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EORTC protocol 1307
(EudraCT number 2013-000684-85)

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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Statistical Analysis Plan
Version 1.0

Date
24 01 2017

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1 List of abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CCD	clinical cut-off date
CI	confidence interval
CR	complete response
CRF(s)	case report form(s)
CT	contrast-enhanced computed tomography (CT)
CTC	common terminology criteria
CTCAE	common terminology criteria for adverse events
ECG	electrocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC	European Organisation for Research and Treatment of Cancer
ER	estrogen receptor
FAR	final analysis report
FDA	Food and Drug Administration
FU	follow-up
GGT	gamma glutamyltransferase
HR	hormone receptor
HRQoL	Health-related quality of life
HER-2	human epidermal growth factor receptor 2
IDMC-PFS	Independent Data Monitoring Committee report for the interim analysis for futility for PFS
IDMC-OS	IDMC report for the interim analysis for OS
INR	international normalized ratio
ITT	Intent-to-treat
IQR	interquartile range
IV	intravenous(ly)
LDH	lactate dehydrogenase
LLN	lower limit of normal
MedDRA	medical dictionary for regulatory activities
MRI	magnetic resonance imaging

MRP	medical review plan
ORR	overall response rate
OS	overall survival
OS-AR	analysis report for the final analysis of the overall survival endpoint (OS-AR)
PD	progressive disease
PT	preferred term (AE term)
aPTT	activated partial thromboplastin time
PTT	partial thromboplastin time
PR	progesterone receptor
PRO	patient-reported outcomes
PFS	progression-free survival
QD	quaque die (once daily)
QLQ-C30	quality of life questionnaire C30
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
TTQ	time to HRQoL deterioration
ULN	upper limit of normal
WBC	white blood cell

2 Background

2.1 Scope

This Statistical Analysis Plan (SAP) describes the statistical analyses that will be performed for:

- the Independent Data Monitoring Committee (IDMC) report for the interim analysis on futility for progression-free survival (IDMC-PFS)
- the final analysis report (FAR)
- the IDMC report for the interim analysis for overall survival (IDMC-OS)
- the analysis report for the final analysis of the overall survival endpoint (OS-AR)

of the intergroup European Organization for the Research and Treatment of Cancer (EORTC)-1307-BCG, BIG5-13, TESARO PR-30-5010-C protocol, titled "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." Section 7 provides an overview table documenting which of the analyses described in Section 6 will be performed for which report.

The reports will be prepared by the EORTC according to EORTC standard operating procedures and Policies. The FAR will include all results needed to prepare publication of the primary results. A separate SAP will be made for the translational research analyses.

The FAR and OS-AR will be programmed and prepared by the EORTC study statistician and statistical analyst (if applicable). The IDMC-PFS and IDMC-OS will be prepared and presented to the IDMC by the reporting statistician. The IDMC-PFS and IDMC-OS reports are confidential documents, the contents of which will only be accessible to the IDMC, IDMC administrator, and the EORTC reporting statistician, until the end of the trial.

The specifications detailed in the present analyses plan will supplement but never supersede the key specifications in the protocol, (namely the sections on "analysis of primary or key secondary endpoints" "analysis population" and "method"). Any change with respect to the specifications in the protocol will be explicitly mentioned and justified.

2.2 Trial design [as in protocol version 6, January 13, 2017]

This is a Phase III, randomized, two-arm, open-label, multicenter, superiority study to compare niraparib with physician's treatment choice in patients with HER2-negative *gBRCA*^{mut} breast cancer. After registration, eligible patients will be randomized 2:1 to:

Arm 1: niraparib orally at a dose of 300 mg daily (QD) on a continuous dosing regimen
Arm 2: physician's choice amongst one of the following 4 single agents (intravenous [IV] eribulin, IV or oral vinorelbine, IV gemcitabine, or oral capecitabine), according to the nationally available and approved treatment (Gemcitabine will be administered as single agent as per National Comprehensive Cancer Network [NCCN] guidelines. In France, gemcitabine is not allowed 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 benefitting from treatment and do not meet any other treatment discontinuation criteria.

See also the trial scheme in Figure 1.

Clinic visits will be conducted at the beginning of every cycle (ie, 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 6 weeks ± 7 days for the first 12 months, then every 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.

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.

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.

The IDMC was 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 patients participating in the study. The membership, key responsibilities of the IDMC, and the corresponding procedures were defined in an IDMC charter.

2.3 Sample size [as in protocol version 6, January 13, 2017]

At least 306 $gBRCA^{mut}$ patients, confirmed by the centralized test, will need to be randomized.

The primary analysis population for efficacy (including primary PFS and OS analyses) constitutes all randomized patients who have a germline BRCA mutation per central laboratory results (Myriad Genetics, Inc., USA, hereafter referred to as "Myriad")

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 who are 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 PFS analysis (primary endpoint), an interim analysis will be performed on OS, using an O'Brien-Fleming alpha spending function (protocol Section 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 324 patients will need to be randomized 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 up to 350 $gBRCA^{mut}$ patients in the primary efficacy analysis population.

The PFS analysis is designed 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. If final analysis is done by the end of enrollment, all PFS events occurred by the end of enrollment will be included in the analysis. 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. 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.

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.

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.

2.4 Objectives of the trial [as in protocol version 6, January 13, 2017]

2.4.1 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).

2.4.2 Secondary objectives

2.4.2.1 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).

2.4.2.2 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)

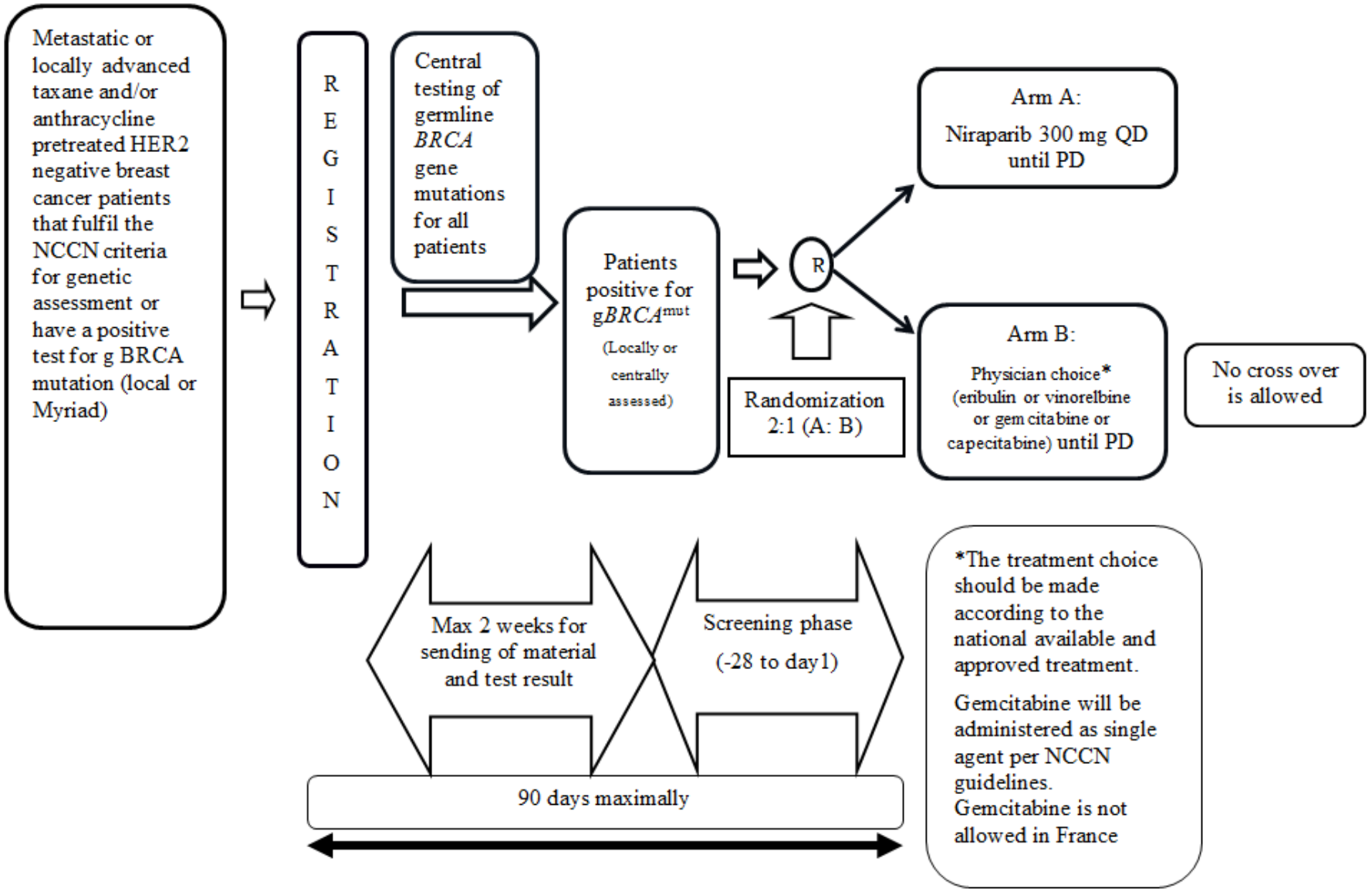
7. To describe subsequent therapies and potential relationships with outcomes

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).

Figure 1: Study Scheme



NCCN: National Comprehensive Cancer Network, QD: quaque die (once daily), PD: Progressive disease, gBRCA^{mut}, germline BRCA mutation.

3 Study conduct

Safety data will be reviewed on a regular basis by the medical review team, as documented in the medical review plan (version 1.1, June 4, 2015).

The medical review team includes EORTC representatives (clinical research physician, pharmacovigilance manager), as well as a clinical representative from the sponsor (TESARO) and the study coordinator. The medical review plan (MRP) describes the procedures and practices to be conducted by the medical team for this study, to ensure that the medical data generated from the trial are valid and reliable and that early recognition, identification, and reporting of events that affect patient safety are maintained during the trial.

Additionally, an IDMC will process a systematic, periodic review of all the safety data in the study. This process is documented in the study's IDMC charter (version 1.0, February 17, 2015). The medical review team can also request an additional IDMC review in the event that safety problems are identified for which independent advice is sought.

No outcome data is included in any of the safety reviews, apart from an overview of the secondary malignancies and deaths and their causes. See Appendix 2 for an overview of the information provided to IDMC for the safety review.

No efficacy results will be presented before the data are mature for the primary analysis according to EORTC policy 009 (version 4.2, March 3, 2015).

The FAR will contain a summary of all important amendments, a summary of the first interim analysis for futility, as well as any important issues related to the study conduct.

4 Quality assurance

The primary analysis of the FAR will undergo an independent validation by a statistician from EORTC. He/she will independently program the primary efficacy endpoint and the centrally confirmed intent-to-treat (ITT) population, based on the information provided in this SAP. The calculated variables are compared on the basis of a one-to-one comparison, and discrepancies are resolved.

The following analyses will undergo an independent EORTC validation:

- IDMC-PFS: PFS per central review assessment and the centrally confirmed ITT population
- IDMC-OS: the OS endpoint and the centrally confirmed ITT population
- OS-AR: the OS endpoint and the centrally confirmed ITT population

5 Conventions

5.1 Data Display

Unless explicitly mentioned otherwise, the following data display settings will be applied.

- Listings will always include: the patient id, the patient's institution, and the randomized treatment arm. Additional variables will be added on a case-by-case basis.
- **Frequency tables will be tabulated by the randomized treatment arm. For all categorical variables, the levels of the variables as they appear on the case report form (CRF) will be reported (with %)**. Categories with a text field specification will be tabulated as categories and then supplemented by a listing with the following information for patients fulfilling the specific condition: value of the item and text field contents).
- Delays: Dates relating to events prior to study enrollment 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 will be presented using the median, interquartile range (IQR), and range. For example, on the randomization checklist, the date of first cancer diagnosis will be presented as the time elapsed (in days, weeks, months, or years, as appropriate) since the day of the first diagnosis and the date of entry on study (date of randomization – last administration/diagnosis +1). Other delays (eg,. retreatment delays) are presented as continuous variables using the median, IQR, and range.

- Continuous variables for which a coding system exists (such as for laboratory data) will be recoded into categories (for AEs, the grading scale specified in the protocol will be used).
- Other continuous variables (for example age or dose) will be presented using the median, IQR, and range (minimum, maximum).
- If appropriate, continuous data may also be presented in categories (for example, age may also be grouped in decades).
- To convert a time interval from days to months, the interval will be divided by 30.5. To convert a time interval from days to years, the interval will be divided by 365.25.
- When the value of a variable is missing on formcrg1 or formcrg2, but is provided on formrg1 or formrg2, the corresponding data entry on the rg1 or rg2 form will be reported. For each variable, the applicable cases will be listed.
- When for some patients the value of a variable is unknown or missing, these patients will be classified in a separate category, "missing," for that variable.
- To facilitate the reading process, long listings may be included in the appendix of the FAR. They will then be referred to in the corresponding section of the FAR.

5.2 Data cleaning

- Patients who had a positive test by both Myriad (central laboratory) and another laboratory will be coded as having a BRCA mutation by Myriad on formrg2 and formcrg2.
- In the event of an unknown date, where a timeframe is known between for the event, the date in the middle of that timeframe will be entered. If the timeframe is not known, a query will be issued.

See the Conventions List for EORTC study 1307-BCG (version 1.0, May 26, 2014) for additional data cleaning conventions.

5.3 Notations in this SAP

- Variable names on the case report forms (CRFs) will be displayed in *italic*.
- The study CRFs will be referred to by either their SAS form code or the form name. See Appendix 1 for an overview of the SAS form codes and form names of the CRFs that are used in this SAP.
- Variables names containing a "-" refer to a sequence of variables, e.g., *dtsptrtn1-6* refers to *dtsptrtn1, dtsptrtn2, dtsptrtn3, dtsptrtn4, dtsptrtn5 and dtsptrtn6*.

6 Statistical analyses

6.1 Implementation of clinical cut-off date and data selection

For the IDMC-AR and the FAR, the clinical cut-off date (CCD) will be determined as the date when the number of required events is estimated to be reached, using the frequency of the events for PFS per central review.

For the OS-AR, the CCD will be determined as the date when the number of required events is estimated to be reached, on the basis of events of overall survival in the centrally confirmed ITT population.

A CCD will be applied removing forms containing patient visit data after the CCD. This will be implemented as follows:

- Screening failure form:
  The form is removed when "date of screening failure (*dtsf*) > CCD."

- The following forms are removed when the patient was randomized after the CCD:

formrg2, formcrg2, disease history form, medical history form, medical review form, initial measurements form, physical examination form at screening, myelosuppression history form.
These forms are removed when "*dor2* > CCD".

- Previous and concomitant medication form:
  The form is removed when "date of visit (*dtvisitpcm*) > CCD".

- Biochemistry form:
  The form is removed when "date of visit (*dtbio*) > CCD."

- Hematology form:
  The form is removed when "date of visit (*dthem*) > CCD."

- Follow-up measurements form:
  The form is removed when "date of visit (*dtassfm*) > CCD."

- Protocol Treatment forms:
  The form is removed when the last treatment-related date > CCD
  The last treatment-related date for formtrtc = *dtsptrtc*
  The last treatment-related date for formtrte = the maximum of *dtadme1-2*
  The last treatment-related date for formtrtg = the maximum of *dtadmg1-3*
  The last treatment-related date for formtrtn = the maximum of *dtsptrt* and *dtsptrtn1-6*
  The last treatment-related date for formtrtviv = the maximum of *dtadmv1-3*
  The last treatment-related date for formtrtvo = *dtsptrtv*

- Adverse events form:
  The form is removed when "start date (*aestdtc*) > CCD."

- End of treatment form:
  The form is removed when "date of last treatment administration (*dtlast*) > CCD."

- Follow-up form:
  The form is removed when "date of visit (*dtassfu*) > CCD," except for the survival section.
  The survival section is removed when "date last known to be alive/date of death (*dtssfu*) > CCD."

- Quality of life form:
  The form is removed when "today's date (*Q331*) > CCD."

- Health economics questionnaire:
  The form is removed when "date completed by patient (*Q527*) > CCD."

- Independent central review:
  The records in the rs dataset from the central review data export are removed when "Date/Time of Response Assessment (*RSDTC*) > CCD."

6.2 Patient availability

6.2.1 Accrual

The following information concerning accrual will be reported:

- Recruitment rate (accrual over time): A graph displaying the cumulative accrual over time and the expected accrual will be presented. A separate graph will be produced to report the number of patients registered and the number randomized in the study.
- A table with the total number of patients and percentage of patients recruited, by institution and by group, will be presented, ordered by descending volume of accrual.

6.2.2 Follow-up

The following information on the duration of follow-up (FU) in the full ITT population (Section 6.2.4) will be reported. The follow-up reporting will be repeated in the centrally confirmed ITT population (Section 6.2.4) in the appendix of the analysis report.

- FU duration by treatment arm and overall estimated by the inverse Kaplan-Meier method (Schemper & Smith, 1996): patients who died are censored on their death date (Section 6.11.1) and other patients have an event on their last follow-up date as defined below:

  The last follow-up date is calculated as the maximum of the following dates (if available):

  - End of treatment form: date of last treatment administration (*dtlast*), date last known to be alive/death (*dtssof*)
  - Follow-up form: date of visit (*dtassfu*), date last known to be alive/death (*dtssfu*)
  - Follow-up measurements form: date of visit (*dtassfm*)
  - Initial measurements form: date of visit (*dtassim*)
  - Treatment forms: last treatment-related date (Section 6.1)
  - AE forms: start date of event (*aestdtc*), stop date of event (*aeendtc*) if available
  - ECG form: date of visit (*dtecg*) if number of ECG performed at this visit (*nrecg*) > 0
  - Biochemistry form: date of visit (*dtbio*) if analysis was performed (*nybio* =1)
  - Hematology form: date of visit (*dthem*) if analysis was performed (*nyhem* =1)
  - Physical examination form: date of physical examination (*dtpe*) if performed (*nype* =1)
  - Date of randomization (*dor2*)
  - Date of screening (*dor)*

6.2.3 Eligibility

The following information on eligibility in the full ITT population (Section 6.2.4) will be reported. The eligibility reporting will be repeated in the centrally confirmed ITT population (Section 6.2.4) in the appendix of the analysis report.

- Table with eligibility status (formDM01: *nyeligteam*) and main reason for ineligibility (formDM01 *eligr,* for *nyeligteam=0*) by randomized treatment arm, as assessed by the medical review team
- Listing of ineligible patients together with main reason for ineligibility (formDM01: *eligr, txeligr,* for patients with *nyeligteam=0*)
- Listing of patients who entered with a waiver on some eligibility criteria (formDM01: *eligr, txeligr, nyeligteam,* for patients with *nyeligdev =1*)
- Listing or table of patients with deviation(s) to some eligibility criteria that are declared as eligible by the medical review team (formDM01: *eligr, txeligr,* for patients with *nyelig =1 and nyeligteam=1*)

6.2.4 Patient populations

The following patient populations will be used in the analyses:

- Screening population: all screened/registered patients. Tables for the screening population will contain 4 columns:
  - column 1: patients who were screened, not randomized, and declared a screening failure
  - column 2: patients who were screened, not (yet) randomized, and not (yet) declared a screening failure
  - column 3: patients who were randomized to physician choice
  - column 4: patients who were randomized to niraparib.

- Centrally confirmed ITT population: all randomized patients with a centrally confirmed germline BRCA mutation. Analyses involving the ITT population will group patients by the randomized treatment arm, which does not necessarily correspond to the treatment they received.

  Patients are considered to have a centrally confirmed germline BRCA mutation when on the CENBRCA form either
  - a "Variant in BRCA 1 (*NYBRCA1CEN* = 1)" is reported which is either "Positive for a deleterious mutation" or "Genetic variant, suspected deleterious" (*INTER1CEN in* (1,2)),
  - a "Variant in BRCA 2 (*NYBRCA2CEN* = 1)" is reported which is either "Positive for a deleterious mutation" or "Genetic variant, suspected deleterious" (*INTER2CEN in* (1,2)), or
  - a "BRCA1 and/or BRCA2 rearrangement found (*BRCAREARRCEN* = 1)" is reported which is either "Positive for a deleterious mutation" or "Genetic variant, suspected deleterious" (*INTERREARRCEN* in (1,2)).

  Note that this population corresponds to the ITT population specified in the protocol, which is the primary analysis population for all efficacy analyses.

- Full ITT population: all randomized patients. Analyses involving the ITT population will group patients by the randomized treatment arm, which does not necessarily correspond to the treatment they received.

  Note that the distinction is made between full and centrally confirmed ITT population to ensure that those patients who were randomized, but were not confirmed centrally to have a germline BRCA mutation after randomization, are still accounted for in this report.

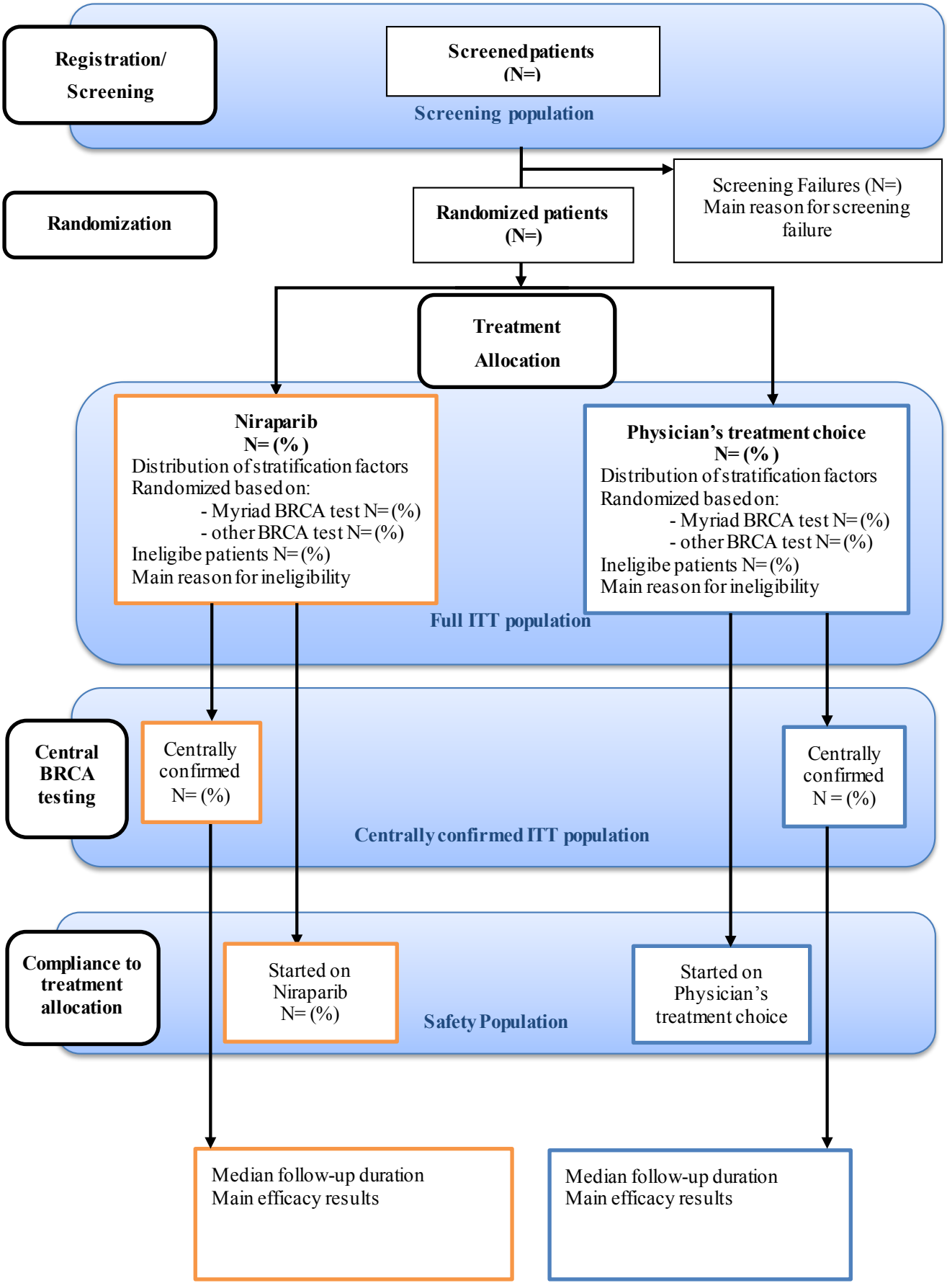
- Per-protocol population: all patients in the centrally confirmed ITT population who are eligible according to medical review (Section 6.2.3) and started on their randomized treatment (received at least 1 dose of the allocated drug). Analyses involving the per-protocol population will group patients by the randomized treatment arm, which corresponds to the treatment they actually received.

- Safety population: all randomized patients who started on their allocated treatment (received at least 1 dose of the allocated drug). Analyses involving the safety protocol population will group patients by the randomized treatment arm, which corresponds to the treatment they actually received.

A table will document the number of patients included/excluded in each of the analysis populations (by treatment arm, if applicable). Also, the main reason for exclusion from each analysis population will be documented, eg, for the full ITT population, the reason for exclusion is the main reason for screening failure (formsf: *sf1*, *txsf1*).

6.4 Study Flow Chart

The following study flow chart will be completed in the FAR.



6.5 Baseline characteristics

All baseline characteristics will be reported in the full ITT population unless explicitly specified otherwise. The baseline characteristics reporting will be repeated in the centrally confirmed ITT population, the safety population and the per protocol population in the appendix of the analysis report.

6.5.1 Baseline patient and tumor characteristics

6.5.1.1 Baseline patient and tumor characteristics at screening/registration

The following characteristics will be reported in the screening population:

- Gender (*sex*, formcrg1)
- Age at screening (median, IQR, range, by decades). *dor1* (on formcrg1) – *dob* (on patient form))
- Patient meets one of the criteria for further genetic assessment according NCCN guidelines (formcrg1: *nygenass*)
- Previously detected (prior to screening/registration) germline BRCA mutation? (formcrg1: *nyprevmut*)
- HER2 status (formcrg1: *nyhistbc*)
- Physician's choice of intended treatment for control arm (formrg1: *physchoicerg1*)

6.5.1.2 Baseline patient and tumor characteristics at randomization

- Ethnicity (formmh: *eth*)
- Race (formmh: *race*)
- Gender (*sex*, formcrg1)
- Age at randomization (median, IQR, range, by decades). *dor1* (on formcrg1) – *dob* (on patient form)
- Germline BRCA1 or BRCA2 mutation (at randomization)? (formcrg2: *nybrcamut*)
- Estrogen receptor (ER) status (formcrg2: *er*)
- Progesterone receptor (PR) status (formcrg2: *pr*)
- HER2 status (formcrg1: *nyhistbc*)
- Hormone receptor (HR) status. The HR status is calculated from the ER and PR status. It will be reported as positive when the ER status and/or the PR status is positive. It will reported as negative when both the ER and PR status are negative.
- Visceral disease? (formcrg2: *nyviscel*)
- Presence of bone metastases? (formim: *boneinvim=1, 2 or 3*)
- Presence of brain mets? (formim: *braininvim=1, 2 or 3*)
- Eastern Cooperative Oncology Group (ECOG) performance status (formph: *ecog* for *visitpe* = 0)

6.5.2 Stratification factors

- A table with the value of the stratification factors as entered at time of randomization
    - visceral disease: yes vs no (formrg2: *qval211*)
    - histology: triple negative versus ER/PR positive (formrg2: the maximum of *qval23* and *qval24*)
    - number of lines of prior cytotoxic chemotherapy for advanced/metastatic disease: 0-1 or 2 (formrg2: *qval212*)
- Listing of patients (and corresponding stratification factors) for whom there are inconsistencies between the values declared during randomization versus those updated prior to the database lock date for the report.

6.5.3 Medical history

- History of myelosuppression (formmh: *nymyh*). In the event that a patient has a history of myelosuppresion, the information on the myelosuppression history form will be listed (formmyh: *myhevent*, *myhgrade*, *dtstmyh*, *dtspmyh*, *txregimpyh*, *txtrtmyh*).

6.5.4 Disease history

Related to the initial diagnosis and primary/adjuvant treatment of the current breast cancer (per disease history form):

- Time interval between first pathological diagnosis of breast cancer and date of randomization (median, IQR, range)
- Stage at initial diagnosis (formdh: *stageinit*)
- T status at initial diagnosis (formdh: *tstage*)
- N status at initial diagnosis (formdh: *nstage*)
- M status at initial diagnosis (formdh: *mstage*)
- Histology at initial diagnosis (formdh: *thist*, *txthist*)
- Grade at initial diagnosis (formdh: *tgrad*)
- Additional biopsy performed for metastatic/recurrent disease (for patients who were M0 at diagnosis)? (formdh: *nyaddbx*) If yes, histology and grade after biopsy (formdh: *thistbx*, *txthistbx*, *tgradbx*)
- Surgery performed for primary tumor? (formdh: *nysurgproc*)
- (Neo-)adjuvant chemotherapy received? (formdh: *setadj*) If yes, the regimen, time interval between initial diagnosis and first progression (formdh: *regimadj*, *txregimadj*, *dtrecadj- dtdiag*)
- Endocrine therapy given? (formdh: *nyendoadj*) If yes, the regimen (formdh: *txendoadj*)
- Radiotherapy given? (formdh: *nyrxadj*)

Related to treatment of the current breast cancer in the metastatic setting:

- Number of chemotherapy regimens given for the current breast cancer in the metastatic setting (formdh: *nrregimmet*)

  For patients who received at least 1 regimen: the type of first regimen, the duration of treatment, and the response to this treatment (formdh: *regim1*, *txregim1*, *dtspregim1-dtstregim1*, *respregim1*)

  For patients who received at least 2 regimens: the type of second regimen, the duration of treatment, and the response to this treatment (formdh: *regim2*, *txregim2*, *dtspregim2-dtstregim2*, *respregim2*)
- Total duration of chemotherapy given for the current breast cancer in the metastatic setting (formdh: the sum of [*dtspregim2-dtstregim2]* and *[dtspregim1-dtstregim1*])
- Endocrine therapy given? (formdh: *nyendomet*) If yes, the regimen (formdh: *txendomet*)
- Radiotherapy given? (formdh: *nyrtmet*) If yes, a listing of the type (formdh: *txrtmet*)
- Other systemic therapy (not entered above)? If yes, a listing of the type, the response to this treatment, the last administration date, and the date of randomization (in the current study)

Related to ovarian cancer, for female patients only:

- Prior diagnosis of ovarian cancer? (formdh: *nypriorovdh*) If yes, stage (formdh: *stageovdh*)

Related to other invasive malignancies:

- Cancer history other than metastatic breast cancer or ovarian cancer? (formdh: *nycanchist*) If yes, a listing of the type, the date of diagnosis of the malignancy, last treatment for the malignancy (formdh: *txcanc, dtdiagcanc, dtsptrtcanc*).

6.5.4.1 BRCA testing

The following variables will be tabulated 3 times, in 3 different populations:

- the screening population

- the full ITT population
- the centrally confirmed ITT population, restricted to those patients who were randomized after a germline BRCA mutation detected at a different lab than Myriad (formcrg2: *nybrcamutnot*=2):

BRCA testing before screening:

- Previously detected germline BRCA mutation (formcrg1: *nyprevmut*)

BRCA testing before randomization:

- germline BRCA1 or BRCA 2 mutation? (formcrg2: *nybrcamutnot*)

Central BRCA testing results:

Were results from central BRCA mutation testing received? (yes, if formcenbrca is received). If yes:

- Variant in BRCA 1 or 2? (1, 2, both 1 and 2, neither 1 nor 2) (formcenbrca: *nybrca1cen* and *nybrca2cen*)
- If variant in BRCA 1 or both: specify the interpretation (formcenbrca: *inter1cen*)
- If variant in BRCA 2 or both: specify the interpretation (formcenbrca: *inter2cen*)

Previous BRCA testing results:

Was a second BRCA mutation test performed outside the context of this protocol? (yes, if formothbrca is received). If yes:

- Location of BRCA mutation test? (formothbrca: *locbrca*)
- Variant in BRCA 1 or 2? (1, 2, both 1 and 2, neither 1 nor 2) (formothbrca: *nybrca1loc* and *nybrca2loc*)
- If variant in BRCA 1 or both: specify the interpretation (formothbrca: *inter1loc*)
- If variant in BRCA 2 or both: specify the interpretation (formothbrca: *inter2loc*)

6.6 Compliance to the protocol

Compliance will be reported in the full ITT population, and repeated in the centrally confirmed ITT population in the appendix of the analysis report.

6.6.1 Central medical review of compliance to protocol

- Were there protocol treatment deviations as described in the MRP? (formdm01: *devia*) If yes, the type of violation (formdm01: *violev*)
- Were there protocol treatment deviations as described in the MRP that were judged as severe violations by the medical review team? (formdm01: *nydeviateam*) If yes, the type of violation (formdm01: *violev*)

6.6.2 Compliance to treatment allocation

Definitions:

- A patient is defined to have started on niraparib if at least 1 dose is reported on the niraparib treatment form during cycle 1 (formtrtn: max(*dosen*, *dose1n*, *dose2n, dose3n, dose4n, dose5n, dose6n*) > 0 for *cycletrn =1*)
- A patient is defined to have started on capecitabine if at least 1 dose is reported on the capecitabine treatment form during cycle 1 (formtrtc: max(*dosec*, *dose1c*, *dose2c, dose3c, dose4c, dose5c*) > 0 for *cycletrc =1*)
- A patient is defined to have started on eribulin if at least 1 dose is reported on the eribulin treatment form during cycle 1 (formtrte: max(*dosee1*, *dosee2*) > 0 for *cycletre =1*)
- A patient is defined to have started on gemcitabine if at least 1 dose is reported on the gemcitabine treatment form during cycle 1 (formtrtg: max(*doseg1*, *doseg2, doseg3*) > 0 for *cycletrg =1*)

- A patient is defined to have started on intravenous (IV) vinorelbine if at least 1 dose is reported on the IV vinorelbine treatment form during cycle 1 (formtrtviv: max(*dosev1*, *dosev2, dosev3*) > 0 for *cycletrv =1*)
- A patient is defined to have started on oral vinorelbine if at least 1 dose is reported on the oral vinorelbine treatment form during cycle 1 (formtrtvo: max(*dosev*, *dose1v, dose2v, dose3v, dose4v, dose5v*) > 0 for *cycletrvo =1*)
- A patient is defined to have started on physician's treatment choice if he/she started on capecitabine, eribulin, gemcitabine, IV vinorelbine, or oral vinorelbine.

The following information regarding treatment compliance will be reported:

- Treatment actually started (niraparib, physician's treatment choice, other, no information available) (using the definition above). If the patient did not start the allocated treatment, the reason why (formdm01: *txdevia*).
- For patients who started on another treatment or for whom no treatment information is available in the database, a listing will be provided, including any additional information concerning the treatment actually received (stored in the medical review form textboxes). (formdm01: *txdevia*, *txdmisrev*)

6.6.3 Other compliance measures

Related to the timing of the tumor measurements:

- average difference between 2 successive tumor measurement of the same patient (median, IQR, range) (formfum: *dtassfm – dtassfm[-1],* where the formfum forms are sorted by patient in ascending order on *dtassfm*, and with *dtassfm[-1]* being the previous value of *dtassfm* for the same patient)
- Histogram of the difference between 2 successive tumor measurement of the same patient (all patients, all time points). Bar width will be 3 days. (formfum: *dtassfm – dtassfm[-1]*)
- Histogram of the timing of all the tumor measurements (all patients, all time points) relative to the theoretical measurement dates as set from start of treatment (per protocol). Bar width will be 5 days. (formfum: *dtassfm* – [closest theoretical date of per protocol schedule])

Related to the assessment of the hematologic toxicity:

- Did the patient receive weekly blood tests during first month from start of treatment? (yes/no).
  Availability of a hematology form (formlbhem: *nyhem=1, dthem*) for the following 4 dates: start of treatment + 7 days (± 3 days), start of treatment + 14 (± 3 days), start of treatment + 21 (± 3 days), start of treatment + 28 (± 3 days)

- Did the patient receive weekly blood tests for 1 month following the first dose reduction for hematologic toxicity? (yes/no).
  For patients with a dose reduction due to a hematologic toxicity (investigator reported on the treatment form), availability of a hematology form (formlbhem: *nyhem=1, dthem*) for the following 4 dates: date of first dose reduction due to hematological toxicity + 7 days (± 3 days), date of first dose reduction due to hematological toxicity + 14 (± 3 days), date of first dose reduction due to hematological toxicity + 21 (± 3 days), date of first dose reduction due to hematological toxicity + 28 (± 3 days).

6.7 Exposure to treatment

The exposure will be reported in the safety population.

6.7.1 Protocol therapy

Protocol therapy consists of niraparib or physician's treatment choice among IV eribulin, IV or oral vinorelbine, IV gemcitabine, or oral capecitabine. Dose modifications for physician's choice drugs will be done according to the respective product package insert or local practice. Therefore, calculated dose reductions/interruptions and dose intensities will not be reported for the physician's choice arm.

Niraparib, capecitabine, and oral vinorelbine are oral drugs with a daily administration schedule. The cycles for these drugs were defined as 3 week time-intervals, irrespective of interruptions. The other drugs have an IV administration route, with normal cycle duration of 3 weeks. Cycle duration will be longer in the event that the next cycle needs to be delayed, eg, due to toxicity.

For IV. drugs, the treatment duration (in days) will be calculated as:

(first dose of last cycle +21 - first dose of first cycle) + 1

For oral drugs, the treatment duration (in days) will be calculated as:
(last dose administration - first dose administration) + 1

6.7.1.1 Treatment received

- The frequency of patients who received at least 1 dose of niraparib will be presented.
- The frequency of patients who received at least 1 dose of physician's treatment choice will be presented, including the type of regimen.
- A table showing the planned versus received regimen for patients randomized to the physician's treatment choice arm will be presented.

6.7.1.2 Duration of treatment

The following data will be displayed:

- Number of patients who have stopped protocol treatment and who are still on protocol treatment.
- Number of cycles of protocol therapy received (until database lock) (the maximum of: *totcyc* [formeot], *cycletrc* [formtrtc], *cycletre* [formtrte], *cycletrn* [formtrtn], *cycletrg* [formtrtg], *cycletrvo* [formtrtvo] and *cycletrv* [formtrtviv]). This will be reported separately for patients who have stopped protocol treatment and who are still on protocol treatment.
- Duration of protocol therapy (until database lock, in months) (Section 6.7.1). This will be reported separately for patients who have stopped protocol treatment and who are still on protocol treatment.

  Average cycle duration in weeks (median, IQR, range, and in categories: <2, 2 - <2.5, 2.5 - 3.5, >3.5 - 4, >4 weeks). Cycle duration calculated as the difference between the start dates of 2 subsequent treatment cycles
- Maximum cycle duration in weeks - (median, IQR, range, and in categories: <2, 2 - <2.5, 2.5 - 3.5, >3.5 - 4, >4 weeks). Cycle duration as calculated above.

6.7.1.3 Relative dose intensity for the Niraparib arm

The observed dose intensity is calculated as the total dose received divided by the duration of protocol therapy in days. For the definition of the duration of protocol therapy, see Section 6.7.1.

The relative dose intensity is calculated as the observed dose intensity (in days) divided by the theoretical dose intensity (in days), eg, for niraparib, the theoretical daily dose intensity equals 100 mg.

Relative dose intensity will be reported as median, IQR, and range, and in the following categories: ≤70%, >70-90%, >90-110%, >110-120%, >120%

6.7.1.4 Dose reductions and interruptions (calculated) for the niraparib arm

A dose reduction is defined as any dose administration of ≤ 90% of the theoretical dose for any of the protocol drugs. Dose interruptions are not reported as dose reductions, but are reported separately.

A dose interruption is defined as any dose administration of 0 for any of the protocol drugs prior to stopping protocol treatment. In the event that a dose of 0 is reported in the last cycle and there is no end treatment form available for this patient (at time of database lock), this case will count as a dose interruption and the patient is assumed to still be on treatment.

- Frequency of patients with a dose reduction of niraparib. In the event of dose reduction, the cycle and reason of first dose reduction

- Frequency of patients with a dose interruption of niraparib. In the event of an interruption, the cycle and reason of first dose interruption

6.7.2 Further anti-tumor treatment (after stop of protocol treatment)

The following variables will be reported in the group of patients who stop protocol treatment and for whom follow-up information is available for at least 2 months after stopping protocol treatment (to allow for sufficient survival/follow-up to have started a new treatment).

Additionally, the analyses will include the next line of treatment following disease progression. This will be reported in a subgroup, specifically those patients with progressive disease on protocol treatment.

- Any chemotherapy administration? (formfu: maximum of *nyctxfu*)
- Any radiotherapy? (formfu: maximum of *nyrtfu*)
- Any surgery? (formfu: maximum of *nysurgfu*)
- Any hormonal therapy? (formfu: maximum of *nyhorfu*)
- Any targeted agents? (formfu: maximum of *nytarfu*) If yes, specification of the first new targeted therapy given following the end of protocol treatment (formfu: *txtarfu*)
- Any other treatment? (formfu: maximum of *nyothfu*) If yes, specification of the first new other therapy given following the end of protocol treatment (formfu: *txothfu*)
- Niraparib given in compassionate use program? (formfu: the maximum of *nircompuse*)

The molecularly targeted treatments and other treatment might be further categorized into meaningful drug classes based on medical review.

6.8 Safety evaluations

All safety and tolerability evaluations based on the clinical database will be reported in the safety population. AE grading will be described according to CTC version 4.0.

For the reporting in this section, "during protocol treatment" is defined as:

- The Adverse Events: The time period from start of treatment up to (and including) 30 days after the last protocol treatment administration date, as reported on the end of treatment form (formeot: *dtlast*). In the event that there is no end of treatment form received at time of database lock, all AEs/laboratory results from start of treatment will be reported.
- For hematology and biochemistry: The time period from start of treatment up to the study medication termination visit (formlbhem: *visithem=1,2,3 or 4,* formlbbio: *visitbio=1 or 2*).

6.8.1 Hematology

The category "missing" means that the corresponding laboratory test was never performed during treatment. When the laboratory test was performed at least once, but the required normal ranges were not provided, this is reported as "upper limit of normal [ULN] not reported" or "lower limit of normal [LLN] not reported."

Certain laboratory results are reported both on the hematology form and on the AE form. These variables will be reconciled during database cleaning.

- The worst grade during protocol treatment will be tabulated for the following laboratory tests/ preferred terms:

  Hematology form: white blood cell (WBC) count, neutropenia, lymphopenia, thrombocytopenia, anemia

  AE form: febrile neutropenia, anemia, neutrophil count decreased, lymphocyte count decreased, neutrophil count decreased, platelet count decreased, white blood cell decreased
- Listing of the grade ≥ 3 AEs that meet these criteria. This listing will include the baseline laboratory value and corresponding grade.

6.8.2 Biochemistry

The category "missing" means that the corresponding laboratory test was never performed during treatment. When the laboratory test was performed at least once, but the required normal ranges were not provided, this is reported as "ULN not reported" or "LLN not reported".

Certain laboratory results are reported both on the biochemistry form and on the AE form. These variables will be reconciled during database cleaning.

- The worst grade during protocol treatment will be tabulated for the following laboratory tests/ preferred terms:

  Biochemistry form: hypoalbuminemia, alkaline phosphatase, SGPT, amylase, SGOT, hyperbilirubinemia, blood urea nitrogen (BUN) abnormality, hypercalcemia, hypocalcemia, serum creatinine, gamma glutamyltransferase (GGT), hyperglycemia, hypoglycemia, hyperkalemia, hypokalemia, lactate dehydrogenase (LDH) abnormality, lymphopenia, hypermagnesemia, hypomagnesemia, hypernatremia, hyponatremia, hyperbilirubinemia.

  AE form: hypercalcemia, hyperglycemia, hyperkalemia, hypermagnesemia, hypernatremia, hypoalbuminemia, hypocalcemia, hypoglycemia, hypokalemia, hypomagnesemia, hyponatremia, serum amylase increased, GGT increased, alanine aminotransferase (ALT) increased, alkaline phosphatase (ALP) increased, aspartate aminotransferase (AST) increased, blood bilirubin increased, creatinine increased.

- Listing of the grade ≥ 3 AEs that meet these criteria. This listing will include the baseline laboratory value and corresponding grade.

6.8.3 Adverse Events

Adverse events will be tabulated by preferred term within the System Organ Class (SOC); however, for the following SOCs, AEs will be pooled across the preferred terms: Eye disorders (EYE), Hepatobiliary disorders (HEP), Immune system disorders (IMM), Injury, poisoning and procedural complications (INJ), Musculoskeletal and connective tissue disorders (MUS), Pregnancy, puerperium and perinatal conditions (PRE), Skin and subcutaneous tissue disorders (SKI), Social circumstances, Surgical and medical procedures (SUR).

The preferred term will always be included in the listings. The report will include:

- Table containing the worst grade of all reported AEs classified under the specific SOC/preferred during protocol treatment.
- Listing of all AEs during protocol treatment. The listing will include the preferred term, the date of randomization, the date of event onset, the stop date of the event, whether this event is serious, the relationship to protocol treatment, and the action that was taken with respect to the protocol treatment. This listing will be organized by the treatment received and the SOC. Within those sections, the items will be sorted by the grade and preferred term.
- Table containing the worst grade of all reported AEs classified under the specific SOC/preferred term during protocol treatment that are reported to be related or likely related to the protocol treatment.

6.8.4 Serious Adverse Events

Tables of the serious adverse events (SAEs) will be provided by the EORTC pharmacovigilance department. Unlike the data presented in other sections of the report, SAE data are based on the safety database. The safety database will be reconciled with the clinical database prior to database lock.

The following tables will be reported:

- Study safety overview per treatment arm

Randomized Treatment arm	# SAE terms	# SAR terms	# SUSAR terms	# Deaths	# Toxic deaths
Niraparib					
Physician's choice					

SAE = serious adverse event; SAR = serious adverse reaction; SUSAR = suspected, unexpected, serious adverse reaction; Toxic death = cases with at least one SAR term with fatal outcome, ie, a death judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the study treatment. The study safety overview table lists the number of reported SAE terms, SAR terms and SUSAR terms per treatment received and the number of reported death and toxic death cases. There can be multiple reported terms within one case, but as a patient can only die once, it is the numbers of deaths and toxic death cases which are listed (instead of terms).

The column # SAE terms displays a count of all SAEs; all events which are reported as 'serious' (ie,1 seriousness criterion) regardless of relationship to the study treatment. This implies that the number of SAE terms also includes the number of SAR terms (and SUSAR, deaths, and toxic deaths terms).

The column # SAR terms displays a count of all SARs; all SAEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the study treatment. This implies that the number of SARs also includes the number of SUSAR and toxic deaths terms.

The column # SUSAR terms displays a count of all SUSARs; all SARs which are considered as unexpected.

The column # Deaths displays a count of all cases with at least 1 SAE term with fatal outcome, regardless of relationship to study treatment. This implies that the number of death cases also includes the number of toxic death cases.

The column # Toxic deaths displays a count of all cases with at least one SAR term with fatal outcome, ie,. a death judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the study treatment. *Note*, a toxic death can also be a SUSAR and vice versa, but this is not always the case.

- Suspected Unexpected Serious Adverse Reactions (SUSARs) by SOC and preferred term

Identification Number	Randomized Treatment arm	SOC	Preferred term	Count by Preferred term

- Toxic deaths by SOC and preferred term

Identification Number	Randomized Treatment arm	SOC	Preferred term	Count by Preferred term

- Line Listings of Serious Adverse Reactions (SAR)

Randomized Treatment arm	Institution identifier	Patient ID	case ID (for internal reference)	Seriousness Criteria	Reported Term (verbatim term)	Grade (CTCv4.0)	Event Start Date	Event Stop Date	Outcome	Treatment	Relationship to Treatment
Niraparib											
Physician's choice											

- Cumulative Summary Tabulation of Serious Adverse Events (SAE)

SOC	Preferred term	**Events in Niraparib arm**	**Events in Physician's choice arm**	Total number of events
Blood and lymphatic system disorders	Febrile bone marrow aplasia			
	Febrile neutropenia			
	Neutropenia			
Blood and lymphatic system disorders Total				
Gastrointestinal disorders	Abdominal pain			
	Diarrhoea			
	Nausea			
	Vomiting			
Gastrointestinal disorders Total				
…				
Grand Total				

- Cumulative Summary Tabulations of Serious Adverse Reactions (SAR)

SOC	Preferred term	**Events in Niraparib arm**	**Events in Physician's choice arm**	Total number of events
Blood and lymphatic system disorders	Febrile bone marrow aplasia			
	Febrile neutropenia			
	Neutropenia			
Blood and lymphatic system disorders Total				
…				
Grand Total				

6.9 Reasons for stopping treatment

Reasons for stopping treatment will be reported in the full ITT population. The reporting will be repeated in the centrally confirmed ITT population in the appendix of the analysis report.

- Is patient still on protocol treatment? (end of treatment form)

If not:

- Reason for stopping protocol therapy (end of treatment form)

6.10 Disease status

Disease status will be reported in the full ITT population, and entails the tabulation of the following event frequency. The reporting will be repeated in the centrally confirmed ITT population, the safety population and the per protocol population in the appendix of the analysis report.

- Disease progression, type of first event. This variable will be categorized as follows:
    1. Progressive disease (PD) both per investigator assessment and central independent review
    2. PD per investigator assessment, not confirmed by review
    3. PD per central independent review, not reported by the investigators
    4. Start of new anticancer treatment in absence of PD (by central review or investigator reported)
    5. No PD

Patients will be classified in one of these 5 categories based on their status at the time of evaluation. For the definitions of the aforementioned dates, see Section 6.11.1. When dates do not differ by more than 7 days, the corresponding events are considered to have happened instantaneously for the above classification.

For patients classified as "Start of new anticancer treatment," #4 above, the frequency of patients for whom clinical progression (not radiologically confirmed) was reported by the investigator prior to the start of new anticancer therapy, will be reported.

- Death. The patient is reported to have died if *ssof*=2 (formeot) or *ssfu*=2 (formfu); otherwise the patient is considered alive. In the event that the patient died, the main cause of death will be provided: *rdeadfof, txrdeadof* in case *ssof=2* (formeot) or *rdeadfu txrdeadfu* in case *ssfu=2* (formfu)
- Listing of early death, defined as death occurring within 90 days from randomization.
- Listing of patients who die on treatment (= up to 30 days post protocol treatment stop). Second primary malignancy. The patient is reported to have a second primary malignancy if *nynew=1* (formfu) or *dtnewof* is reported (formeot). If yes, a listing of the site/type: *txnew* in case *nynew=1* (formfu) or *txnewof* in case *dtnewof* is reported (formeot).

6.11 Statistical inference on efficacy endpoints

Efficacy analyses will be reported in the centrally confirmed ITT population, unless explicitly mentioned otherwise. The following analyses will be provided as supplementary statistics to the primary test for each efficacy endpoint. The primary test itself will be covered in the subsection for each endpoint.

- Kaplan-Meier curves by randomized treatment arm will be shown. Medians - if reached - will be presented with a 2-sided 95% confidence interval (CI) based on the nonparametric method (Brookmeyer & Crowley, 1982).
- A univariate Cox proportional hazards model with the randomized treatment as a factor and stratified by the randomization factors will be used to estimate the treatment hazard ratio and its 2-sided 95% CI. The proportional hazards assumption will be assessed by means of the graphical and numerical method based on cumulative sums of martingale-based residuals (Lin, Wei, & Ying, 1993). The method will be implemented using the 'asses' statement in the 'phreg' procedure of SAS, using the default settings. In the event that the proportional hazards assumption does not hold, how the hazard ratio changes over time will be explored by means of models involving treatment interaction with (a function of) time. The results will be displayed graphically.

6.11.1 Definitions

The following definitions for the death date, disease progression date by independent central review, and disease progression date per investigator assessment will be applied throughout the report:

- Death date
  If the patient died (according to the definition in Section 6.10), the death date is calculated as the minimum of: *dtssof* if *ssof*=2 (formeot) and *dtssfu* for follow-up forms with *ssfu*=2 (formfu); otherwise the date of death is empty.

- Disease progression date by independent central review
  The progression date is calculated from the independent central review data export, in the form rs, as the minimum of *RSDTC* for those patients for whom *RSACPTFL* = "Y" and *RSTEST*="Overall Response" and *RSORRES*="PD". If the date is missing, the patient is considered to not have a disease progression by independent central review

- Disease progression date per investigator assessment
  The progression date is calculated as the minimum of: *dtprfm* (formfum), *dtpdof* (formeot) and *dtpdradfu* (formfu). If the date is missing, the patient is considered to not have a disease progression per investigator assessment. Note that this definition implies that if the patient stops protocol treatment due to a non-radiologic (clinical) progression, this will not count as a disease progression.

- Clinical disease progression (non-radiologic) date per investigator assessment
  The clinical progression date is calculated as the minimum of: *dtcpdof* (formeot) and *dtpdclinfu* (formfu).

- Date of start of new anticancer treatment
  The minimum of *dtctxfu, dtrtfu, dtsurgfu, dthorfu, dttarfu, dtothfu* (formfu). If the date is missing, the patient is considered to not have started a new anticancer treatment.
  Any date relating to an anticancer treatment identified by medical review on the concomitant medication form will be taken into account in the calculation of this date.

6.11.2 Primary endpoint: Progression-free Survival by independent central review

This endpoint is defined as the time from randomization until the minimum of the date of death (Section 6.11.1) and the date of disease progression per independent central review. The independent central review process is documented in the Independent Review Charter (version 1.0, November 27, 2013)

For the primary analysis, PFS will be censored according to Food and Drug Administration (FDA) guidance on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, appendix table A. The application of the guidance will be detailed below:

This endpoint considers the following as events:

- death (Section 6.10)
- disease progression per independent central review

If the patient did not experience an event, he/she will be censored. See table 1 below for more detailed censoring and event rules for this endpoint.

A documented central independent radiologic assessment is defined as the independent central radiologic review for a radiologic (CT or MRI) disease assessment, taking place before the start of the new anticancer treatment (Section 6.11.1), if applicable.

Table 1: Censoring rules for the endpoint of progression-free survival by independent central review

Condition	Date of event /censoring	Censoring	Event
No baseline tumor assessments	Date of randomization	Yes	No
Documented Progression	Date of radiological assessment showing disease progression	No	Yes
No documented progression, no death	Date of last documented central independent radiologic assessment In the event that only baseline tumor assessments are available, the date of randomization	Yes	No
Treatment discontinuation for undocumented progression, or toxicity, or any other reason (apart from documented progression)	Date of last documented central independent radiologic assessment	Yes	No
New anticancer treatment started	Date of last documented central independent radiologic assessment before initiation of new anti-cancer treatment	Yes	No
Death before first PD assessment	Date of death	No	Yes
Death in between 2 adequate assessment visits *	Date of death	No	Yes
Death or progression after more than 1 missed adequate assessment visit *	Date of last documented central independent radiologic assessment before the missed visits	Yes	No

* Adequate on-protocol imaging requires an assessment every 6 weeks (± 7 days) until Month 12, and every 9 weeks (± 7 days) thereafter, from start of protocol treatment until progression or start of subsequent anticancer treatment.

The primary test will be performed at the 1-sided 0.025 significance level. 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). The randomization factors will be used as the strata for this 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).

The aforementioned analysis on the primary endpoint will undergo an independent validation by an EORTC statistician. The independent EORTC statistician will independently program the analysis, based on the information provided in this SAP. The output of this analysis will be compared and discrepancies will be resolved.

Sensitivity analyses

- The analysis mentioned above will be repeated in the per protocol population, to assess the robustness of the primary result.
- The analysis mentioned above will be repeated in the full ITT population, to assess the robustness of the primary result when including patients who were not centrally confirmed to be BRCA-positive.
- A non-stratified log-rank test will also be performed to assess the robustness of the primary result.
- A multivariate Cox model will be fitted to assess the robustness of the treatment effect when adjusting for (potential) prognostic factors and (potential) imbalances therein. The Cox model (with Breslow ties) will be constructed based on a backward stepwise selection method, with a two-sided 0.10 cutoff for selection, and forcing treatment arm to stay in the model. The following factors will be considered for inclusion in the model:
    - Age (< 55,55-70,>70)
    - ECOG performance status (0 vs 1-2)
    - visceral disease (yes, no)
    - histology (ductal, lobular, other)
    - number of lines of prior cytotoxic chemotherapy (not including hormonal therapy) for advanced/metastatic disease (0, 1-2)
    - prior platinum treatment (no vs yes)
    - germline mutation (BRCA-1 vs BRCA-2 vs both)

  Cases with missing values for 1 of the above factors are excluded from the model (when the factor is included in that model).

  The reporting of this analysis will contain in 1 table:

    - the fitted univariate Cox models for each of the factors (Hazard ratio for each factor and 95% 2-sided Wald CI)
    - the fitted full multivariate Cox model (Hazard ratio for each factors and 95% 2-sided Wald CI)
    - the multivariate Cox model after model selection as described above (hazard ratio for each factor and 95% 2-sided Wald CI, Type III test p-value for each factor)

Homogeneity of results across subgroups

Subgroup analyses will be performed for the following baseline factors by means of Cox models (with Breslow ties) including the factor of interest and the randomized treatment if the subgroup contains at least 10% of the patients of the centrally confirmed ITT population:

- Age (< 55,55-70,>70)

- Race (Ashkenazi Jewish descendant, White or Caucasian, Black, Native Hawaiian or Other Pacific Islander, Asian, American Indian or Alaska Native, Other)
- geographic region (US, Europe, Israel)
- ECOG performance status (0 vs 1-2)
- visceral disease (yes, no)
- histology (ductal, lobular, other)
- number of lines of prior cytotoxic chemotherapy (not including hormonal therapy) for advanced/metastatic disease, (0, 1-2)
- prior platinum treatment (no vs yes)
- germline mutation (BRCA-1 vs BRCA-2 vs both)

These subgroup analyses will be reported as forest plots containing the treatment effect hazard ratios and 95% 2-sided Wald CIs in each subgroup originating from the Cox model.

Two key subgroup analyses are defined: those by prior platinum treatment and the subgroups by BRCA mutation type. These two subgroup analyses will be supplemented with Kaplan-Meier curves by randomized treatment in each subgroup separately, as well as a stratified logrank test (97.5% 1-sided significance level) within each subgroup.

The subgroup analysis by BRCA mutation was already identified as a secondary endpoint in the protocol (Section 2.2.2). The key subgroup analysis for prior platinum treatment is added in this SAP, after the eligibility criteria related to prior platinum treatment have been weakened in amendment 4.0.

6.11.3 Secondary efficacy endpoints

6.11.3.1 Overall survival (OS) (key secondary endpoint)

This endpoint considers the following as events:

- death (Section 6.10)

This endpoint is defined as the time from randomization until the date of death (Section 6.11.1), if the patient died. If the patient did not experience an event, he/she will be censored at the last follow-up date (Section 6.2.2).

The primary analysis of this endpoint will be performed using a stratified log-rank test, performed at the 1-sided 0.025 significance level, in the OS-AR. The randomization factors will be used as the strata for this test.

Sensitivity analyses

- The analysis mentioned above will be repeated in the per protocol population, to assess the robustness of the primary result
- The analysis mentioned above will be repeated in the full ITT population, to assess the robustness of the primary result when including patients who were not centrally confirmed to be BRCA positive.
- A non-stratified log-rank test will also be performed to assess the robustness of the primary result.
- A multivariate Cox model will be fitted to assess the robustness of the treatment effect when adjusting for (potential) prognostic factors and (potential) imbalances therein. The Cox model (with Breslow ties) will be constructed based on a backward stepwise selection method, with a two-sided 0.10 cutoff for selection, and forcing treatment arm to stay in the model. The following factors will be considered for inclusion in the model:
    - Age (< 55,55-70,>70)
    - ECOG performance status (0 vs 1-2)
    - visceral disease (yes, no)
    - histology (ductal, lobular, other)
    - number of lines of prior cytotoxic chemotherapy (not including hormonal therapy) for advanced/metastatic disease (0, 1-2)
    - prior platinum treatment (no vs yes)
    - germline mutation (BRCA-1 vs BRCA-2 vs both)

Cases with missing values for 1 of the above factors are excluded from the model (when the factor is included in that model).

The reporting of this analysis will contain in 1 table:

- the fitted univariate Cox models for each of the factors (Hazard ratio for each factor and 95% 2-sided Wald CI)
- the fitted full multivariate Cox model (Hazard ratio for each factors and 95% 2-sided Wald CI)
- the multivariate Cox model after model selection as described above (hazard ratio for each factors and 95% 2-sided Wald CI, Type III test p-value for each factor)

6.11.3.2 Progression-free Survival (PFS) per investigator assessment of progression

This endpoint is defined as the time from randomization until the minimum of the date of death (Section 6.11.1) and the date of disease progression, as reported by the investigator.

For the primary analysis, per protocol, the definition for investigator reported PFS is the same as for PFS per central review, using investigator-reported PD dates instead of centrally reviewed PD dates. This is detailed below:

This endpoint considers the following as events:

- death (Section 6.10)
- disease progression as reported by the investigator (Section 6.11.1)

If the patient did not experience an event, he/she will be censored. See table 2 below for more detailed censoring and event rules for this endpoint.

A documented radiological assessment is defined as the radiologic (CT or MRI) disease assessment taking place before the start of the new anticancer treatment (Section 6.11.1), if applicable.

Table 2: Censoring rules for the endpoint of progression-free survival per investigator assessment

Condition	Date of event /censoring	Censoring	Event
No baseline tumor assessments	Date of randomization	Yes	No
No documented progression, no death	Date of last documented radiologic assessment In the event that only baseline tumor assessments are available, the date of randomization	Yes	No
Documented Progression	Date of radiological assessment showing disease progression	No	Yes
Treatment discontinuation for undocumented progression, or Toxicity or any other reason (apart from documented progression)	Date of last documented radiologic assessment	Yes	No
New anti-cancer treatment started	Date of last documented radiologic assessment before initiation of new anti-cancer treatment	Yes	No
Death before first PD assessment	Date of death	No	Yes
Death in between 2 adequate assessment visits *	Date of death	No	Yes
Death or progression after more than one missed adequate assessment visits *	Date of last documented radiologic assessment before the missed visits	Yes	No

* Adequate on-protocol imaging requires an assessment every 6 weeks (± 7 days) until Month 12 and every 9 weeks (± 7 days) thereafter, from start of protocol treatment until progression or start of subsequent anticancer treatment.

The main analysis of this endpoint will be performed using a stratified log-rank test, performed at the 1-sided 0.025 significance level. The randomization factors will be used as the strata for this test.

Sensitivity analyses

- The analysis mentioned above will be repeated in the per protocol population, to assess the robustness of the primary result.
- The analysis mentioned above will be repeated in the full ITT population, to assess the robustness of the primary result when including patients who were not centrally confirmed to be BRCA positive.
- A non-stratified log-rank test will also be performed to assess the robustness of the primary result.

6.11.3.3 Response to treatment

Response to treatment will be reported **for all patients** in the centrally confirmed ITT population by randomized treatment arm:

- Tabulation of the best overall response to treatment (complete response [CR], partial response, stable disease [SD], disease progression [PD], early death, not assessable/evaluable) by medical review (formdm01: *respev*).
- Tabulation of overall response rate (CR or partial response) by medical review (formdm01: *respev=1,2* versus *respev=3,4,5,8*); for each treatment arm, the response rate if supplemented by a 2-sided 95% CI (Pearson-Clopper method). The Pearson's chi-square test for association will be performed to compare the overall response rate (ORR) between treatment arms and the corresponding p-value will be displayed.

Duration of response to treatment will be reported in the efficacy population, restricted to those patients who obtained a response (CR or partial response) by medical review (formdm01: *respev=1,2*), by randomized treatment arm.

- The duration of response is calculated as the time from response until the first event of investigator-reported disease progression or death whichever occurs earlier (Section 6.11.3.2). The same censoring rules as for investigator-reported disease progression apply (Section 6.11.3.2). The duration of response will be reported using the Kaplan-Meier method. Kaplan-Meier curves by randomized treatment arm will be shown. Medians - if reached - will be presented with a 2-sided 95% CI, based on the nonparametric method (Brookmeyer & Crowley, 1982).

6.11.3.4 Time to treatment failure

Time to treatment failure considers the following as events:

- End of protocol treatment for any reason (including death) (formeot: *dtlast*)
- Disease progression as reported by the investigator (Section 6.11.1)

Time to treatment failure is defined as the time from randomization until the date of the first event (date of last treatment administration on end of treatment form). If the patient does not experience an event, he/she will be censored at the last dose date or last tumor assessment date whichever occurs later (Section 6.2.2).

Patients that never started any protocol treatment will be censored at time of randomization.

The main analysis of this endpoint will be performed using a stratified log-rank test, performed at the 1-sided 0.025 significance level. The randomization factors will be used as the strata for this test.

Sensitivity analyses

- The analysis mentioned above will be repeated in the per-protocol population, to assess the robustness of the primary result
- The analysis mentioned above will be repeated in the full ITT population, to assess the robustness of the primary result when including patients who were not centrally confirmed to be BRCA-positive.
- A non-stratified log-rank test will also be performed to assess the robustness of the primary result.

6.12 Interim analysis for futility for progression free survival

This interim analysis will be reported in the centrally confirmed ITT population.

PFS by central independent review will be analyzed as specified in Section 6.11.2.

A CCD for the interim analysis will be determined based on an estimate of when the required 93 events will be reached. At time of database lock, the true number of observed events can be slightly more or less than 93. 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 and the minimum total target number of events of 137 will be used for the interim futility analysis of PFS (i.e. the information fraction for futility analysis is equal to the number of events observed at the interim analysis divided by 137). The futility boundary will be assessed by the EAST 6 software).

Based on the accrual rate and PFS median assumptions, the enrollment will be done after 137th event and the final PFS analysis will be done at the end of enrollment. The information fraction calculated based on 137 events will be larger than the information fraction calculated based on the total number of events at the end of enrollment. This larger information fraction will yield a smaller hazard ratio futility boundary which allows the trial to be stopped more easily if the experiment drug is not efficacious.

In order to fully evaluate the interim data, the projected numbers of PFS and OS events by the end of enrollment will be provided in the IDMC reports. The projections will be done using the interim data based on the following:

1. Past accrual and projected future accrual
2. Observed PFS rates and assumptions going forward
3. Observed death rates and assumptions going forward.

6.13 Interim analysis for overall survival

An interim analysis for overall survival will be reported in the centrally confirmed ITT population at the time of the final PFS analysis.

This interim analysis will be performed using the locked database for the FAR. OS will be analyzed as specified in Section 6.11.3.1.

The interim analysis rule for early efficacy will be assessed using the EAST 6 software, using the original design (i.e. target number of events) as implemented in the protocol (version 6, January 13, 2017). The interim analysis will utilize O'Brien-Fleming type boundaries derived from the Lan DeMets alpha spending function based on the actual number of events observed at the time of the interim analysis.

6.14 Quality of Life

Before the database lock for the FAR, the database will be checked for compliance to the HRQoL schedule detailed in Section 10.4.1 of the protocol (version 6, January 13, 2017). The following considerations are subject to the outcome of this compliance review and will be detailed in a separate SAP which will be finalized before the database lock.

Statistical considerations

Data from the EORTC quality of life questionaire-C30 (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 are linearly converted to 0-100 scales.

The primary health-related quality of life (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 (Section 6.10)
- disease progression (Section 6.11.1)
- 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/quality-of-life (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.

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% CIs.

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, disease 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 the event that a significant difference is found in TTQ, the endpoint will be split up by its various events (death, disease progression, and the selected scales) 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 2 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 statistical estimation and corresponding 95% CI. For the 2 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.

Missing data

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

To check the potential impact of missing HRQoL data 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, multiple 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 who 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 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 the event that overall compliance is deemed too low (< 50%), only an exploratory analysis will be performed in lieu of the main analysis.

7 Overview table for the 4 analysis reports

Section	Section title	IDMC-PFS	FAR	IDMC-OS*	OS-AR
6.2	Patient availability	X	X		X (only sections 6.2.2 and 6.2.4)
6.5	Baseline characteristics	X	X		
6.6	Compliance to the protocol	X	X		
6.7	Exposure to treatment	X	X		X (limited to relative dose intensity and number of cycles received)
6.8	Safety evaluations	X	X		X
6.9	Reasons for stopping treatment	X	X		X
6.10	Disease status	X	X (excluding deaths not pertaining to the primary endpoint)	X (limited to deaths)	X
6.11.2	Primary endpoint: PFS by independent central review		X		X
6.11.3.1	Overall survival	X (excluding sensitivity analyses)			X
6.11.3.2	PFS per investigator assessment		X		X
6.11.3.3	Response to treatment		X		X
6.11.3.4	Time to treatment failure		X		X
6.12	Interim analysis for futility for PFS	X			
6.13	Interim analysis for overall survival			X	

6.14	Quality of Life		X		X

* In addition, the IDMC is supplied with the FAR

8 Bibliography

Brookmeyer, R., & Crowley, J. (1982). A confidence interval for the median survival time. *Biometrics*, 29-41.

Lin, D., Wei, L., & Ying, Z. (1993). D.Y. Lin, L.J. Wei et al (1993). Checking the Cox model with cumulative sums of martingale-based residuals. *Biometrika*, 557-572.

Schemper, M., & Smith, T. (1996). A note on quantifying follow-up in studies of failure time. *Controlled clinical trials*, 343-346.

9 Appendix 1: List of case report forms (CRFs)

SAS Form code	Form name
form905	health economics questionnaire
form930	QoL C-30
formae	adverse events form
formcenbrca	central BCRA mutation test form
formdm01	medical review form
formdh	disease history form
formmh	medical history form
formeot	end of treatment form
formfu	follow-up form
formfum	follow-up measurements form (RECIST 1.1)
formim	initial measurements form (RECIST 1.1)
formlbbio	biochemistry form
formlbhem	hematology form
formmyh	myelosuppresion history form
formnllab	normal ranges lab form
formothbrca	previous brca mutation test form
formpe	physical examination form
formsf	screening failure form
formtrtc	capecitabine treatment form
formtrte	eribulin treatment form
formtrtg	gemcitabine treatment form
formtrtn	niraparib treatment form
formtrtviv	IV vinorelbine treatment form
formtrtvo	oral vinorelbine treatment form
formrg1	screening-registration form (values provided at time of screening)
formrg2	eligibility checklist form (values provided at time of randomization)
formcrg1	screening-registration form (potentially corrected values)
formcrg2	eligibility checklist form (potentially corrected values)
patient	patient identifier form

10 Appendix 2: Tables and listing to be provided to IDMC for safety review

Output Type (T/L/F)	Number	Title	Analysis Set
Accrual information			
T	I.1	Cumulative Proportion of Subjects Randomized by Calendar Time	Full ITT population
F	F.1	Subject Accrual over time	Screening population
T	I.2	Subject Accrual by site	Screening population
T	I.3	Number of patients registered per site	Screening population
F	F.2	Number of patients registered per site	Screening population
T	I.4	Accrual by country	Screening population
Study Conduct and Patient Disposition			
T	C1	Eligibility status	Full ITT population
L	C.2	Listing of ineligible patients	Full ITT population
T	C.3	Compliance to treatment allocation	Full ITT population
T	C.4	Patient disposition and reason for discontinuation	Full ITT population
L	C.5	Listing of patients who are not treated as randomized	Full ITT population
Kaplan-Meier	C.6	Time to protocol treatment discontinuation	Full ITT population
T	C.7	Distribution of stratification factors	Full ITT population
L	C.8	Listing of patients who are lost-to-follow-up/withdrew from study	Full ITT population
Baseline data			
T	B.1	Demographic characteristics	Full ITT population
T	B.2	Primary Diagnoses and time since diagnosis	Full ITT population
T	B.3	Baseline Characteristics (incl. ECOG Performance Status)	Full ITT population
Study Treatment Exposure			
T	T.1	Number of cycles received	Safety population
T	T.2	Dose Interruptions, Reductions - overall	Safety population
T	T.3	Dose Interruptions, Reductions – by cycle	Safety population
T	T.4	Reason for first dose interruption/reduction	Safety population
T	T.5	Reason for stopping protocol treatment	Safety population
Adverse Events Data			
T	A.1	Discontinuations Due to toxicity	Safety population
T	A.2	Temporary Discontinuations or Dose Reductions Due to toxicity	Safety population

T	A.3	Overall Summary of Adverse Events (worst grade during treatment)	Safety population
Kaplan-Meier	F.3	Kaplan-Meier Plots of Time to First Occurrence of Most Common Treatment Related grade 3-4 Adverse Events	Safety population
T	A.4	Cause of Death	Safety population
L	A.5	Listing of Deaths and the cause	Safety population
L	A.6	Listing of serious Adverse Events	Safety database
L	A.7	Listing of (likely) treatment related adverse events that led to drug discontinuation	Safety population
L	A.8	Listing of grade ≥ 3 Adverse events	Safety population
Laboratory Data			
T	L.1	Laboratory Results Summary by Maximum CTC Grade (Hematology, Cycle 1)	Safety population
T	L.2	Laboratory Results Summary by Maximum CTC Grade (Hematology, By Cycle, All cycles)	Safety population
T	L.3	Laboratory Results Summary by Maximum CTC Grade (Chemistries, All Cycles)	Safety population
T	L.4	Laboratory Results Summary by Maximum CTC Grade (Chemistries, Cycle 1)	Safety population
L	L.5	Listing of CTC grade ≥ 3 (chemistries/hematology)	Safety population