC Quality of Life Questionnaire (EORTC QLQ-C30)

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

Appendix J: List of drugs that are substrates or inhibitors of P- glycoprotein

Substrates	**Inhibitors**
Aliskiren	Amiodarone
Ambrisentan	Azithromycin
Colchicine	Captopril
Dabigatran etexilate	Carvedilol
Digoxin	Clarithromycin
Everolimus	Conivaptan
Fexofenadine	Cyclosporine
Imatinib	Diltiazem
Lapatinib	Dronedarone
Maraviroc	Erythromycin
Nilotinib	Felodipine
Posaconazole	Itraconazole
Ranolazine	Ketoconazole
Saxagliptin	Lopinavir and Ritonavir
Sirolimus	Quercetin
Sitagliptin	Quinidine
Talinolol	Ranolazine
Tolvaptan	Ticagrelor
Topotecan	Verapamil

Source: Guidance for Industry, Drug Interaction Studies, February 2012