NRG ONCOLOGY

NSABP PROTOCOL B-55/BIG 6-13

ClinicalTrials.gov NCT02032823

A Randomised, Double-Blind, Parallel Group, Placebo-Controlled Multi-Centre Phase III Study to Assess the Efficacy and Safety of Olaparib Versus Placebo as Adjuvant Treatment in Patients with Germline *BRCA1/2* Mutations and High Risk HER2 Negative Primary Breast Cancer Who Have Completed Definitive Local Treatment and Neoadjuvant or Adjuvant Chemotherapy

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations (U.S. Institutions only): the Alliance for Clinical Trials in Oncology, ECOG-ACRIN Cancer Research Group, NRG Oncology, and SWOG.

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Protocol B-55/6-13 IND #122443 (olaparib), sponsored by NRG Oncology, Inc.

STUDY DRUG	NSC#	DRUG SUPPLY
Olaparib	747856	AstraZeneca, through the NCI

NRG ONCOLOGY
NSABP PROTOCOL B-55/BIG 6-13

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A randomised, double-blind, parallel group, placebo-controlled multi-centre Phase III study to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with germline *BRCA1/2* mutations and high risk HER2 negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy

Sponsor: *AstraZeneca Ab, 151 85 Södertälje, Sweden*

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PROTOCOL SYNOPSIS

A randomised, double-blind, parallel group, placebo-controlled multi-centre Phase III study to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with germline *BRCA1/2* mutations and high risk HER2 negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy

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Study centre(s) and number of patients planned

The study will be conducted in approximately 25 countries worldwide. Approximately 700 centres (in the US and Rest of the World countries) will be initiated to randomise approximately 1800 patients. Additional countries and sites may be added dependent on recruitment rates.

Approximately 150 randomised patients* will be analysed for pharmacokinetic (PK) at those sites that have confirmed that they are able to collect the PK assessment samples. PK sampling will be performed in a subset of patients who sign optional PK Informed consent. PK sampling will not be done in the US.

Study period		Phase of development
Estimated date of first patient enrolled	Q1 2014	III
Estimated date of last patient completed	2028	

* No placebo samples will be analyzed unless requested.

Objectives

Primary Objective

The primary objective is to assess the effect of adjuvant treatment with olaparib on Invasive Disease Free Survival (IDFS)

Safety Objective

To assess the safety and tolerability of adjuvant treatment with olaparib

Secondary Objectives

1. To assess the effect of adjuvant treatment with olaparib on overall survival (OS)

2. To assess the effect of adjuvant treatment with olaparib on Distant Disease Free Survival (DDFS)

3. To assess the effect of adjuvant treatment with olaparib on the incidence of new primary contralateral invasive breast cancer, primary contralateral non-invasive breast cancer, new primary ovarian cancer, new primary fallopian tube cancer and new primary peritoneal cancer

4. To assess the effect of olaparib on patient reported outcomes using the FACIT-Fatigue and EORTC QLQ-C30 questionnaires

5. To assess the efficacy of olaparib in patients identified as having a deleterious or suspected deleterious variant in either of the *BRCA* genes using variants identified with current and future germline *BRCA* mutation assays (gene sequencing and large rearrangement analysis)

6. To determine the exposure to olaparib (in plasma) in patients receiving olaparib as adjuvant therapy.

Exploratory Objectives

The exploratory objectives of this study are:

1. To assess the consistency of treatment effects on efficacy endpoints across potential or expected prognostic factors, including the baseline stratification factors with special emphasis on hormone receptor status

2. To explore methods for estimating overall survival (OS) adjusting for the impact of confounding by subsequent therapies, specifically the control arm receiving subsequent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitors or platinum salts

3. To explore whether resistance mechanisms to olaparib can be identified through analysis of tumour and blood sample derivatives (cells, plasma and protein and nucleic acid derivatives) - archival tumour samples (mandatory*), tumour sample at

recurrence (optional) and blood samples at baseline, 30 days post study treatment and on disease recurrence (mandatory)

*For adjuvant patients, this refers to the surgical specimen; for neoadjuvant patients, both the pre-treatment core biopsy and the surgical specimen with residual disease are requested but only one is mandatory. If the surgery tumour blocks are available, but cannot be submitted, sites may submit a portion of invasive tumour from the original block, either by taking at least one core of at least 3 mm in diameter, or by splitting the original block in two parts, and re-embedding one in a new block for central submission. If blocks containing pre-neoadjuvant treatment core biopsies are available but cannot be submitted, sections mounted on glass slides prepared from the block can be provided. If tumour sample can't be provided as requested above or if it's not available, approval by Study Team for patient's entry into the trial is required.

4. To determine the frequency of and describe the nature of *BRCA* mutation/s in tumour samples and to compare this with germline *BRCA* mutation status

5. To conduct future exploratory research into factors that may influence development of cancer and/or response to treatment (where response is defined broadly to include efficacy, tolerability or safety). This may be performed on the collected and stored tumour and blood samples

6. To collect and store DNA according to each country's local and ethical procedures for future exploratory research into genes/genetic variation that may influence response (i.e. distribution, safety, tolerability and efficacy) to study treatments and/or susceptibility to disease (optional)

Study delivery model

This is a collaborative study being coordinated worldwide by the Breast International Group (BIG) in partnership with Frontier Science (FS), NRG Oncology (NCI supported National Clinical Trials Network Group) and AstraZeneca (AZ). Two versions of this protocol have been written to cover this global adjuvant breast cancer study. One protocol version covers all patients recruited outside of the US (where AZ is the sponsor) and one protocol version covers patients recruited within the US (where NRG Oncology is the sponsor). The two versions of the protocol are identical in terms of study objectives and scientific content and only differ in logistical content appropriate for the country(ies) they cover (i.e. drug distribution, mechanisms for SAE reporting during the study, etc.). Based on current recruitment rates, it is expected that approximately 230 patients will be randomised under the US protocol and approximately 1570 patients will be randomised under the Rest of the World protocol.

The trial will use one randomisation system and report as one single study. The initial collection of the patients' data will be done using two databases (one for the US patients and one for all other patients outside of the US). The two databases will be set up using the same standards and eCRFs to ensure consistency in the data collection. The data from both databases will be combined into a single consolidated database at regular, pre-specified intervals. All study endpoints as well as reports for periodic review by the Independent Data Monitoring Committee

(IDMC) will be analysed and reported from the single combined reporting database held by Frontier Science on behalf of BIG.

Study design

This is a randomised, double-blind, parallel group, placebo-controlled multi-centre Phase III study to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with germline *BRCA1/2* mutations and high risk HER2 negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy.

Patients will be randomised in a 1:1 ratio to either olaparib or placebo. Randomisation will be stratified by hormone receptor status (ER and/or PgR positive/HER2 negative versus TNBC), by prior neoadjuvant versus adjuvant chemotherapy, and prior platinum use for breast cancer (yes versus no).

Eligible patients with deleterious or suspected deleterious *gBRCA* mutations and high risk HER2 negative breast cancer should be randomised in the trial ideally within a maximum of 8 weeks of completing their last treatment modality (chemotherapy and definitive local or locoregional treatment), but in no case longer than 12 weeks. Randomised patients will receive study treatment for up to a maximum of 12 months. All patients will have safety assessments every 2 weeks during the first month, every 4 weeks for the following 5 months (up to week 24) and 3 monthly for the remaining 6 months of study treatment plus 30 days after its discontinuation. All randomised patients will have clinical assessment visits for approximately 10 years following their randomisation into the study, or until an IDFS endpoint due to a breast cancer related distant relapse, whichever comes first. They then enter the annual survival follow-up phase of the trial, which will continue until 10 years after the last patient is randomised. No clinic visits will be required during the survival follow-up phase; information may be collected via telephone, medical records or death registries.

Target patient population

Patients eligible for the trial are those with a deleterious or suspected deleterious germline *BRCA* mutation (defined by local or central Myriad testing) with high risk HER2 negative primary breast cancer who have completed definitive local treatment, and neoadjuvant or adjuvant chemotherapy. Definitions of high risk HER2 negative patients are provided below.

1. For patients who underwent initial surgery and received adjuvant chemotherapy

   - TNBC patients must have been axillary node-positive-(≥pN1, any tumour size) or axillary node negative (pN0) with invasive primary tumour pathological size > 2 cm (≥pT2).

   - ER and/or PgR positive/HER2 negative patients must have had ≥ 4 pathologically confirmed positive lymph nodes.

2. For patients who underwent neoadjuvant chemotherapy followed by surgery

   – TNBC patients must have residual invasive breast cancer in the breast and/or resected lymph nodes (non pCR)

   – ER and/or PgR positive/HER2 negative patients must have residual invasive cancer in the breast and/or the resected lymph nodes (non pCR) AND a CPS&EG score ≥3. (Clinical stage (CS), estrogen receptor status (E), nuclear grade (G), and post-treatment pathologic stage (PS) – a disease scoring system). Instructions how to calculate CPS&EG score (Mittendorf et al 2011; Jeruss et al 2008) are provided in Appendix H.

Germline *BRCA1* and *BRCA2* (*gBRCA*) testing

Local *gBRCA* testing results, if available, can be used for establishing eligibility. If local *gBRCA* testing results are not available, central testing will be provided for those patients who otherwise appear to be eligible. Irrespective of the availability of local *gBRCA* testing results, all patients must provide a sample for central *gBRCA* testing.

Central tumour analyses (e.g. somatic *BRCA1/2* functional status, ER/PgR and HER2 status)

Archival tumour samples must be provided for all patients.

For adjuvant patients, this refers to the surgical specimen; for neoadjuvant patients, both the pre-treatment core biopsy and the surgical specimen with residual disease are requested but only one is mandatory. If the surgery tumour blocks are available, but cannot be submitted, sites may submit a portion of invasive tumour from the original block, either by taking at least one core of at least 3 mm in diameter, or by splitting the original block in two parts, and re-embedding one in a new block for central submission. If blocks containing pre-neoadjuvant treatment core biopsies are available but cannot be submitted, sections mounted on glass slides prepared from the block can be provided. If tumour sample can't be provided as requested above or if it's not available, approval by Study Team for patient's entry into the trial is required.

Study treatment, dosage and mode of administration

AstraZeneca's Pharmaceutical Development, R&D Supply Chain will supply olaparib and matching placebo as green film-coated tablets to the Pharmaceutical Management Branch, Division of Cancer Therapy and Diagnosis, National Cancer Institute.

Patients will be randomised in a 1:1 ratio to one of the following treatments:

- 12 months treatment with olaparib tablets p.o. 300 mg twice daily (two 150 mg tablets in the morning and two 150 mg tablets in the evening)

- 12 months treatment with matching placebo tablets p.o. twice daily (two tablets in the morning and two tablets in the evening)

Stratification

Patients will be stratified at randomisation by the following baseline factors:

- Hormone receptor status (ER and/or PgR positive/HER2 negative versus TNBC)

  NOTE: In cases of multifocal, multicentric or synchronous bilateral invasive disease, stratification is based on the status of the lesion considered at highest risk (at the investigator's discretion) that was used to determine eligibility.

- Neoadjuvant versus adjuvant chemotherapy
- Platinum therapy for current breast cancer: Yes/No

Within this study, patients will not be provided with olaparib post discontinuation of study treatment. Patients and investigators will not be routinely unblinded to study treatment prior to the final overall survival (OS) analysis. Unblinding is allowed only in the case of compelling medical or safety reasons (Section 5.4.2).

Outcome(s):

- Primary outcome
  - Invasive Disease Free Survival (IDFS)
- Secondary outcomes
  - Overall Survival (OS)
  - Distant Disease Free Survival (DDFS)
  - New primary contralateral breast cancers (invasive and non-invasive), new primary ovarian cancer, new primary fallopian tube cancer, and new primary peritoneal cancers in patients at risk for these events
  - FACIT-Fatigue symptom scale score and EORTC-QLQ-C30 global health status, functional, and symptoms scales/items scores
  - IDFS, DDFS and OS based on patients with *gBRCA* mutations confirmed by the central test (only required if population differs from the ITT (intention to treat) population)
  - Pharmacokinetic analysis
- Safety outcomes
  - Adverse Events (AE), physical examination, vital signs including blood pressure (BP), pulse, and laboratory findings including clinical chemistry and haematology

- Exploratory outcomes
  - Potential retrospective biomarker (mandatory) & pharmacogenetic research (optional)
  - Adjusted overall survival estimates (if applicable)

Statistical methods

The primary endpoint of the study is IDFS and patients will be randomised 1:1 to either olaparib 300 mg b.i.d. (twice daily) or matching placebo.

Approximately1800 patients will be randomised into the study. If the true hazard ratio for the comparison of olaparib versus placebo in terms of IDFS is 0.7 then with 330 events, the analysis of IDFS will have 90% power to demonstrate a statistically significant difference in IDFS, assuming a 2-sided 5% significance level. It is estimated the study will take approximately 5 years to complete recruitment of approximately 1800 patients. The primary analysis will be triggered by the occurrence of 330 IDFS events (required for overall 90% power to detect a HR of 0.7). Assuming a nonuniform recruitment, the primary analysis is estimated to occur approximately 6 years from the start of randomisation.

An interim analysis for superiority will be performed once a minimum of 165 IDFS events have been observed from the first 900 patients recruited. It is estimated that this analysis will occur approximately 5.3 years after the first patient is randomised. Consideration of futility will also be made at the time of interim analysis.

Safety data will be summarised descriptively in terms of AEs, vital signs, clinical chemistry & haematology and physical exam and will include all patients who received at least one dose of olaparib or placebo.

Patient reported outcomes and health related quality of life (HRQoL) will be assessed through the planned correlative study using the FACIT-Fatigue and the EORTC QLQ-C30 questionnaires.

An analysis of IDFS, DDFS and OS will be conducted based on patients with *gBRCA* mutations confirmed by the central test, if this population differs from the primary ITT population. Similar sensitivity analyses will be performed based on ER and/or PgR positive/HER2 negative and TNBC subsets as defined by the central laboratory testing.

Full details of all the statistical analyses will be documented in the SAP. Version 1.0 of the SAP will be prepared prior to first subject in (FSI).

Pharmacokinetic analysis

The plasma concentration-time data will be analysed by non-linear mixed effects modelling in order to evaluate the pharmacokinetic characteristics of olaparib, quantify variability in the pharmacokinetics, identify demographic or pathophysiological covariates, which may explain the observed variability and explore exposure-response relationships.

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INFORMATION RESOURCES

NRG Oncology (http://www.nrgoncology.org)		
NRG Oncology	Nova Tower 2 Two Allegheny Center – Suite 1200 Pittsburgh, PA 15212-5402	Phone: 412-339-5300
NRG Oncology Statistics and Data Management Center (SDMC)	One Sterling Plaza 201 North Craig Street, Suite 500 Pittsburgh, PA 15213	Phone: 412-624-2666 Fax: 412-624-1082 (General office fax)
Questions/problems regarding IRB review & informed consent	NRG Oncology Pittsburgh Department of Regulatory Affairs	Phone: 412-339-5300 E-mail: regulatory@nsabp.org
Submission of IRB approval	CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103	Submit to the CTSU via the Regulatory Submission Portal (www.ctsu.org)
Questions concerning eligibility and clinical aspects of the trial	NRG Oncology Pittsburgh Clinical Coordinating Department	Phone: 1-800-477-7227 E-mail: ccdPGH@NRGOncology.org
Study entry information (see Section 5.2)	NRG Oncology SDMC Patient Entry Coordinator	Phone: 412-383-4900
Request for kits for tumor and blood sample collections	*Refer to the B-55/6-13 Pathology and Correlative Science Instructions in the B-55 Web page of the CTSU Member Web site at https://www.ctsu.org.*	
Arrangement for return of blocks that are not to be stored	NRG Oncology Biospecimen Bank - Pittsburgh	Phone: 412-697-6611 E-mail: NRGbiobankPGH@NRGOncology.org
Questions concerning drug orders, shipments, transfers, and returns of olaparib (see Section 5.5)	NRG Oncology SDMC	Phone: 412-624-2666 Fax: 412-624-1082
	For mail (USPS): Pharmaceutical Management Branch, CTEP, DCTD NCI Shady Grove Room 5W228, MSC 9725 9609 Medical Center Drive Bethesda, MD 20892-9725 ***For express courier:*** Pharmaceutical Management Branch, CTEP, DCTD NCI Shady Grove Room 5W228, MSC 9725 9609 Medical Center Drive Rockville, MD 20850	Phone: 240-276-6575 Fax: 240-276-7893 E-mail: PMBAfterHours@mail.nih.gov

Continued on next page.

INFORMATION RESOURCES (continued)

Requests for unblinding (including 24-hour emergency unblinding)	NRG Oncology SDMC	Phone: 412-624-2666
Questions concerning expedited adverse event reporting (see Section 6.4.8)	NRG Oncology SDMC B-55/6-13 AE Reporting Nurse	Phone: 412-383-2557 Fax: 412-624-1082 E-mail: SAEReportingPGH@NRGOncology.org
Submission of patient-completed questionnaires (see Section 6.1.2)	NRG Oncology SDMC B-55/6-13 Data Manager	Phone: 412-624-2666 Fax: 412-622-2115 *Refer to the B-55/6-13 Data Forms on the B-55 Web page of the CTSU Member Web site at https://www.ctsu.org.*
Submission of data forms/questions concerning data management and Medidata Rave	NRG Oncology SDMC B-55/6-13 Data Manager	Phone: 412-624-2666 *Refer to the B-55/6-13 Data Forms on the B-55 Web page of the CTSU Member Web site at https://www.ctsu.org.*

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using Oncology Patient Enrollment Network (OPEN), which can be accessed at https://www.ctsu.org/ OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to Section 6.1.2 for further instructions. Submit patient-completed questionnaires to the NRG Oncology as directed on the worksheet. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submission.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU Members' website is managed through the Cancer Therapy and Evaluation Program-Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For clinical questions (i.e., patient eligibility and treatment-related), contact the Clinical Coordinating Department at NRG Oncology at 1-800-477-7227 or by e-mail at ccdPGH@NRGOncology.org.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or email: CTSU General Information Line – 1-888-823-5923 or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org.		

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.4.5)
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute Myeloid Leukaemia
ANC	Absolute neutrophil count
APTT	Activated Partial Thromboblastin Time
ASCO	American society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area Under Curve
b.i.d	Twice daily
BP	Blood Pressure
BRCA	Breast cancer susceptibility gene
BUN	Blood Urea Nitrogen
CA-125	Cancer antigen-125
cfDNA	Circulating free DNA
CHO	Chinese hamster ovary
CI	Confidence Interval
$Cmax_{ss}$	Maximum concentration at steady state
$Cmin_{ss}$	Minimum concentration at steady state
CNS	Central Nervous System
CPS&EG	Clinical stage (CS), estrogen receptor status (E), nuclear grade (G), and post-treatment pathologic stage (PS) - a disease scoring system
CR	Complete Response
CRF (eCRF)	Case Report Form (electronic/paper)
CRO	Contract Research Organisation
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computerised Tomography
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation or special term	Explanation
CTEP	Cancer Therapy Evaluation Program
CTEP-AERS	CTEP Adverse Event Reporting System
CTEP-IAM	CTEP Identity and Access Management
CTSU	Cancer Trials Support Unit
DAE	Discontinuation of study treatment due to Adverse Event
DCIS	Ductal carcinoma *in situ*
DCO	Data cut off
DCTD	Division of Cancer Treatment and Diagnosis
DDFS	Distant disease free survival
DFS	Disease free survival
DNA	Deoxyribonucleic acid
DSB	Double strand break
DUS	Disease under Study
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECOG performance status	Eastern Cooperative Oncology Group performance status using scales and criteria to assess how a patient's disease is progressing
EORTC QLQ-C30	The European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core questions 30
ER	Estrogen receptor
ESMO	European Society for Medical Oncology
ESTRO	European Society for Radiation and Oncology
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Measurement questionnaire
FAS	Full Analysis Set
FFPE	Formalin Fixed Paraffin Embedded
FSH	Follicle Stimulating Hormone
g*BRCA* mutation or g*BRCA*m	The term "g*BRCA* mutation" is used to refer to a germline *BRCA*1 or *BRCA*2 mutation classified as "deleterious" or "suspected deleterious" in accordance with the American College of Medical Genetics and Genomics recommendations for standards for interpretation and reporting of sequence variants
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor

Abbreviation or special term	Explanation
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HER2	Human Epidermal Growth Factor Receptor 2
Hgb	Hemoglobin
HR	Hazard Ratio
HRD	Homologous Recombination Deficiency
HRQoL	Health Related Quality of Life
IAM	Identity and Access Management
IB	Investigators Brochure
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries, the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IDFS	Invasive Disease-free Survival
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
IIBTR	Ipsilateral invasive breast tumour recurrence
INR	International Normalised Ratio
IPCW	Inverse Probability of Censoring Weighting
IRB	Institutional Review Board
ISH	In Situ Hybridisation (includes FISH, DISH, CISH)
ISS	Investigator Sponsored Study
ITT	Intention To Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LDH	Lactic Dehydrogenase
LIMS	Laboratory Information Management System
LLOQ	Lower Limit of Quantification
LSI	Last Subject in
LSLV	Last Subject Last Visit
MCH	Mean Cell Haemoglobin
MCHC	Mean Cell Haemoglobin Concentration

Abbreviation or special term	Explanation
MCV	Mean Cell Volume
MDS	Myelodysplastic Syndrome
MMRM	Mixed Model for Repeated Measures
MRI	Magnetic Resonance Image
MTD	Maximum Tolerated Dose
MTP	Multiple testing procedure
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCTN	National Clinical Trials Network
NSABP	National Surgical Adjuvant Breast and Bowel Project
NSC	National Service Center
NSCLC	None Small cell lung cancer
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
OD	Once Daily
OPEN	Oncology Patient Enrollment Network
OR	Objective Response
ORR	Objective Response Rate
OS	Overall survival
PARP	Polyadenosine 5'diphosphoribase [poly (ADP ribose)] polymerisation
pCR	Pathological Complete Response
PD	Pharmacodynamics
PFS	Progression Free Survival
PFS2	Time to second progression
PgR	Progesterone receptor
PGx	Pharmacogenetic research
PI	Principal Investigator
PK	Pharmacokinetics
PMB	Pharmaceutical Management Branch
PO	*Per Os* (by mouth)
PRO	Patient Reported Outcome
QOL	Quality of Life

Abbreviation or special term	Explanation
QT/QTc	A measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle (c indicates the corrected value for this time period)
RBC	Red Blood Cells
RECIST	Response Evaluation Criteira in Solid tumours. This study will use modified RECIST version 1.1.
REML	Restricted Maximum Likelihood
RPSFT	Rank Preserving Structural Failure Time
RSS	Regulatory Support System
SAE	Serious adverse event (see definition in Section 6.4.6).
SAP	Statistical Analysis Plan
SCLC	Small Cell Lung Cancer
SD	Stable Disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SNB	Sentinel Node Biopsy
SSB	Single Strand Break
STEEP	Standardised Terms for Efficacy Endpoints
Study treatment	Study treatment is the treatment to which patient was randomised. In this study it is either olaparib or placebo
TN1-3	TNM classification. Axillary node positive disease regardless of the tumour size
TNBC	Triple negative breast cancer
TPC	Chemotherapy of physician's choice
ULN	Upper Limit of Normal
WBC	White Blood Cells
WBDC	Web Based Data Capture
Wt	Wildtype (patients without evidence of *BRCA1* or *BRCA2* deleterious or suspected deleterious mutations)

1. INTRODUCTION

1.1 Background

1.1.1 Breast cancer and its treatment

Breast cancer is a life-threatening disease and is the second leading cause of cancer death among women. In 2013, an estimated 232,340 new cases of invasive breast cancer were expected to be diagnosed among US women, and approximately 39,620 women were expected to die from breast cancer (American Cancer Society 2013). In the European Community, the estimated age adjusted annual incidence in 2008 was 88.4/ 100 000 and the mortality 24.3/100 000 (Aebi et al 2011).

Approximately 5% of breast cancers are associated with a mutation in the *BRCA1* and/or *BRCA2* gene with approximately 3% associated with the *BRCA1* gene (generally presenting with TNBC phenotype) and approximately 2% associated with the *BRCA2* gene (generally ER/PgR positive phenotype). In the general population, *BRCA* mutation carriers have an increased relative risk of breast cancer. The presence of *BRCA1* mutations is associated with a lifetime risk of breast cancer of 60 to 70% and a lifetime risk of ovarian cancer of 20 to 45% (Antoniou et al 2003). *BRCA*2 mutations are associated with lifetime risk of breast cancer of 40 to 60% in women and 5 to 10% in men and a lifetime risk of ovarian cancer of 10 to 20%. Rare individuals carry deleterious mutations in both *BRCA1* and *BRCA2* genes.

In breast cancer, there are differences between *BRCA1* and *BRCA2* mutation carriers. Approximately 70% of breast cancer patients with *BRCA1* mutations present as triple negative breast cancer (TNBC). In contrast, patients carrying mutations in the *BRCA2* gene are more likely to be positive for expression of the estrogen receptor in their breast cancer while approximately 20% will have triple negative cancers (Mavaddat et al 2012).

Although there are phenotypic differences in breast cancers resulting from *BRCA1* or *BRCA2* mutations, their important commonality is that mutations in either gene result in tumours that are deficient in homologous recombination, making both appropriate for treatment with polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitors whereby the process of synthetic lethality can be exploited. In a previous AstraZeneca sponsored Phase II proof of concept study in patients with breast cancer carrying *BRCA* mutations (Study D0810C00008), approximately 60% of cases were *BRCA1* mutations (the other 40% were *BRCA2* mutations) with 55% of tumours overall triple negative in phenotype. In this study, anti-tumour activity was seen in patients with either *BRCA1* or *BRCA2* mutations (Tutt et al 2010).

Given the small size of the *BRCA* subpopulation in breast cancer, information comparing the outcome from this subpopulation with the overall breast cancer population is based on reports from a number of small studies (Robson et al 2004, Rennert et al 2007, Bordeleau et al 2011, Goodwin et al 2012), and firm conclusions cannot be drawn. The overall body of evidence suggests that once baseline prognostic factors (such as hormone receptor and HER2 status) and treatment are taken into account, patients with *BRCA* mutations have a similar outcome to their sporadic counterparts (Huzarski et al 2013). This is in contrast to patients with *BRCA1*/*BRCA2*-

related ovarian cancer who have an improved survival compared with non-carriers, particularly if they receive platinum-based therapy.

Currently, there are no approved treatments specific for germline *BRCA1/2* mutated breast cancer patients and these patients are treated according to their hormone receptor and HER2 status.

1.1.2 Triple Negative Breast Cancer (TNBC)

TNBC is a particular subset of breast cancer defined by lack or low immunohistochemical expression of ER, PgR and HER2 (IHC 0, 1+ or 2+ /FISH non-amplified) and represents approximately 12-17% of breast cancer overall (Foulkes et al 2010). Although it is a heterogeneous group, patients with TNBC have generally poor prognosis (Metzger-Filho et al 2010). The fundamental clinical characteristic of TNBC is early recurrence with likely early visceral metastases, as well as shorter period from time to recurrence to death as compared with other breast cancer types (Dent et al 2007). Chemotherapy remains the ultimate treatment option for those patients with varied impact on long-term prognosis. No targeted treatment has been developed for TNBC, in contrast to endocrine treatment and anti-HER2 treatments, which have significantly improved the clinical outcomes in ER/PgR positive and HER2 positive breast cancer patients, respectively. The standard clinical practice for early stage TNBC following completion of definitive local and systemic chemotherapy treatment is observation. Therefore, TNBC patients having a poor prognosis and limited treatment options present an unmet need for targeted treatment development.

1.1.3 Adjuvant chemotherapy for TNBC

The majority of patients presenting with early TNBC receive adjuvant chemotherapy. The first randomised Phase III study specifically conducted in early TNBC is the BEATRICE study- an Open Label 2-arm Study to Evaluate the Impact of Adjuvant Bevacizumab on Invasive Disease Free Survival in Triple Negative Breast Cancer (Cameron et al 2013). In this study, 2591 patients with resected early TNBC were randomised to receive adjuvant anthracycline and/or taxane chemotherapy with or without bevacizumab, followed by bevacizumab monotherapy for 12 months. The trial did not meet its primary objective of prolonging invasive disease free survival (IDFS). The 3-year IDFS for both arms of the study was approximately 83%. It was commented that this 3-year IDFS was better than anticipated; however, it should be noted that 63% of patients in the trial were node negative, and ~36% had tumours < 2cm. There are no published robust long-term data for subgroups (e.g. different nodal status or *BRCA* mutated tumours) of TNBC treated with standard of care chemotherapy.

1.1.4 Neoadjuvant chemotherapy for TNBC

It is assumed that approximately a third to half of the patients with TNBC will receive chemotherapy in the neoadjuvant setting. The key prognostic information following neoadjuvant chemotherapy is whether patients have residual disease or have had a pathological complete response (pCR; absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes). Individual patients who achieve pCR following neoadjuvant chemotherapy have significant improvement in both disease-free survival (hazard ratio (HR) 0.48, 95% CI: 0.37-0.63) and overall survival (HR 0.48,

95% CI: 0.33-0.69) compared with patients with residual invasive disease (Mieog et al 2007). An M.D. Anderson, single institution experience reported 46% pCR rate achieved in a small number of *BRCA1* mutated (n=57) breast cancer patients following anthracycline/taxane neoadjuvant chemotherapy (Arun et al 2011). In TNBC, the prognosis of patients who experience pCR is very similar to that for patients with other breast cancer subtypes with less than 10% developing a distant recurrence at 5 years. However, those patients with TNBC who do not experience pCR have a much poorer prognosis (Liedtke et al 2008, Carey 2011). A recently published meta-analysis of anthracycline and taxane containing neoadjuvant chemotherapy trials showed that of 911 patients with TNBC, 282 patients (31%) experienced a pCR (Von Minckwitz et al 2012). Compared with these patients, patients who did not experience a pCR were at higher risk of earlier recurrence over time (HR 6.02, 95% CI: 3.92-9.25) and at higher risk of earlier death over time (HR 12.41, 95% CI: 5.82-26.49). These results highlight the need to develop further treatment options to improve the prognosis of TNBC patients who do not achieve pCR after neoadjuvant chemotherapy.

1.1.5 ER/PgR positive HER2 negative breast cancer with germline *BRCA* mutations

While most breast cancers arising in patients with germline *BRCA* mutations are associated histologically with the TNBC phenotype, some - particularly those with underlying germline *BRCA2* mutations - display a non-TNBC phenotype (Honrado et al 2006; Maddavat et al 2012). Atchley et al 2008 found positivity for ER /PgR receptor expression in more than 60% of patients with documented germline *BRCA2* mutations and in about 30% of patients with documented *BRCA1* mutations.

Traditionally, these patients have been treated in the same manner as ER/PgR positive patients with either unknown or wildtype *BRCA* status. However, ER/PgR positive, HER2 negative patients with *BRCA2* mutations have been shown to have higher risk of recurrence and death than similar patients without mutations (Tryggvadottir et al 2013), suggesting that the current management of these patients could be suboptimal.

This could be particularly true for high-risk ER/PgR positive, HER2 negative breast cancer patients. Results from NSABP B-38, a trial which employed modern anthracycline and taxane regimens in the adjuvant setting, showed that hormone receptor positive patients with 4 or more positive axillary nodes at surgery had a 3 year DFS of 83%, which is comparable to the 3-year DFS of node negative TNBC (Swain et al 2013).

Similar considerations can be applied to the neoadjuvant setting. In a recently published, FDA co-sponsored meta-analysis looking into the association between the achievement of pCR and long-term clinical benefit, pCR rates in patients with ER and/or PgR positive, HER2 negative tumours were between 8% to 16%, as opposed to 34% in TNBC (Cortazar et al 2014). While all published subgroups in that analysis indicated clinical benefit (longer recurrence-free survival) for those patients achieving a pCR, the associated prognostic value varied *quantitatively* as evidenced by HRs between 0.24 (TNBC patients) and 0.63 (low grade ER and/or PgR positive, HER2 negative tumours with an upper bound of the confidence interval [CI] being slightly above 1.0). A robust association between failure to achieve pCR and event-free survival was demonstrated in patients with ER and/or PgR positive, HER2 negative Grade 3 tumours. Specifically, the HR for event-free survival in that patient group was found to be almost the same

(0.27) as the HR for event-free survival in patients with TNBC (0.24). This demonstrates that for carefully selected, high risk ER and/or PgR positive, HER2 negative patients, failure to achieve pCR can have relatively similar prognostic value as in patients with TNBC who have residual disease after neoadjuvant chemotherapy.

1.1.6 PARP inhibition as a therapeutic strategy target for *BRCA* mutated breast cancer

PARP inhibition is a novel approach to targeting tumours with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair. Tumours with homologous recombination deficiencies (HRD), such as ovarian or breast cancers in patients with germline *BRCA1/2* mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumour types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

BRCA1 and *BRCA2* defective tumours are intrinsically sensitive to PARP inhibitors, both in tumour models *in vivo* (Rottenberg et al 2008, Hay et al 2009) and in the clinic (Fong et al 2009). The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair (Helleday 2011, Murai et al 2012). Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by homologous recombination repair. Olaparib has been shown to inhibit selected tumour cell lines in vitro and in xenograft and primary explant models as well as in genetic *BRCA* knockout models, either as a stand-alone treatment or in combination with established chemotherapies (data on file at AstraZeneca).

Olaparib is a potent PARP inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents.

1.1.7 Pre-clinical experience

The pre-clinical experience is fully described in the current version of the olaparib IB.

1.1.8 Toxicology and safety pharmacology summary

Olaparib has been tested in a standard range of safety pharmacology studies e.g., dog cardiovascular and respiratory function tests, and the rat Irwin test. There were no noticeable effects on the cardiovascular or respiratory parameters in the anaesthetised dog or any behavioural, autonomic or motor effects in the rat at the doses studied.

Rodent and dog toxicology studies have indicated that the primary target organ of toxicity is the bone marrow with recovery seen following withdrawal of olaparib. *Ex vivo* studies have confirmed that olaparib is cytotoxic to human bone marrow cells.

Olaparib was not mutagenic in the Ames test but was clastogenic in the Chinese hamster ovary (CHO) chromosome aberration test *in vitro*. When dosed orally, olaparib also induced

micronuclei in the bone marrow of rats. This profile is consistent with the potential for genotoxicity in man.

Reproductive toxicology data indicate that olaparib can have adverse effects on embryofoetal survival and development at dose levels that do not induce significant maternal toxicity.

Further information can be found in the current version of the olaparib IB.

1.1.9 Clinical experience

Clinical experience with olaparib is fully described in the current version of the olaparib IB.

1.1.9.1 Olaparib monotherapy studies in breast cancer patients

Study D0819C00003

Olaparib demonstrated a statistically significant improvement in PFS in Study D0819C00003 (OlympiAD), a randomised Phase III study comparing olaparib to chemotherapy of physician's choice (TPC) in the treatment of *gBRCAm* HER2 negative metastatic breast cancer. At 77% maturity, PFS by blinded independent central review was significantly longer in patients treated with olaparib vs. TPC (HR 0.58; 95% CI 0.43-0.80; p=0.0009; 7.0 vs 4.2 months, respectively). Results in the East Asian and White sub-populations were consistent with these findings. PFS2 (time to second progression; investigator-assessed) was also longer in the olaparib arm (HR 0.57; 95% CI 0.40-0.83). Objective response rate was 59.9% and 28.8% in the olaparib and TPC arms, respectively. Final analysis of OS at 64% maturity revealed a median OS of 19.3 months for olaparib vs 17.1 months for TPC (HR 0.90; 95% CI 0.66-1.23) (Robson et al 2017).

Study D0810C00002

Study D0810C00002 was a Phase I open-label, dose escalation and cohort expansion study in 98 patients with solid tumours. Patients in the dose-escalation cohort received olaparib at doses ranging from 10 mg daily to 600 mg twice daily (b.i.d.); whereas all patients in the dose-expansion cohort received olaparib at 200 mg twice daily after the MTD was identified as 400 mg b.i.d. The main tumours by type were ovarian (54 [55.1%]), breast, (13 [13.3%]); colon (5 [5.1%]), prostate (4 [4.1%]) and skin cancers (4 [4.1%]). Overall 23 patients were *BRCA* mutation carriers; of these, 19 patients had *BRCA* mutated ovarian, breast, or prostate cancer and were evaluable for response. Forty-seven percent (9/19) of the patients had an objective response as defined by Response Evaluation Criteria in Solid Tumors (RECIST), and 63% (12/19) had stable disease for at least 4 months (Fong et al 2009).

Study D0810C00008

Study D0810C00008 was a Phase II proof-of-concept study initiated as an open-label, single-arm, international, multicenter study to assess the efficacy and safety of olaparib given orally b.i.d. in patients with *gBRCA1* and *gBRCA2* mutations and advanced breast cancer. Patients had a median of 3 previous chemotherapy regimens and approximately half of the patients had TNBC. The primary objective was to assess the efficacy of the capsule formulation at 2 different doses of olaparib in terms of ORR (overall response rate) in patients with advanced breast cancer. Patients received olaparib at a dose of 400 mg b.i.d. or 100 mg b.i.d. continuously in

28-day cycles, for multiple cycles, until no further clinical benefit was apparent or the patient was withdrawn from the study. The cohorts were conducted in sequence, the 400 mg b.i.d. group first (n=27) followed by the 100 mg b.i.d. group (n=27). In the ITT analysis set, the confirmed RECIST ORR overall was 11/27 (41%) at 400 mg b.i.d. and 6/27 (22%) at 100 mg b.i.d. Responses were seen in both g*BRCA*1 and g*BRCA*2 carriers. Median time to progression was 5.3 months for the 400 mg b.i.d. group and 3.7 months for the 100 mg b.i.d. group (Tutt et al 2010).

Study D0810C00020

Study D0810C00020 was a Phase II open-label, non-randomised study of olaparib in patients with known *gBRCA* or high-grade serous/undifferentiated ovarian cancer and patients with known *gBRCA* or TNBC. All patients received olaparib 400 mg b.i.d. until disease progression or until the investigator believed it was in the best interest of the patient to stop treatment. Tumour response data was analysed in 64 ovarian (*BRCA* or serous ovarian) and 26 breast (*BRCA* or triple negative) cancer patients who received olaparib 400 mg b.i.d. Germline *BRCA* mutations were present in 11 of the 26 breast cancer patients. Median number of prior chemotherapies in the breast cancer group was 3 (range: 1 to 7). Over 70% of the breast cancer patients had received 3 or more previous lines of prior chemotherapy, with a median of 35.3 months from diagnosis to start of treatment with olaparib. None of the breast cancer patients achieved a RECIST response. However, 63% of the patients with *BRCA* mutations had an overall best response of SD lasting 8 weeks or more. The median PFS in this cohort was 3.6 months in this group (Gelmon et al 2011).

Study D0810C00042

Study D0810C00042 was a Phase II, open label, non-randomised, non-comparative, multicenter study in patients with advanced cancers who had confirmed germline *BRCA1* and/or *BRCA2* mutations. A total of 62 breast cancer patients were recruited, all of whom received at least 3 prior lines of therapy (with a median of 6 prior regimens). Eight (12.9%) of the breast cancer patients had an OR and the median duration of response was 204 days. At 16 weeks, disease control was observed in 23 (37.1%) patients. The median PFS (progression free survival) was 3.68 months. The median OS was 11.01 months; the survival rate at 6 months was 74.6%, and at 1 year was 44.7% (Kaufman et al 2014).

The details on the pivotal phase II data in ovarian cancer patients as well as olaparib combination with chemotherapy are presented in the Investigator Brochure.

1.2 Research hypothesis

Following completion of definitive local and systemic neoadjuvant or adjuvant chemotherapy treatment, giving olaparib tablet 300 mg b.i.d (twice daily) in the adjuvant setting for up to 12 months in patients with germline *BRCA* mutations and high risk, Stage II-III HER2 negative primary breast cancer has superior efficacy and acceptable tolerability profile as compared with no further treatment. The efficacy in this study will be assessed by the primary analysis of IDFS defined as the time from randomisation to the date of first treatment failure that is loco-regional, distant recurrence, new invasive cancer or death from any cause. Supportive efficacy analyses include assessment of distant disease free survival and overall survival.

1.3 Rationale for conducting this study

The aim of the proposed phase III study is to obtain a reliable evaluation of whether olaparib monotherapy following completion of definitive local and systemic neoadjuvant or adjuvant chemotherapy is sufficiently safe and provides clinically meaningful benefit in the proposed indication.

The primary endpoint of the trial is IDFS, defined as the time from randomisation to date of first treatment failure that is loco-regional or distant recurrence or new cancer or death from any cause. IDFS is further detailed according to the standardised STEEP system definition (Hudis et al 2007) as one of the following:

- Ipsilateral invasive breast tumour recurrence (IIBTR): invasive breast cancer involving the same breast parenchyma as the original primary.
- Regional invasive breast cancer recurrence: invasive breast cancer in the axilla, regional lymph nodes, chest wall, and skin of the ipsilateral breast.
- Distant recurrence: metastatic breast cancer that has either been biopsy confirmed or clinically diagnosed as recurrent invasive breast cancer.
- Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause.
- Contralateral invasive breast cancer.
- Second primary non-breast invasive malignancies (i.e. excluding new in situ carcinomas at any site). Second primary non-breast invasive malignancies include hematologic malignancies and MDS. Squamous or basal cell skin cancers will not be counted as primary endpoint events.

Considering the tendency of TNBCs to metastasise to viscera more often than other types of breast cancer, and knowing the generally incurable nature of those with metastases, a secondary endpoint of DDFS will be measured to support the primary endpoint of IDFS and help characterise the secondary endpoint of OS.

In addition to TNBC, the study will also allow patients with positive hormone receptor status as long as they are HER2 negative, who have a germline *BRCA* mutation and fulfil additional criteria for high recurrence risk (see Section 4.1 Inclusion Crit. 3A, 3B, 4b). While events in these patients might not accumulate at exactly the same rate as in g*BRCA*m TNBC, extrapolations from the metastatic setting (Tutt et al 2010) support the expectations that these patients will also benefit from adjuvant olaparib treatment.

In addition, PARP and *BRCA* function has been linked to estrogen and other hormone receptor transcriptional function (Zhang et al 2013, Schiewer et al 2013), supporting the expectation that additive/synergistic effects could manifest when combining hormonal treatments with olaparib in hormone receptor positive patients with g*BRCA*m status. Recent preclinical data by Nardone et

al 2015 indicate that olaparib may enhance endocrine therapy efficacy and circumvents resistance; as a consequence, addition of olaparib to hormonal treatment might confer additional treatment benefits in patients with high recurrence risk.

Hence, hormone receptor positive g*BRCA*m patients will be allowed to receive hormonal treatments at any time during the study. Based on in vitro P450 inhibition and induction data, olaparib would not be expected to alter the PK of standard hormonal therapies used in the adjuvant setting (tamoxifen, aromatase inhibitors with or without ovarian suppression). Based on a preliminary analysis from an ongoing olaparib/hormonal treatment study sponsored by AstraZeneca (Study D081CC00001) there was no indication for clinically relevant drug-drug interaction between olaparib and the anti-hormonal agents tamoxifen, letrozole or anastrozole.

All patients will be followed for local recurrence, distant recurrence (including subsequent sites of recurrence), new cancers and overall survival for a minimum of 10 years, in order to fully describe the long-term impact of adjuvant olaparib therapy.

1.3.1 Rationale for central *BRCA* mutation test at Myriad Genetics, Inc.

The FDA has indicated that the *BRCA1* and *BRCA2* mutation assay will need to be approved as a companion diagnostic in the US.

Myriad Genetics, Inc. has been chosen as a partner in developing a companion diagnostic for *BRCA1* and *BRCA2* testing because it has extensive experience in *BRCA1* and *2* mutation detection. Myriad keeps the most comprehensive database on *BRCA1* and *2* gene mutations and their clinical relevance. Furthermore, Myriad has an established laboratory infrastructure, which supports high volume testing with turnaround times that can meet the needs of a clinical trial.

1.4 Benefit/risk and ethical assessment

As of 20 March 2015, approximately 3862 patients with ovarian, breast, gastric, pancreatic, and a variety of other solid tumours are estimated to have received treatment with olaparib in AstraZeneca-sponsored, investigator-sponsored, and collaborative group studies and a Managed Access Programme. Olaparib has been given as either monotherapy (an estimated 2327 patients) or in combination with other chemotherapy/anticancer agents (an estimated 1535 patients). Many of these combination studies are ongoing. An estimated 1835 patients to date have received the capsule formulation of olaparib, 27 patients have received both the capsule and tablet formulation, and 2000 patients have received the tablet formulation. Approximately 878 patients have received comparator or placebo across the olaparib development programme.

An analysis of monotherapy data across 13 AstraZeneca sponsored monotherapy studies in 1006 patients with ovarian cancer and other non-ovarian solid tumours who have been given olaparib capsules estimated that 16.0% (161/1006) of patients had been exposed to olaparib capsules for ≥12 months, 8.3% (84/1006) for > 18 months and 4.1% for > 24 months at the time of database closure for the respective studies. Twenty-one patients (2.1%) had received ≥ 48 months of olaparib exposure. From the available data to date, there is no evidence of any unexpected toxicity following long-term olaparib (capsule) monotherapy exposure.

In a Phase I study in ovarian cancer patients (Study DO810C00024) the 300 mg b.i.d. monotherapy tablet regimen was considered to have an acceptable tolerability profile relative to the 400 mg b.i.d. capsule and has been determined to be the recommended olaparib monotherapy tablet dose for future studies with olaparib using the tablet formulation. Olaparib as monotherapy at doses up to 400 mg b.i.d. (capsule formulation) and 300 mg b.i.d. (tablet formulation) is generally well tolerated, with most common AEs including nausea, fatigue, vomiting, and anaemia. They were mainly mild-to-moderate (CTCAE Grade ≤ 2) in severity.

In addition, in a small number of patients MDS/AML or pneumonitis have been observed and identified as important risks.

Important Potential Risks

Myelodysplastic syndrome/acute myeloid leukaemia

There have been 21 reports of myelodysplastic syndrome (MDS) and/or acute myeloid leukaemia (AML) in patients treated with olaparib as of 20 March 2015; 14 cases in olaparib monotherapy trials and 7 cases in olaparib combination studies with carboplatin and paclitaxel (n=4) or cediranib (n=1), irinotecan and cisplatin (n=2). A total of 3862 patients are estimated to have received olaparib, giving a cumulative incidence of 0.5% for MDS/AML. Two additional reports of MDS have been received from a blinded study (D0816C00002) in which the treatment of the 2 patients (olaparib or placebo) is unknown, and if these patients are considered to have been on olaparib treatment, the estimated incidence would be 0.6%. MDS was also reported for 2 patients who were known to have received placebo or a comparator in the olaparib trial programme (1 patient received placebo in Study D0810C00019 and 1 patient received liposomal doxorubicin in Study D0810C00012). The 21 olaparib-treated patients and two patients on blinded treatment had primary ovarian, peritoneal, fallopian tube cancer (n=20), pancreatic cancer (n=2) or breast cancer (n=1) and 18 of them had germline *BRCA1/2* mutations (3 cases *BRCA* status unknown; 2 cases negative). It has been hypothesised that a deficiency in the expression of *BRCA* genes may leave patients more vulnerable to the adverse effects of chemotherapy, and therefore, at an increased risk of MDS/AML as a result of cancer treatment (Cole and Strair 2010). Eleven patients had received olaparib for ≤ 12 months (5 patients had < 6 months exposure, 6 patients had 6 to 12 months exposure) and the other 12 cases occurred following longer than 12 months olaparib exposure (2 patients following 12-18 months exposure, 2 patients 18-24 months and 8 patients following > 2 years exposure to olaparib).

The median time to onset of t-AML from ovarian cancer diagnosis is reported as approximately 5.5 years (Gupta et al 2007; Vay et al 2011). The overall standardised incidence ratio (8.68 overall) varies over time - 12.07 within 1 to 5 years, 10.81 within 5 to 10 years and 2.30 after 10 years (Morton et al 2013).

Eighteen of the 23 patients died: in 12 of these patients, MDS/AML or myelodysplasia was recorded as either a primary or secondary cause of death. The other 6 deaths were reported as follows: 1 due to cerebral haemorrhage and disseminated intravascular coagulation, 1 due to complication of double umbilical cord blood transplantation and 4 due to disease progression (2 ovarian cancer, 1 breast cancer [patient had a prior history of ovarian cancer treated with platinum-based chemotherapy] and 1 pancreatic cancer). In 5 patients, the event of MDS/AML

is reported as ongoing as of the 20 March 2015. All patients had other potential features that may be contributing factors for the development of MDS/AML. All patients had received previous chemotherapy with DNA damaging agents including platinum, with many patients having extensive previous chemotherapy with multiple treatment regimens over multiple years including carboplatin, taxanes, anthracyclines, other alkylating and DNA damaging agents and radiotherapy.

Since bone marrow is known to be a target organ for olaparib toxicity, increased risk of MDS/AML with long-term exposure to olaparib cannot be excluded. However, there is insufficient data at present to evaluate this relationship. Moreover, while non-clinical data suggest bone marrow progenitor cell populations are reduced temporarily following olaparib treatment, there is no evidence to date linking olaparib treatment to the generation of abnormal bone marrow precursors. Furthermore, all patients who developed MDS/AML had extensive prior chemotherapy and while it is not possible to exclude the contribution of olaparib, it must be considered that there were other potential contributing factors in all cases. Preclinical data also suggest potential benefit with PARP inhibitors in MDS/AML and clinical trials are now underway to assess this effect (Gaymes et al 2008). The risk of developing MDS/AML as a long term toxicity in breast cancer patients with stage I-III disease exposed to standard dose adjuvant chemotherapy including alkylator and anthracycline with or without taxane, is estimated to be around 0.5% varying between 0.37% and 1.16% (Praga et al 2005, Smith et al 2003, Hershman et al 2007, Burnell et al 2010, Aebi et al 2011). Both alkylators and topoisomerase II inhibitors (anthracyclines) have been associated with treatment related MDS/AML. The risk is perceived as low and not outweighing the benefit of adjuvant chemotherapy in breast cancer patients. To ensure robust safety monitoring, patients in this clinical trial will have safety assessments every two weeks during the first month and monthly safety assessments for the first 6 months of treatment followed by 3 monthly assessments until completion of treatment (maximum 12 months treatment). In addition, an Independent Data Monitoring Committee (IDMC) will review the emerging safety data from the trial in an unblinded fashion. Long term safety follow-up will be implemented in the trial. Clinical guidelines for managing bone marrow toxicity are implemented as part of the safety management plan (Section 5.5.12.4).

Pneumonitis

As of 20 March 2015, 14 patients out of a total of 3862 patients, estimated to have received olaparib, have reported pneumonitis, giving a cumulative incidence of 0.36% for pneumonitis. Six additional reports of pneumonitis have been received from 4 blinded studies, where the treatment of the patients is unknown (3 either olaparib or placebo; 2 either olaparib + paclitaxel or placebo + paclitaxel and 1 olaparib + abiraterone or placebo + abiraterone). If these patients were considered to have been on olaparib treatment, the estimated cumulative incidence would be 20/3862 (0.52%). Pneumonitis was also reported for 2 patients (1%) of 190 patients that received placebo or comparator in the olaparib trial programme (1 patient on placebo in Study 19 and 1 patient on paclitaxel in Study 39). The patients were treated with olaparib for breast cancer (n=3), ovarian cancer (n=6), non-small cell lung cancer (NSCLC) (n=4), small cell lung cancer (SCLC) (n=1), pancreatic cancer (n=1), gastric cancer (n=3), prostate cancer (n=1) and thymic cancer (n=1). The reports of pneumonitis presented with no consistent clinical pattern and were heavily confounded by a number of pre-disposing factors (including disease under investigation, underlying pulmonary disease, pre-existing medical conditions, smoking history

and/or previous chemotherapy and radiotherapy). The majority of patients had received prior radiotherapy and/or chemotherapy and had other risk factors within the medical histories including pneumonitis, interstitial lung fibrosis, dyspnoea, haemoptysis, chest infection, allergic asthma, pleural effusion, pleural metastases, and smoking. Five patients had current SCLC or NSCLC. An independent review of available chest computed tomography (CT) scans and radiographs associated with the reports of pneumonitis concluded that there appeared to be no clear consistent clinical pattern.

Investigation of any new or worsening pulmonary symptoms has been implemented as part of the safety management plan (Section 5.5.12.5).

New Primary Malignancies other than MDS/AML

Overall, the number of reports of new primary malignancies is low, with 24 events (in 22 patients) being reported to 20 March 2015 in 3862 olaparib treated patients (0.57%) and one event (bladder cancer) reported in the placebo arm of the double-blind Study 19. Three additional reports of new primary malignancies have been received from 1 blinded study for the maintenance treatment of ovarian cancer (D0818C00001, tablet formulation), where the treatment of the patients is unknown (either olaparib or placebo). If these patients are considered to have been on olaparib treatment, the estimated cumulative incidence would be 0.65%.

The types of new primary malignancies reported in the 22 patients on olaparib treatment were breast cancer, colon cancer, lung neoplasm malignant, gastric cancer, plasma cell myeloma, basal cell carcinoma, skin cancers, neoplasm skin, squamous cell carcinoma, malignant melanoma, malignant muscle neoplasm, pre-cursor T-lymphocytic lymphoma/leukaemia, tongue cancer and papillary thyroid carcinoma. The 3 patients on blinded treatment reported new primary breast cancer malignancies.

Of the 25 patients (22 on olaparib, 3 on blinded treatment) subsequently diagnosed with a new primary malignancy, the majority were reported whilst receiving study treatment (21 patients). In 4 patients the event was reported after olaparib discontinuation (within 60 days after olaparib discontinuation in 2 patients, and more than 240 days after olaparib discontinuation in 2 patients).

The duration of treatment for the 25 patients was

- <6 months for 5 patients
- 6 to 12 months for 8 patients
- 12 to 18 months for 2 patients
- 18 to 24 months for 3 patients
- >2 years for 7 patients.

The type of new primary cancers reported were generally in line with secondary cancers observed in ovarian and breast cancer populations reported in the literature (Bergfeldt et al 1995,

Fowble et al 2001, Wesolowski et al 2007), or were cancers such as skin cancer, known to be the most common cancer in the general population and associated with high cure rates.

Ovarian cancer patients have been reported to have an increased risk of developing second primary malignancies. Patients with germline *BRCA* mutations are at risk of developing other primary cancers notably breast cancer. Ginsburg et al 2010 reported higher rates of skin cancers in patients with *BRCA1* (1.6%) and *BRCA2* (3.0%) mutations.

There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all 22 olaparib treated patients and the 3 on blinded treatment. All patients had previously received various chemotherapy agents including multiple cycles of DNA damaging platinum containing chemotherapies, taxanes, anthracyclines and other alkylating and DNA damaging agents. Four patients were reported to have had prior radiotherapy. Twenty-two patients had a documented breast cancer gene mutation (*BRCA* 1 or 2). Seven of the 25 patients had previous medical histories of cancer (ovarian, cervix, breast, peritoneal) and 3 patients with skin cancers either had previous basal cell carcinoma reported or skin lesions evident prior to study treatment.

There is insufficient evidence for an association between olaparib treatment and the development of new primary malignancies in the clinical trial programme to date. The risk is perceived as low and not outweighing the benefit of adjuvant chemotherapy in breast cancer patients. An IDMC will review the emerging data from the trial in an unblinded fashion.

Potential benefit

A Marketing Authorisation Application was approved in EU/EEA on 16 December 2014 for the indication 'LYNPARZA monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.'

A New Drug Application was approved in the US on 19 December 2014 for the indication 'LYNPARZA monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.'

Olaparib tablet formulation was approved in January 2018 for patients with deleterious or suspected deleterious *gBRCAm*, HER2-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine treatment.

Phase II clinical studies have investigated the effect of olaparib either as monotherapy or in combination with other chemotherapy agents in cancer patients. In patients carrying germline *BRCA* mutations, monotherapy studies in patients with heavily pre-treated breast cancer have reported an ORR of up to 41%.

In ovarian cancer patients, the pivotal phase II study D0810C00019, a double-blind, randomised study assessed the efficacy of olaparib 400 mg b.i.d. capsules as a maintenance treatment

following platinum-based chemotherapy in patients with platinum sensitive relapsed high grade serous ovarian cancer. The PFS following olaparib maintenance therapy was significantly longer compared with the placebo group (HR 0.35; 95% CI: 0.25, 0.49; p<0.00001) in the overall population. In the subgroup of patients with *BRCA* mutant ovarian cancer, the effect was even greater with a PFS HR of 0.18 (95% CI: 0.11, 0.31; p<0.00001; median 11.2 versus 4.3 months). An interim analysis of OS was performed at 58% maturity. In the overall population, the analysis demonstrated a non-statistically significant numerical advantage for olaparib-treated patients (OS HR 0.88; 95% CI 0.64-1.21; p=0.43808) and there was again a greater effect in the *BRCA*-mutated subgroup: the OS HR was 0.74 (95% CI 0.46 to 1.19; p=0.20813) with a numerical advantage in median OS observed with olaparib (median 34.9 months versus 31.9 months with placebo). Among the 62 placebo-treated patients with *BRCA* mutations, 14 switched to a PARP inhibitor post progression.

Based on these results and data from the full clinical program to date, it is anticipated that in the adjuvant setting, olaparib will have a positive benefit risk profile for the treatment of the small well-defined population of high-risk HER2 negative primary breast cancer patients with *BRCA* mutations.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective is to assess the effect of adjuvant treatment with olaparib on Invasive Disease Free Survival (IDFS).

2.2 Secondary objectives

The secondary objectives of this study are:

1. To assess the effect of adjuvant treatment with olaparib on overall survival (OS)

2. To assess the effect of adjuvant treatment with olaparib on Distant Disease Free Survival (DDFS)

3. To assess the effect of adjuvant treatment with olaparib on the incidence of new primary contralateral breast cancers (invasive and non-invasive), new primary ovarian cancer, new primary fallopian tube cancer and new primary peritoneal cancer

4. To assess the effect of olaparib on patient reported outcomes using the FACIT-Fatigue and EORTC QLQ-C30 questionnaires

5. To assess the efficacy of olaparib in patients identified as having a deleterious or suspected deleterious variant in either of the *BRCA* genes using variants identified with current and future *BRCA* mutation assays (gene sequencing and large rearrangement analysis)

6. To determine the exposure to olaparib (in plasma) in patients receiving olaparib as adjuvant therapy

2.3 Safety objective

To assess the safety and tolerability of adjuvant treatment with olaparib

2.4 Exploratory objectives

The exploratory objectives of this study are:

1. To assess the consistency of treatment effects on efficacy endpoints across potential or expected prognostic factors, including the baseline stratification factors with special emphasis on hormone receptor status.

2. To explore methods for estimating overall survival (OS) adjusting for the impact of confounding by subsequent therapies, specifically the control arm receiving subsequent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitors or platinum salts

3. To explore whether resistance mechanisms to olaparib can be identified through analysis of tumour and blood sample derivatives (cells, plasma and protein and nucleic acid derivatives) - archival tumour samples (mandatory*), tumour sample at recurrence (optional), and blood samples at baseline, 30 days post study treatment and on disease recurrence (mandatory)

   *For adjuvant patients, this refers to the surgical specimen; for neoadjuvant patients, both the pre-treatment core biopsy and the surgical specimen with residual disease are requested, but only one is mandatory. If the surgery tumour blocks are available, but cannot be submitted, sites may submit a portion of invasive tumour from the original block, either by taking at least one core of at least 3 mm in diameter, or by splitting the original block in two parts, and re-embedding one in a new block for central submission. If blocks containing pre-neoadjuvant treatment core biopsies are available but cannot be submitted, sections mounted on glass slides prepared from the block can be provided. If tumour sample can't be provided as requested above or if it's not available, approval by Study Team for patient's entry into the trial is required.

4. To determine the frequency of and describe the nature of *BRCA* mutation/s in tumour samples and to compare this with germline *BRCA* mutation status

5. To conduct future exploratory research into factors that may influence development of cancer and/or response to treatment (where response is defined broadly to include efficacy, tolerability or safety). This may be performed on the collected and stored tumour and blood samples

6. To collect and store DNA according to each country's local and ethical procedures for future exploratory research into genes/genetic variation that may influence response (i.e. distribution, safety, tolerability and efficacy) to study treatments and/or susceptibility to disease (optional)

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design, flow chart and study schedules

This is a randomised, double-blind placebo controlled multicentre, phase III study to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with germline *BRCA1/2* mutations and high risk HER2 negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy.

Randomised patients will receive study treatment for up to a maximum of 12 months. All patients will have safety assessments every 2 weeks during the first month, every 4 weeks for the following 5 months (up to week 24) and 3 monthly for the remaining 6 months of study treatment, plus 30 days after its discontinuation. Efficacy assessments (medical history and physical examination) will be performed on a 3 monthly basis during the first 2 years following end of study treatment, followed by 6 monthly assessments for years 3, 4 and 5 and annually thereafter. Radiological tests to exclude a second primary breast cancer (ipsilateral and/or contralateral) are mandatory before enrolment (within 12 months prior to Screening PART 1) and during study participation (starting at week 24 and yearly thereafter) for patients with any remaining intact breast tissue. The preferred tests are mammogram or magnetic resonance imaging (MRI; MRI preferred for patients below 50 years of age). For patients who underwent a bilateral mastectomy, with no remaining breast tissue, a physical examination is sufficient and radiological tests are not mandatory. For patients who underwent a bilateral mastectomy, as well as for male patients, clinical exam may be supplemented by ultrasound exams at investigator's discretion. Evidence of disease recurrence or new primary cancer will require histopathological and/or radiological confirmation.

Patients who develop loco-regional recurrence should have cytological/histological confirmation. Loco-regional recurrence should be treated with curative intent when possible. Appropriate imaging (CT, MRI bone and/or PET scan) of the chest/abdomen/pelvis or any other area as clinically indicated (MRI preferred to examine CNS (central nervous system) if new neurological symptoms occur) should be performed at the time of local recurrence to exclude further spread of the disease.

Distant recurrence should be diagnosed by radiological/imaging examination and every attempt should be made for histopathological confirmation when metastatic lesion is accessible for biopsy.

If the patient meets the IDFS endpoint due to a breast cancer related distant relapse, the patient will enter the survival follow-up phase of the trial, with annual assessments from the date of distant relapse, which will continue until 10 years after the last patient is randomised. No clinic visits will be required during the survival follow-up phase; information may be collected via telephone, medical records or death registries. During the survival follow-up phase, in addition to vital status, the following information will be collected (if available): specific cancer therapies (only first line treatment for first breast cancer recurrence and any subsequent regimens

containing PARP inhibitors or platinum received by the patient at any time), sites of metastases and any other new cancer.

If the IDFS endpoint is met due to events other than distant relapse, the patient will continue the efficacy assessment visit study schedule until breast cancer related distant relapse occurs, or approximately 10 years following their randomisation into the study, whichever occurs first. They will then enter the survival follow-up phase of the trial.

See Section 5.8.1 for guidelines on study visits for any patient discontinuing prior to completing 52 weeks of study treatment.

Figure 1 Study Flow Chart

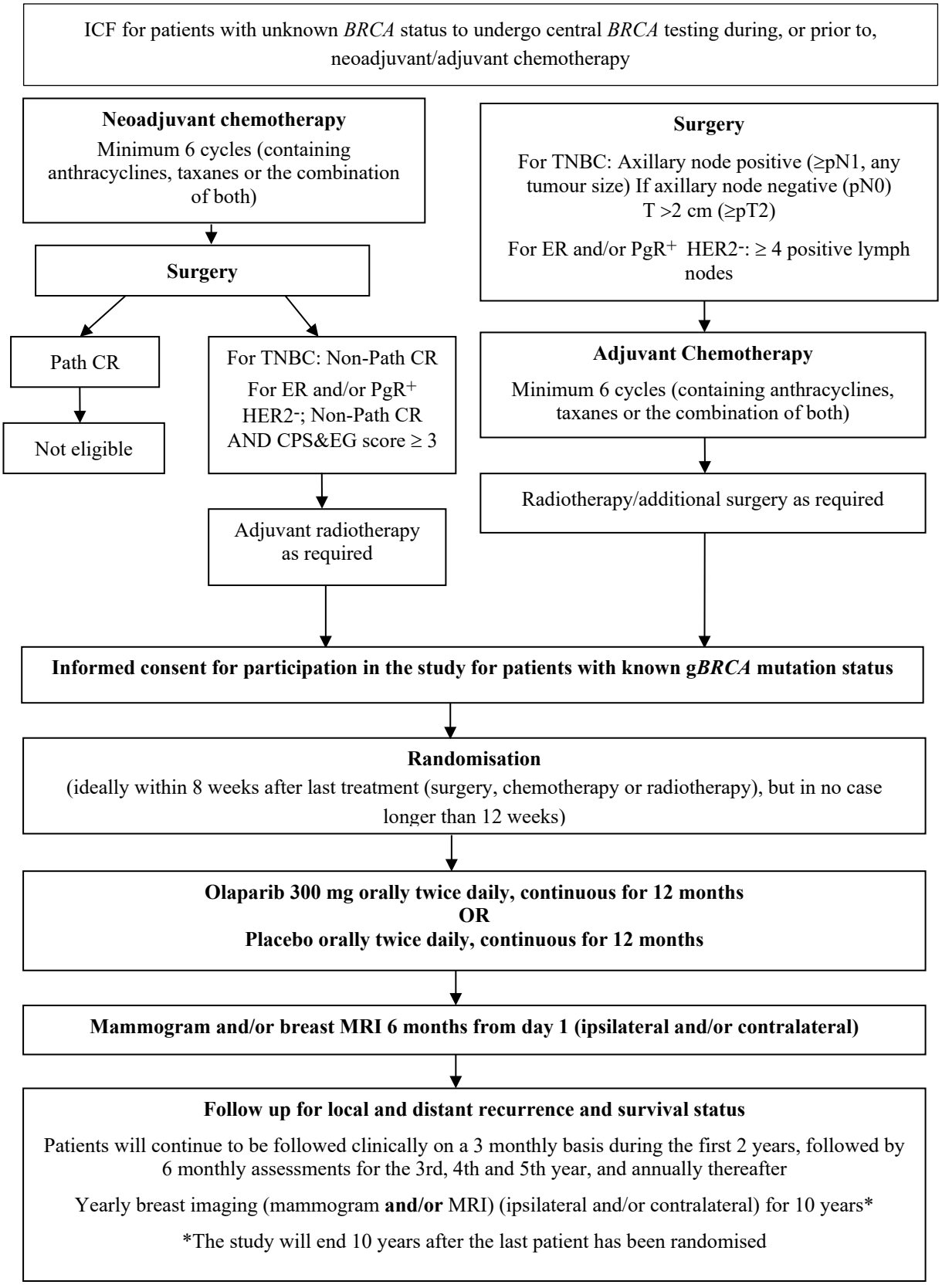


Figure 2 Screening Plan

Screening PART 1 – Patients with Unknown g*BRCA* Mutation Status:

- Only those patients who **do not** know their g*BRCA* mutation status prior to entry in to the study

These patients will undergo screening assessments as described for PART 1 in Table 1. Screening PART 1 is conducted to determine if the patient is considered **eligible to undergo the *BRCA* status blood test**. Once PART 1 has been successfully completed and patients have had a *BRCA* test, these patients will continue to PART 2 and have all procedures performed as described for PART 2 (see Table 1)

Screening – PART 2 – ALL Patients (Patients with Known g*BRCA* Mutation Status):

- Those patients who already know their g*BRCA* mutation status **and** have a deleterious or suspected deleterious mutation to undergo screening assessments as described for PART 2 (see Table 1)
- Those patients originally with unknown g*BRCA* status who have completed screening PART 1 and now have a confirmed deleterious or suspected deleterious mutation should undergo screening assessments as described for PART 2 (see Table 1)

Table 1 Study Schedule - Screening (PART 1 and PART 2)

Day	**Any time prior, during or after neoadjuvant/adjuvant chemotherapy or radiotherapy** **PART 1 [a]** **(ONLY Patients requiring a *gBRCA* status Myriad test before randomisation)**	**-28 to 0 days** **PART 2** **(Patients with confirmed g*BRCA* status by Myriad or if *BRCA* status is known prior to study entry [j])**
Informed consent	X [b,c]	X [j]
Demographics (date of birth)	X	X
Medical and surgical history [d]		X
Prior cancer therapies including radiotherapy		X
Inclusion/exclusion criteria	X (all ** criteria)	X
ECOG Performance Status		X
Physical examination		X
Vital signs		X
ECG [f]		X [g]
Haematology / clinical chemistry/Coagulation [o]		X
Urinalysis [h]		X
Pregnancy test [i]		X
EORTC QLQ-C30 [n]		X
FACIT-Fatigue [n]		X
Blood sample for determination of *BRCA* status via Myriad	X	X [e]
Blood sample for assessment of current and future *BRCA* mutation assay(s) [c]	X	X [e]
Concomitant medications		X
Archival tumour sample (FFPE) (mandatory) [k]		X
Surgical tumour sample (FFPE) (post neoadjuvant chemotherapy (mandatory)) [k]		X

Table 1 Study Schedule – Screening (PART 1 and PART 2)

Day	**Any time prior, during or after neoadjuvant/adjuvant chemotherapy or radiotherapy** **PART 1 [a]** **(ONLY Patients requiring a *gBRCA* status Myriad test before randomisation)**	**-28 to 0 days** **PART 2** **(Patients with confirmed g*BRCA* status by Myriad or if *BRCA* status is known prior to study entry [j])**
Radiological assessment to exclude metastatic breast cancer (where applicable) [l]		X
Family history of cancer		X
Serious Adverse Events [m]	X (only SAEs due to study procedures)	X (SAEs only)

a The time period is to allow those patients that require a Myriad g*BRCA* sample to have the test taken and the results returned prior to randomisation.

b It is recommended that patients that require the Myriad g*BRCA* sample testing are to be consented for *BRCA* testing and participation in the trial prior or during neoadjuvant/adjuvant chemotherapy prior to entering the study.

c Any patient who consents to study related Myriad g*BRCA* status testing, must also have a blood sample taken at the same time for the purpose of developing and validating a future mutation assay.

d Include history of blood transfusion within previous 120 days from start of study treatment and the reasons e.g. bleeding. Additionally CPS+EG score components should be collected (Clinical stage (CS), estrogen receptor status (E), nuclear grade (G), and post-treatment pathologic stage (PS)) for the non-pCR patients who received prior neoadjuvant chemotherapy. Instructions on how to calculate the CPS&EG score (Mittendorf et al 2011; Jeruss et al 2008) are provided in Appendix H.

e Samples to be taken in screening PART 2 only for patients with known g*BRCA* mutation who have not completed PART 1.

f ECG recordings should be performed once the patient has been in the supine position for at least 5 minutes.

g ECG assessments to be completed within 28 days before randomisation.

h Urinalysis (dipstick) should be performed at screening. After screening, urinalysis will only be required if clinically indicated.

i Women who are not postmenopausal or have not undergone hysterectomy must have a negative urine or serum pregnancy test within 28 days prior to randomisation and a confirmatory test on Day 1 before starting study treatment. If the results are positive the patient is ineligible.

j Patients for whom their g*BRCA* status is already known, should be consented to the study within 28 days prior to randomisation.

k Mandatory for all randomised patients i.e. for adjuvant patients this refers to the surgical specimen; for neoadjuvant patients, both the pre-treatment core biopsy and the surgical specimen with residual disease are requested but only one is mandatory. If the surgery tumour blocks are available, but cannot be submitted, sites may submit a portion of invasive tumour from the original block, either by taking at least one core of at least 3 mm in diameter, or by splitting the original block in two parts, and re-embedding one in a new block for central submission. If blocks containing pre-neoadjuvant treatment core biopsies are available but cannot be submitted, sections mounted on glass slides prepared from the block can be provided. If tumour sample can't be provided as requested above or if it's not available, approval by Study Team for patient's entry into the trial is required. Samples will only be sent to the study bio-repository once the patient has been randomised.

l Patients considered at high risk of having disseminated disease (i.e. those with locally advanced disease, clinical N2-3 or pathological N1-3 with the exception of pN1a in adjuvant patients are expected to have a CT/MRI scan of the Thorax/Abdomen/Pelvis or any other area as clinically indicated and a bone scan **or** a CT

scan with bone windows at any point between diagnosis of the current breast cancer and randomisation to rule out metastatic breast cancer. (Note PET/CT scan may be used as an alternative imaging technique and precludes the need for bone scan). Radiological tests to exclude a second primary breast cancer (ipsilateral and/or contralateral) are mandatory before enrolment (within 12 months prior to Screening PART 1) for patients with any remaining intact breast tissue. The preferred tests are mammogram or MRI (MRI preferred for patients below 50 years of age). For patients who underwent a bilateral mastectomy, with no remaining breast tissue, a physical examination is sufficient and radiological tests are not mandatory. For patients who underwent a bilateral mastectomy, as well as for male patients, clinical exam may be supplemented by ultrasound exams at investigator's discretion.

To rule out metastatic breast cancer, patients with screening ALT/AST or ALP above institutional upper limit of normal should have liver ultrasound, CT or MRI at any time point between diagnosis of current breast cancer and randomisation. Screening bone scan is required if ALP and/or corrected calcium level are above the institutional upper limit. (Note PET/CT scan may be used as an alternative imaging technique).

m Serious adverse events must be captured from time of consent. In Screening PART 1 of the study only SAEs related to a study procedure will be collected. In Screening PART 2 all SAEs will be collected.

n EORTC QLQ-C30 + FACIT-Fatigue will be collected prior to randomisation once eligibility is confirmed.

o Coagulation analysis only required at baseline.

Table 2 Study Schedule – On treatment (Year 1)

Visit Number	**2**	**3**	**4**	**5-9 (Every 4 weeks)**	**10-11 (Every 3 months (14 weeks))**	**Premature study treatment discontinuation g**	**Follow-up 30 days after last dose of study medication (all patients)**
Week	**0**	**2**	**4**	**8, 12, 16, 20, 24**	**38, 52**		
Day	**1**	**15**	**29**				
Visit Window		**±3d**	**±3d**	**±1 week**	**±2 week**	**+2 week**	**+2 week**
Serum or urine pregnancy test for women of childbearing potential **a**	X		X	X	X		X
ECOG performance status	X **b**						
Vital signs	X **b**		X	X (weeks 12 and 24 only)	X	X	X
Haematology / clinical chemistry **c**	X **b,c**	X	X	X	X	X	X
Recurrent/new cancers assessment (includes physical exam **d**, clinical signs and symptoms)	X			X (weeks 12 and 24 only)	X	X	X
Mammogram and/or breast MRI (ipsilateral and/or contralateral) (MRI preferred for patients younger than 50 years) **e**				X (week 24 only)			
Adverse Events	X	X	X	X	X	X	X

Table 2 Study Schedule – On treatment (Year 1)

Visit Number	**2**	**3**	**4**	**5-9 (Every 4 weeks)**	**10-11 (Every 3 months (14 weeks))**	**Premature study treatment discontinuation g**	**Follow-up 30 days after last dose of study medication (all patients)**
Week	**0**	**2**	**4**	**8, 12, 16, 20, 24**	**38, 52**		
Day	**1**	**15**	**29**				
Visit Window		**±3d**	**±3d**	**±1 week**	**±2 week**	**+2 week**	**+2 week**
Concomitant medications including blood transfusions	X	X	X	X	X	X	X
Demographics **j**	X						
EORTC QLQ-C30				X (week 24 only)	X (week 52 only)		
FACIT-Fatigue				X (week 24 only)	X (week 52 only)		
Biomarker Blood 2 samples (mandatory)	X **i**						X
PGx Blood sample (optional)	X						
Blood sample for PK analysis (optional; after signing PK Informed consent) (subset of patients) **h**			X				
Blood biomarker samples at disease recurrence (Mandatory)	X	X	X	X	X	X	X
Tumour biopsy at disease recurrence (Optional) **k**	X	X	X	X	X	X	X
Olaparib dispensed/returned **f**	X		X	X	X	X	

a Pregnancy tests on serum or urine samples will be performed for women of childbearing potential within 28 days prior to randomisation, on Day 1 of the study prior to commencing treatment, at the time points shown in Table 2 during study treatment and at the 30 day follow up visit. If results are positive the patient is ineligible/must be discontinued from study treatment immediately. Details of the pregnancy tests must be recorded in the patient's medical records and in the CRF.

b If assessed within 7 days before randomisation, it does not need to be repeated on Day 1 of study treatment unless investigator believes that it is likely to have changed significantly.

c Safety blood samples do not need to be repeated on Day 1 of study treatment if they have been assessed within 7 days before randomisation and which must have been done at least 3 weeks after the last dose of chemotherapy, unless the investigator believes that they are likely to have changed significantly. Safety bloods samples are to be collected every 2 weeks during the first 4 weeks, then every 4 weeks until week 24 and then at weeks 38 and 52 of study treatment.

d Physical examination both local and general should be performed at day 1 and then at weeks 12, 24 and 38 and 52 post randomisation until study treatment is discontinued (data is not required to be captured on an eCRF, however any significant changes from baseline must be reported as an AE).

e Radiological tests to exclude a second primary breast cancer (ipsilateral and/or contralateral) are mandatory during study participation (starting at week 24 and yearly thereafter) for patients with any remaining intact breast tissue. The preferred tests are mammogram or MRI (MRI preferred for patients below 50 years of age). For patients who underwent a bilateral mastectomy, with no remaining breast tissue, a physical examination is sufficient and radiological tests are not mandatory. For patients who underwent a bilateral mastectomy, as well as for male patients, clinical exam may be supplemented by ultrasound exams at investigator's discretion.

f Sufficient study treatment should be dispensed for at least each treatment period plus overage, however additional treatment can be dispensed to patients to last longer in accordance with local practice.

g If a patient discontinues prior to completing 52 weeks of study treatment, the patient should have the study treatment discontinuation visit performed followed by the 30-day follow-up visit and site staff completes relevant CRF pages as required. In case of premature treatment discontinuation, only the visits where efficacy assessments are scheduled should be performed i.e. week 12, 24, 38, 52 (as applicable) in Year 1 and all visits in Year 2 onwards. Collection of vital signs, AEs, haematology/clinical chemistry results, and concomitant medications is no longer required. Information on endocrine therapies should be collected and recorded in the clinical database until IDFS endpoint is met due to breast cancer related distant relapse. The date of discontinuation, the reasons, and details of the following specific cancer therapies (first line treatment for breast cancer recurrence and any subsequent regimens containing PARP inhibitors or platinum received by the patient at any time) should also be recorded on the eCRF. In case the IDFS endpoint is met due to breast cancer related distant relapse, the patients enters the survival follow-up phase and is assessed annually from the date of distant relapse and until 10 years after the last patient is randomised. In case the IDFS endpoint is met due to other events, the patient will continue the study schedule until a breast cancer related distant relapse occurs or approximately 10 years following their randomisation into the study, whichever occurs first. They will then enter the survival follow-up phase of the trial. During the annual survival follow-up phase, in addition to vital status, the following information will be collected (if available): specific cancer therapies (only first line treatment for first breast cancer recurrence and any subsequent regimens containing PARP inhibitors or platinum received by the patient at any time), sites of metastases and any other new cancers. If a recurrent/new cancer assessment is scheduled within 4 weeks of the study treatment discontinuation visit, it can be performed at the 30 day follow-up visit (for more details see Section 5.8.1).

h PK sampling (optional) to be performed in a subset of patients. Sampling times: pre-dose (before morning dose) plus one sample in each of the following sampling windows: 0 to 0.5 h post dose, > 0.5 to 1.5 h post dose, 3 to 6 h post dose and > 6 to 12 h post dose (before evening dose) preferably on visit 4, day 29. Nevertheless, the samples can also be taken at a later treatment visit, provided that PK consent was obtained beforehand (for details see Section 6.8).

i Blood samples (plasma and serum) for biomarker analysis should be collected on Day 1 prior to first dose of study treatment.

j Race and ethnicity to be collected unless not allowed by local regulation.

k The provision of tumour tissue is encouraged only if clinically appropriate and not considered detrimental to patient care and patient agreed to the optional tumour biopsy in the consent form.

Table 3 Study Schedule - Follow-up Visits (Year 2 onwards)

Visit Number	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**Survival Follow-up (Every 12 months)**
Year	**2**				**3**		**4**		**5**		**6**	**7**	**8**	**9**	**10**	**11+**
Month	**15**	**18**	**21**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**66**	**78**	**90**	**102**	**114**	**126, 138, etc.**
Visit Window	**±1 month**				**±2 months**						**±3 months**					**±3 months**
Recurrent/new cancers assessment (includes physical exam, clinical signs and symptoms)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Mammogram and/or breast MRI (ipsilateral and/or contralateral) (MRI preferred for patients younger than 50 years) **a**		X			X		X		X		X	X	X	X	X	
Subsequent cancer therapy **b**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X**d**
Overall survival assessment																X**d**
EORTC QLQ-C30		X		X												
FACIT-Fatigue		X		X												
Blood biomarker samples at disease recurrence (Mandatory)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tumour sample at disease recurrence (Optional) **c**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
SAE**e**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a Radiological tests to exclude a second primary breast cancer (ipsilateral and/or contralateral) are mandatory during study participation (starting at week 24 and yearly thereafter) for patients with any remaining intact breast tissue. The preferred tests are mammogram or MRI (MRI preferred for patients below 50 years of age). For patients who underwent a bilateral mastectomy, with no remaining breast tissue, a physical examination is sufficient and radiological tests are not mandatory. For patients who underwent a bilateral mastectomy, as well as for male patients, clinical exam may be supplemented by ultrasound exams at investigator's discretion.

b First line treatment for first breast cancer recurrence and any subsequent regimens containing PARP inhibitors or platinum received by the patient at any time need to be recorded. Information on endocrine therapies should be collected and recorded in the clinical database until IDFS endpoint is met due to breast cancer related distant relapse.

c The provision of tumour tissue is encouraged only if clinically appropriate and not considered detrimental to patient care and patient agreed to the optional tumour biopsy in the consent form.

d During the annual survival follow-up phase, information (where available) on further subsequent cancer therapies (see footnote b), sites of metastases and any other new cancers will be collected in addition to vital status.

e All ongoing AEs/SAEs and any new AEs/SAEs identified during the 30 calendar days follow-up period after last dose of study medication must be followed to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up or in survival follow-up. If an investigator learns of any SAEs, including death, at any time after a patient has completed the 30 days post treatment follow-up period, and he/she considers there is a reasonable possibility that the event is causally related to the study treatment, the investigator should report it according to SAE reporting procedures for this study. Any cases of MDS/AML, any new second primary malignancies or diagnoses of pneumonitis occurring after the 30-day follow-up period should be reported as a SAE, regardless of investigator's assessment of causality, knowledge of the treatment arm, and irrespective of the timing of the event in relation to study therapy. Non-melanoma invasive skin cancers and all cases of carcinoma in situ need to be reported as a non-serious AE unless at least one of the seriousness criteria is met which then requires reporting as a SAE, see Section 6.4.6. If a patient develops MDS/AML full diagnostic details and classification should be provided e.g. bone marrow and cytogenetic analysis reports, see Sections 5.5.12.4 and 6.4.11.5. A questionnaire will be sent to any investigators reporting MDS/AML or new primary malignancies as an aid to provide detailed information on the case.

3.2 Rationale for study design, doses and control groups

3.2.1 Rationale for study design

In this placebo-controlled, double-blinded adjuvant study, TNBC patients and ER and/or PgR positive HER2 negative patients with germline *BRCA* mutations at high risk of recurrence will be randomised to receive monotherapy olaparib 300 mg tablet b.i.d. (twice daily) or corresponding placebo for a maximum of 12 months following completion of their definitive loco-regional treatment and chemotherapy in the adjuvant or neoadjuvant setting.

The rationale for allowing patients with ER and/or PgR positive HER2 negative breast cancer who carry a g*BRCA*m (including gene rearrangements) is provided in Section 1.3.

The use of a placebo comparator to olaparib is considered acceptable in order to objectively test the hypothesis of improved efficacy with the addition of olaparib for up to 12 months as compared to no further therapy (i.e. placebo) in patients with TNBC and endocrine therapy alone in patients with ER and/or PgR positive cancer. By blinding patients and investigators, using placebo control and assessing patients for the disease recurrence at pre-defined intervals, the risk of bias that could affect the interpretation of the IDFS endpoint should be minimised. In line with international clinical guidelines evidence of disease recurrence will be assessed during the regular follow-ups (3 monthly during the first 2 years, 6 monthly during the 3rd, 4th and 5th year and annually afterwards) by medical history, physical examination and mammogram and/or breast MRI (MRI preferred for patients younger than 50 years) (ipsilateral and/or contralateral), unless clinical signs and symptoms require further investigation (Khatcheressian et al 2012). In addition safety follow-ups are implemented during the 12-month study treatment period and 30 days after its discontinuation.

It should be noted that the safety and efficacy of olaparib has been demonstrated in the clinical program using the capsule formulation (400 mg - 8 capsules - twice daily); however, an improved tablet formulation (2 tablets twice daily) has been developed and will be used in this study. The tablet dose of olaparib that will be investigated is 300 mg b.i.d. (twice daily) which is considered similar to the capsule 400 mg b.i.d. (twice daily) dose. This tablet dose has been chosen based on data from Study D0810C00024. Since it has been shown that the capsule and tablet formulations are not bioequivalent, a formulation switch based on bioequivalence has not been possible. The tablet dose of 300 mg b.i.d. is considered to have similar efficacy in terms of tumour shrinkage in ovarian cancer patients with *BRCA* mutations to the 400 mg b.i.d. capsule. The 300 mg b.i.d. tablet dose matches or exceeds the exposure of the 400 mg capsule in terms of AUC, C_{maxss}, and C_{minss}. The tolerability profile of the 300 mg b.i.d. tablet dose in Study D0810C00024 was considered similar to the 400 mg b.i.d. capsule formulation. The most common AEs were consistent with the known safety profile of olaparib, namely low grade nausea, vomiting, fatigue, and anaemia. Further information is provided in the olaparib Investigator's Brochure.

3.2.2 Rationale for patient reported outcomes

The patient population for this study will have had intensive treatments with chemotherapy (neoadjuvant or adjuvant), surgery, and possibly radiation therapy prior to entry and randomisation on this study. Prior research by the NSABP and other investigators has

demonstrated physical disruption and many symptoms at the end of primary treatment (Ganz et al 2011B, Ganz et al 2004). Research has shown that it may take a year or more for the physical and emotional recovery and that symptoms may persist well beyond improvements in health related quality of life (HRQoL) (Ganz et al 2011A, Ganz et al 1998A, Ganz et al 1998B, Ganz et al 2002, Bower et al 2000, Bower et al 2006). Thus, in any studies that are designed to capture patient-reported outcomes (PROs) of treatment, consideration should be given to assessment of both HRQoL and symptoms.

In this trial of olaparib versus placebo, there is an important opportunity to determine whether or not the use of olaparib delays or retards recovery after primary breast cancer treatment, and if so, what aspects of symptoms and HRQoL are impaired. Gelmon et al 2011 reported on a Phase II open label study of olaparib in breast and ovarian cancer patients, in which fatigue was the most common reported toxicity (50-70% of patients) followed by nausea (62-66%), vomiting (35-39%), and decreased appetite (27-36%). In a Phase II study in patients with *BRCA1* or *BRCA2* mutations and advanced breast cancer, fatigue was the most significant toxicity (41% grade 1-2, and 15% grade 3-4) in the cohort given 400 mg twice daily (Tutt et al 2010). These trials did not use PROs, and since they were conducted in patients with advanced disease, there is uncertainty about how much fatigue patients will have in the B-55/6-13 trial. However, since this is the most frequent side effect of olaparib, it is our primary outcome in this placebo-controlled comparison.

The FACIT-Fatigue scale will be used to measure treatment related fatigue. The FACIT-Fatigue measure that is being used in this study is well-established and available in multiple languages.

A standard measure of health-related cancer specific HRQoL, the EORTC QLQ-C30, will be used in this study to track recovery in key domains of HRQoL in the year after initial treatment, and to measure symptoms, with a heightened focus on fatigue and GI symptoms (nausea, vomiting, diarrhea), as these symptoms have been reported with olaparib. The GI symptoms items from the EORTC QLQ-C30 will be used to assess their severity, with the focus on assessments during the treatment period, and in the year following the end of treatment. These self-report instruments have been selected for this study due to the need for reliable and valid translations in multiple languages, given the international scope of this trial and the need to include a large number of participants.

Refer to Section 12.2.3 for patient reported outcomes hypotheses and objectives.

3.2.3 Study Population

Approximately 1800 patients with germline *BRCA* mutations *(gBRCA*m*)* and HER2 negative breast cancer who are at high risk of recurrence will be randomised into the trial.

All patients recruited in the study will be selected based on the following 3 principles:

- **Genetic selection**: Documented germline mutation in *BRCA1* or *BRCA2* that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function). Patients with germline *BRCA1* and/or germline *BRCA2* mutations that are considered to be non-detrimental (e.g. “Variants of uncertain clinical significance” or “Variant of unknown significance” or “Variant, favour polymorphism” or “benign

polymorphism," etc) will not be eligible for the study. In terms of *BRCA* mutation status, the following scenarios are considered:

- Status known: for patients already known to have a g*BRCA* loss of function mutation (known as deleterious or suspected deleterious) the exact sequence variant must be recorded on the eCRF and a copy of the genetic diagnosis must be available at site. These patients may be randomised into the study based on the known status; however, re-confirmation of the loss of function mutation from a blood sample will be undertaken soon after randomisation by Myriad Genetics, Inc.

- Status unknown: The g*BRCA* mutation status must be determined by Myriad Genetics, Inc. prior to randomisation as a loss of function mutation i.e. a known deleterious or suspected deleterious mutation

- **Phenotypic tumour selection**: All patients must have either TNBC or ER and/or PgR positive HER2 negative breast cancer as defined in the eligibility criteria section.

- **Prognostic factor selection**: Patients will be selected based on high risk of recurrence regardless of whether they received their chemotherapy in the adjuvant or neoadjuvant setting. High risk of recurrence will be defined as follows:

  1. For patients who underwent initial surgery and received adjuvant chemotherapy

     - TNBC patients must have been axillary node-positive (≥pN1, any tumour size) or axillary node negative (pN0) with invasive primary tumour pathological size > 2 cm (≥pT2)

     - ER and/or PgR positive/HER 2 negative patients must have had ≥4 pathologically confirmed positive lymph nodes

  2. For patients who underwent neoadjuvant chemotherapy followed by surgery

     - TNBC patients must have residual invasive breast cancer in the breast and/or resected lymph nodes (non pCR)

     - ER and/or PgR positive/HER 2 negative patients must have residual invasive cancer in the breast and/or the resected lymph nodes (non pCR) AND a CPS&EG score ≥3. Instructions on how to calculate the CPS&EG score (Mittendorf et al 2011; Jeruss et al 2008) are provided in Appendix H.

4. PATIENT SELECTION CRITERIA

Investigator(s) should keep a patient screening log of patients who entered pre-study screening.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

Criteria relevant to Part 1 BRCA screening (Table 1) are marked with (**) double asterisk

4.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. **Provision of informed consent prior to any study specific procedures

2. **Female or male patients must be ≥18 years of age

3A. For patients who underwent initial surgery and received adjuvant chemotherapy

- TNBC patients must have been axillary node-positive (≥pN1, any tumour size) or axillary node-negative (pN0) with invasive primary tumour pathological size > 2 cm (≥pT2)
- ER and/or PgR positive/HER 2 negative patients must have had ≥4 pathologically confirmed positive lymph nodes

3B. For patients who underwent neoadjuvant chemotherapy followed by surgery

- TNBC patients must have residual invasive breast cancer in the breast and/or resected lymph nodes (non-pCR)
- ER and/or PgR positive/HER2 negative patients must have residual invasive cancer in the breast and/or the resected lymph nodes (non-pCR) AND a CPS&EG score ≥3. Instructions on how to calculate the CPS&EG score (Mittendorf et al 2011; Jeruss et al 2008) are provided in Appendix H.

4. **Histologically confirmed non-metastatic primary invasive adenocarcinoma of the breast that is one of the two following phenotypes:

a) TNBC defined as:

- ER and PgR negative defined as IHC nuclear staining <1%.

AND

- HER2 negative (not eligible for anti-HER2 therapy) defined as:
  - IHC 0, 1+ without ISH **OR**

- IHC 2+ and ISH non-amplified with ratio less than 2.0 and if reported, average HER2 copy number < 4 signals/cells **OR**
- ISH non-amplified with ratio less than 2.0 and if reported, average HER2 copy number < 4 signals/cells (without IHC)

b) ER and/or PgR positive, HER2 negative breast cancer defined as:

– ER and/or PgR positive defined as IHC nuclear staining ≥ 1%.

AND

– HER2 negative (not eligible for anti-HER2 therapy) defined as:

- IHC 0, 1+ without ISH **OR**
- IHC 2+ and ISH non-amplified with ratio less than 2.0 and if reported, average HER2 copy number < 4 signals/cells **OR**
- ISH non-amplified with ratio less than 2.0 and if reported, average HER2 copy number < 4 signals/cells (without IHC)

Patients with multifocal or multicentric invasive disease are eligible as long as all the lesions for which HER2 characterization is available are HER2 negative.

Patients with synchronous bilateral invasive disease are eligible as long as all the lesions assessed for HER2 on both sides are negative.

In both the above cases, the lesion considered at highest risk for recurrence based on the investigator's discretion will be used for eligibility determination.

5. Documented germline mutation in *BRCA1* or *BRCA2* that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function). Local *gBRCA* testing results, if available, will be used for establishing eligibility. If local *gBRCA* testing results are not available, central testing will be provided for those patients who otherwise appear to be eligible (see Section 6.2.1).

6A. Completed adequate breast surgery defined as:

– The inked margins of breast conservation surgery or mastectomy must be histologically free of invasive breast cancer and ductal carcinoma in situ with the exception of the posterior margin if this margin is the pectoralis major fascia or the anterior margin if this is the dermis. Patients with resection margins positive for lobular carcinoma *in situ* are eligible.

– Patients with breast conservation must have adjuvant radiotherapy. Patients having mastectomy may have adjuvant radiotherapy according to local policy and/or international guidelines.

6B. Completed adequate axilla surgery defined as:

Adjuvant Chemotherapy Patients:

- Sentinel lymph node biopsy alone if negative or if lymph node(s) only contain micrometastases (≤2.0 mm) **OR**
- Positive sentinel lymph node biopsy followed by axillary nodal dissection or radiotherapy as per local guidelines **OR**
- Axillary dissection

Neoadjuvant Chemotherapy Patients:

- Sentinel lymph node biopsy performed *before* neoadjuvant chemotherapy:
  - If negative or if lymph node(s) only contain micrometastases (≤2.0 mm), additional axillary surgery is not required
  - If positive, axillary node dissection or axillary nodal radiotherapy should follow completion of neoadjuvant chemotherapy
- Sentinel lymph node biopsy performed *after* neoadjuvant chemotherapy:
  - If negative, additional axillary surgery not mandated
  - If positive (micrometastases are regarded as positive), additional axillary surgery is required unless the patient is enrolled in a Phase III multicentre clinical trials proposing radiotherapy as alternative treatment of the axilla. The trial must be pre-approved by the OlympiA Executive Committee.
  - Axillary dissection

7. Completed at least 6 cycles of neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes or the combination of both. Prior platinum as potentially curative treatment for prior cancer (e.g. ovarian) or as adjuvant or neoadjuvant treatment for breast cancer is allowed. (For neoadjuvant patients all chemotherapy should be delivered prior to surgery. No further cycles of chemotherapy post-surgery are allowed.)

8. Patients must have adequate organ and bone marrow function measured within 28 days prior to randomisation with no blood transfusions (packed red blood cells and/or platelet transfusions) in the past 28 days prior to testing for organ and bone marrow function as defined below:

- Haemoglobin ≥10.0 g/dL
- Absolute neutrophil count (ANC) ≥1.5 x 10^9/L

- Platelet count ≥100 x 10^9/L
- Total Bilirubin ≤ ULN (institutional upper limit of normal) except elevated total bilirubin <1.5 x ULN due to Gilbert's disease or similar syndrome involving slow conjugation of bilirubin
- AST (SGOT)/ALT (SGPT) ≤2.5 x ULN
- ALP ≤2.5 x ULN

To rule out metastatic breast cancer, patients with screening ALT/AST or ALP above institutional upper limit of normal should have liver ultrasound, CT or MRI at any time point between diagnosis of current breast cancer and randomisation. Screening bone scan is required if ALP and/or corrected calcium level are above the institutional upper limit. (Note: PET/CT scan may be used as an alternative imaging technique).

9. Serum or plasma creatinine ≤1.5 x ULN

10. ECOG performance status 0-1

11A. Women who are not postmenopausal or have not undergone a hysterectomy must have documented negative pregnancy test within 28 days prior to randomisation.

Postmenopausal is defined as one or more of the following:

- Age ≥ 60 yrs
- Age < 60 and amenorrheic for 1 year or more in the absence of chemotherapy and/or hormonal treatment
- Follicle stimulating hormone (FSH) and plasma estradiol levels in the postmenopausal range for women under 60
- Radiation-induced oophorectomy with last menses >1 year ago
- Bilateral oophorectomy

11B. **Women of childbearing potential who are sexually active must agree, with their partners, to the use of two highly effective forms of contraception in combination. This should be started from the signing of the informed consent and continue, throughout the period of taking study treatment and for at least 1 month after the last dose of study drug, or they must totally/truly abstain from any form of sexual intercourse. Male patients must use a condom during treatment and for 3 months after last dose of study drug when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form of contraception (see Appendix E for acceptable methods) if they are of childbearing potential.

12. **Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations

13. Formalin fixed, paraffin embedded (FFPE) tumour sample from the primary tumour, mandatory*.

    *NOTE: For adjuvant patients, this refers to the surgical specimen; for neoadjuvant patients, both the pre-treatment core biopsy and the surgical specimen with residual disease are requested but only one is mandatory. If the surgery tumour blocks are available, but cannot be submitted, sites may submit a portion of invasive tumour from the original block, either by taking at least one core of at least 3 mm in diameter, or by splitting the original block in two parts, and re-embedding one in a new block for central submission. If blocks containing pre-neoadjuvant treatment core biopsies are available but cannot be submitted, sections mounted on glass slides prepared from the block can be provided. If tumour sample can't be provided as requested above or if it's not available, approval by Study Team for patient's entry into the trial is required.

14. Patient should be randomised in the trial ideally within a maximum of 8 weeks of completion of their last treatment (surgery, chemotherapy or radiotherapy), but in no case longer than 12 weeks.

4.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. **Involvement in the planning and/or conduct of the study.

2. Patients who do not have deleterious or suspected deleterious *gBRCA1* and/or *2* mutations but only have *BRCA1* and/or *BRCA2* mutations that are considered to be non-detrimental (e.g., “Variants of uncertain clinical significance” or “Variant of unknown significance” or “Variant, favour polymorphism” or “benign polymorphism” etc.).

3. **Previous randomisation in the present study.

4. **Evidence of metastatic breast cancer. Patient considered at high risk of having disseminated disease (i.e. those with locally advanced disease, clinical N2-3 or pathological N1-3 with the exception of pN1a in adjuvant patients) should have a CT/MRI scan of the Thorax/Abdomen/Pelvis or any other area as clinically indicated and a bone scan **or** a CT scan with bone windows at any point between diagnosis of the current breast cancer and randomisation to rule out metastatic breast cancer. (Note: PET/CT scan may be used as an alternative imaging technique and precludes the need for bone scan). Patients with screening ALT/AST or ALP above institutional upper limit of normal should have liver ultrasound, CT or MRI at any time point between diagnosis of current breast cancer and randomisation. Screening bone scan is required if ALP and/or corrected calcium level are above the institutional upper limit. (Note: PET/CT scan may be used as an alternative imaging technique).

5. **Exposure to an investigational product within 30 days or five half lives (whichever is the longer) prior to randomisation.

6. **Any previous treatment with a PARP inhibitor, including olaparib and/or known hypersensitivity to any of the excipients of study treatment.

7. **Patients with second primary malignancy. **EXCEPTIONS** are:

    - adequately treated non-melanoma skin cancer, curatively treated *in situ* cancer of the cervix, Ductal Carcinoma *in situ* (DCIS) of the breast, stage 1 grade 1 endometrial carcinoma

    - other solid tumours and lymphomas (without bone marrow involvement) diagnosed ≥5 years prior to randomisation and treated with no evidence of disease recurrence and for whom no more than one line of chemotherapy was applied.

8. Resting ECG with QTc >470 msec detected on 2 or more time points within a 24 hour period or family history of long QT syndrome. If ECG demonstrates QTc >470 msec, patient will be eligible only if repeat ECG demonstrates QTc ≤470 msec.

9. Patients receiving systemic chemotherapy within 3 weeks prior to randomisation.

10. Patients receiving adjuvant radiotherapy within 2 weeks prior to randomisation.

11. Concomitant use of known strong CYP3A4 inhibitors (e.g., itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (e.g., ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting study treatment is 2 weeks. Concomitant use of known strong (e.g., phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (e.g., bosentan, efavirenz, modafmil). The required washout period prior to starting study treatment is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.

12. Persistent toxicities (≥CTCAE grade 2) caused by previous cancer therapy, excluding alopecia and CTCAE grade 2 peripheral neuropathy.

13. ** Patients with current or past history of haematologic malignancies and any clonal non-malignant haematological disorder which predisposes the patient to develop a haematological malignancy. Exception: lymphoma (refer to Exclusion Criterion 7).

14. Major surgery within 2 weeks prior to randomisation: patients must have recovered from any effects of any major surgery.

15. Patients considered at 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, extensive bilateral lung disease on High Resolution Computed Tomography scan or any psychiatric disorder that prohibits obtaining informed consent.

16. **Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.

17. Pregnant or breastfeeding women.

18. **Patients with known active Hepatitis B or C

19. **Patients known to be HIV positive with one or more of the following:
    a. Baseline CD4 count of < 250 cells/mm^3
    b. History of AIDS indicator conditions
    c. Anti-retroviral therapy with any potent CYP3A4 inhibitor (see Section 5.6.2)

20. **Previous allogeneic bone marrow transplant.

21. **Whole blood transfusions in the last 120 days prior to entry to the study which may interfere with *gBRCA* testing (packed red blood cells and platelet transfusions are acceptable, for timing refer to inclusion criteria no. 8)

For procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

5.1.1 Meals and dietary restrictions

It is prohibited to consume grapefruit juice while on study therapy.

5.1.2 Contraception

Women of childbearing potential who are sexually active, must agree, to the use of two highly effective forms of contraception in combination (as described in Appendix E). This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for at least 1 month after last dose of study drug, or they must totally/truly abstain from any form of sexual intercourse. Male patients must use a condom during treatment and for 3 months after the last dose of study drug when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form of contraception if they are of childbearing potential. Male patients should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib. For details please refer to Appendix E Acceptable Birth Control Methods.

5.2 Patient enrolment and randomisation and initiation of study treatment

The following section outlines procedures for Screening Registration and for Randomisation, and for ordering Study Drug at randomisation.

1. The Investigator must obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Patients will be assigned a unique patient identifier (E-code) which should be used to identify the patient on the central Myriad sample, the eCRFs in Medidata RAVE and any other trial-related communications.

3. The Investigator must determine patient eligibility. See Sections 4.1 and 4.2.

4. If the patient meets the eligibility requirements, the authorized site staff should randomise the patient using OPEN, answering all questions which are asked by the system including questions relative to the stratification factors.

5. OPEN will randomly assign treatment (olaparib or placebo). The treatment allocation will be blinded for the Investigator and the patient.

6. Randomisation will automatically trigger study drug shipment to the site (except for countries where the initial drug shipment is sent upon activation). Details of drug ordering procedures can be found in Section 5.5.5.

7. Once medication is received, the site personnel can then dispense the medication kit per patient's treatment assignment.

5.2.1 CTEP registration procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		

Documentation Required	IVR	NPIVR	AP	A
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR ***Help Desk*** by email as < RCRHelpDesk@nih.gov >.

5.2.2 CTSU registration procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

5.2.2.1 IRB approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol-specific requirements.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

5.2.2.2 Downloading site registration documents

Site registration forms may be downloaded from the NSABP B-55 protocol page located on the CTSU Members' website.

- Go to https://www.ctsu.org and log in to the Members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the NRG link to expand, then select trial protocol NSABP B-55
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided

5.2.2.3 Requirements for B-55/6-13 site registration

IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

5.2.2.4 Submitting regulatory documents

Submit completed forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

> Regulatory Submission Panel: www.ctsu.org (Members' area) → Regulatory Tab → Regulatory Submission
>
> When applicable, original documents should be mailed to:
> CTSU Regulatory Office
> 1818 Market Street, Suite 3000
> Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

5.2.2.5 Checking your site's registration status

You can verify your site registration status on the Members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the Members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

5.2.3 Procedures for randomisation

Patient eligibility must be established before randomisation is undertaken. Randomisation can be performed for patients who met all eligibility criteria upon completion of all necessary Screening PART 2 procedures to ensure that the study drug is available at site and can be dispensed to the patient preferably during Visit 2 (Day 1).

The randomisation system will use the following stratification factors:

- Hormone receptor status (ER and/or PgR positive/HER2 negative versus TNBC)

  NOTE: In cases of multifocal, multicentric or synchronous bilateral invasive disease, stratification is based on the status of the lesion considered at highest risk (at the investigator's discretion) that was used to determine eligibility.

- Neoadjuvant versus adjuvant chemotherapy

- Platinum therapy for current breast cancer: Yes/No

Eligible patients will be randomised in a 1:1 ratio to one of the following treatments:

- Olaparib tablets p.o. 300 mg twice daily

- Matching placebo tablets p.o. twice daily

It is recommended that patients commence study treatment within 7 days of randomisation, but no later than 21 days.

If, following randomisation, it is discovered that incorrect information on the stratification factors was entered at randomisation, then the correct information should be recorded in the eCRF but the randomisation system will retain the information that was provided at the time of randomisation. The NRG Oncology SDMC must also be notified.

5.2.4 Oncology Patient Enrollment Network (OPEN)

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site

user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU Members' side of the website at https://www.ctsu.org. To an assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the NRG Oncology or CTSU Web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration, including the Patient ID number for the study, and treatment information. Please print this confirmation for your records. Additionally, a transmittal form to be used when faxing the signed consent form to the NRG Oncology SDMC will be provided. If it is necessary to reprint the randomization confirmation or the transmittal form, they can be reprinted through Coordinator Online via the ***View a Patient Entry Report*** under Patient Entry.

Further instructional information is provided on the OPEN tab of the CTSU Member side of the CTSU Web site at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

5.3 Procedures for handling patients incorrectly enrolled or randomised or initiated on study treatment

Patients who fail to meet the inclusion/exclusion criteria must not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule.

Where patients that do not meet the eligibility criteria are randomised in error or incorrectly started treatment, or where patients are subsequently found not to meet the pre-study criteria, a discussion should occur between the Protocol Officer or a Protocol Chair, if the Protocol Officer is not available (see Section 13.1), and the Investigator regarding whether to continue or discontinue the patient from treatment. Once a decision is made, Investigators need to ensure they comply with all applicable requirements for human patient protection and ethical review. The data on these patients will remain in the study database and will be included in appropriate analyses as defined by the Statistical Analysis Plan. Data values provided at the time of randomisation will not be changed. Any corrected values for stratification fields or other randomisation data fields will be recorded elsewhere in the clinical database, leaving the randomisation record to reflect the data actually provided at the time of randomisation.

Contact with the Protocol Officer or a Protocol Chair is to ensure all such decisions are appropriately documented. The NRG Oncology SDMC must also be notified. In situations where an agreement cannot be reached, the patient should have their study therapy stopped but should continue to have efficacy assessments as per the study plan, unless the patient withdraws consent.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

Olaparib and placebo treatment will be blinded.

The active and placebo tablets will be identical and presented in the same packaging to ensure blinding of the study medication.

5.4.2 Methods for unblinding individual patients

The treatment code for an individual patient should not be broken except in medical emergencies and when the appropriate management of the patient requires knowledge of the actual treatment assignment. Following emergency unblinding the investigator should report the unblinding to the Protocol Officer (see Section 13.1), without revealing any treatment information.

Only life-threatening situations should be considered as emergency such as in the cases listed below:

- Study drug was taken by someone else other than the patient by mistake.
- Patient is in a life-threatening condition following intentional or unintentional consumption of study drug in higher doses than indicated.
- Patient admitted to emergency unit with what is regarded as life threatening condition irrespective of potential causal relationship with OLYMPIA study drug, and the treating team has to know the nature of all medications the patient is receiving.

Most other situations not mentioned above are regarded as non-emergency and hence the non-emergency unblinding procedure should apply.

Where a non-emergency unblinding is sought for an individual patient the process will require a discussion with the Protocol Officer (see Section 13.1) to understand the need for unblinding and help minimise any unnecessary unblinding, before the patient is unblinded. However, the final decision as to whether or not to unblind the patient will be made by the Investigator.

Disease progression or medical conditions that are manageable without any compromise to patient care in the absence of knowledge of the treatment received by the patient will not be considered as valid reasons for unblinding.

In both emergency and non-emergency cases, the information on the assigned treatment (i.e. Olaparib or Placebo) should be restricted only to the Principal Investigator and/or personnel involved in the clinical care of the patient as deemed appropriate by the Principal Investigator. This information should not be revealed to the monitor, sponsor or any member of the study team.

Any patient unblinded will need to be immediately discontinued from the study treatment.

The AstraZeneca patient safety team retains the right to break the code for individual SAEs that are unexpected and are suspected to be causally related to the study treatment and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented and the target number of events has been reached.

5.4.3 Procedures for unblinding

When unblinding is required, local investigators must telephone the NRG Oncology SDMC (see Information Resources) and state that they wish to unblind a patient's study drug assignment. The same procedure applies to 24-hour emergency unblinding. A data file is maintained for the study and can be accessed by a limited number of designees within the NRG Oncology SDMC who serve the study in an administrative, nonclinical capacity. NRG Oncology SDMC personnel will require the protocol number (i.e., NSABP B-55/BIG 6-13), the patient ID number (e.g., "E999999"), the patient initials (e.g., "LFM"), and the reason for the unblinding request in order to unblind the study drug assignment. After the confirmation of the indication for unblinding is obtained, the NRG Oncology investigator will be notified immediately of the patient's treatment assignment. A computer record will be created to identify the patient as having been unblinded. The institution is responsible for providing continued follow-up (for patients whose treatment assignment has been unblinded) on the same schedule as indicated in the study protocol for patients who have not been unblinded, unless otherwise specified.

5.5 Treatments

5.5.1 Identity of study treatment

AstraZeneca's Pharmaceutical Development, R&D Supply Chain will supply olaparib and matching placebo to the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) as green film-coated tablets as shown in Table 4 below.

Table 4 Identity of study treatment

Study treatment	Dosage form and strength
Olaparib*	Tablet –100 mg
Olaparib*	Tablet – 150 mg
Placebo to match olaparib	Tablet to match 100 mg olaparib
Placebo to match olaparib	Tablet to match 150 mg olaparib

* Descriptive information for olaparib can be found in the Investigator's Brochure

5.5.2 Doses and treatment regimens

5.5.2.1 Olaparib and matching placebo (study treatment)

The planned dose of 300 mg b.i.d. (twice daily) will be made up of two (2) x 150 mg tablets b.i.d. (twice daily) with 100 mg tablets used to manage dose reductions as explained in Table 5.

Table 5 Study treatment doses and treatment regimens

Total daily dose	Dose twice daily (b.i.d.)	Morning		Evening	
		Number of tablets	Tablet strength	Number of tablets	Tablet strength
600 mg	300 mg	2 tablets	150 mg	2 tablets	150 mg
Initial dose (300 mg twice daily) can be reduced as follows for AEs (no re-escalation allowed):					
500 mg	250 mg	1 tablet	150 mg	1 tablet	150 mg
		1 tablet	100 mg	1 tablet	100 mg
400 mg	200 mg	2 tablets	100 mg	2 tablets	100 mg
Temporary dose levels due to CYP3A inhibitor exposure (re-escalation allowed):					
300 mg	150 mg	1 tablet	150 mg	1 tablet	150 mg
200 mg	100 mg	1 tablet	100 mg	1 tablet	100 mg

As soon as possible following randomisation, patients will be administered olaparib or matching placebo orally twice daily (b.i.d.) at 300 mg for 52 weeks. Two (2) x 150 mg olaparib or matching placebo tablets should be taken at the same time each morning and evening of each day, approximately 12 hours apart with approximately 240 mL of water. The olaparib/placebo tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib/placebo tablets can be taken with a light meal/snack (e.g., two pieces of toast or two biscuits).

If vomiting occurs shortly after the study treatment tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their next allotted dose at the next scheduled time. Patients should not take two doses (4 tablets) at the same time.

Within this study, patients will not be provided olaparib post discontinuation of study treatment. Patients and investigators will not be routinely unblinded to study treatment prior to the final overall survival (OS) analysis.

5.5.3 Olaparib/Placebo

- ***Chemical name***

  4-(3-{[4-(Cyclopropylcarbonyl)piperazin- 1 - yl]carbonyl}-4-fluorobenzyl)phthalazin-1(2H)-one

- ***Trade name***

  Olaparib

- ***Classification***

  Poly (ADP ribose) polymerase 1 inhibitor (PARPi)

- ***CAS registry number***

  763113-22-0

- ***Molecular formula***

  $C_{24}H_{23}FN_4O_3$

- ***Molecular weight***

  434.46

- ***Approximate solubility***

  Olaparib is a crystalline solid. Olaparib is non-chiral. Olaparib shows pH-independent solubility across the physiological range of approximately 0.1 mg/ml.

- ***Mode of action***

  Olaparib (AZD2281, KU-0059436) is a potent inhibitor of poly (ADP-ribose) polymerase enzyme (PARP) that is being developed as a monotherapy as well as well as for combination with chemotherapy, ionizing radiation, and other anti-cancer agents. Poly (ADP-ribose) polymerase inhibition is a novel approach to targeting tumors that have homologous recombination DNA repair (HRR) pathway deficiencies (HRD). In HRD tumors, single agent treatment with olaparib can lead to tumor regression by a process known as synthetic lethality – a result of the accumulation of un-repaired DNA double-strand breaks (DSB) and an unsupportable increase in genomic instability. Olaparib may also enhance the DNA damaging effects of ionizing radiation and chemotherapy.

- ***Description***

  The 100 mg and 150 mg strengths of olaparib tablets are composed of the same constituents. The tablet cores comprise: olaparib, copovidone, colloidal silicon dioxide, mannitol, and sodium stearyl fumarate. The composition of the tablet film-coating is: hydroxypropyl methylcellulose (hypromellose), macrogol 400 (polyethylene glycol 400), titanium dioxide, iron oxide yellow, and iron oxide black.

  Placebo tablets are identical in appearance to olaparib film-coated tablets. These tablets contain: mannitol, microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The composition of the film coat is identical to that of the olaparib film-coated tablet.

- ***How supplied***

  For this study, olaparib and matching placebo will be supplied by AstraZeneca and will be distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Olaparib is presented as a green, film-coated tablet containing 100 mg or 150 mg of drug substance. The placebo tablets do not contain the active drug substance. Both the olaparib and matching placebo tablets are supplied in high-density polyethylene (HDPE) bottles. Each bottle will contain 32-150 mg or 100 mg tablets (olaparib 150 mg or 100 mg) or 0 mg tablets (placebo for olaparib 150 mg or 100 mg) and a desiccant. Bottles are secured with a child-resistant closure; induction-sealed membranes provide tamper evidence.

Olaparib and matching placebo tablets will be distributed in kits. Each kit will consist of a small box containing 2 bottles of olaparib or placebo tablets. Both bottles and kit box will contain patient-specific labels (Section 5.5.11). Each kit will contain a 16 day supply of olaparib or placebo.

- Each 300 mg kit will contain 2 bottles of olaparib or placebo 150 mg tablets
- Each 250 mg kit will contain 1 bottle of olaparib or placebo 100 mg tablets and 1 bottle of olaparib or placebo 150 mg tablets
- Each 200 mg kit will contain 2 bottles of olaparib or placebo 100 mg tablets

- ***Storage***

  All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle specifies the appropriate storage.

- ***Route of administration***

  Oral

- ***Method of administration***

  The olaparib/placebo tablets should be swallowed whole and not chewed, crushed, dissolved, or divided. Olaparib/placebo tablets can be taken with a light meal/snack.

- ***Stability***

  Bottle contents are to be discarded 90 days after the seal is broken. Investigators will be notified when lots have expired.

- ***Patient care implications***

  Pre-clinical data indicate that olaparib can have adverse effects on embryofoetal survival and development. It is not known whether olaparib is excreted in human milk. Therefore, olaparib must not be used during pregnancy or breast-feeding, and patients of childbearing potential must use contraception.

  Refer to Appendix E: Acceptable Birth Control Methods for more information.

5.5.3.1 Drug information

Please refer to Section 5.5.2 for study treatment and the current FDA-approved Investigator's Brochure and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

5.5.4 Obtaining an Investigator's Brochure

Please refer to the current Investigator's Brochure for detailed information regarding olaparib. The olaparib IB can be downloaded from the Members' Area of the NSABP Web site or requested from the CTSU using the CTSU Request for Clinical Brochure Form posted on the CTSU Web site.

5.5.5 Procurement of olaparib (IND #122443, NSC #747856)/placebo

Olaparib (NSC #747856) and matching placebo will be supplied free of charge by AstraZeneca, and will be distributed by the Pharmaceutical Management Branch (PMB), Division of Cancer Therapy Treatment and Diagnosis (DCTD), National Cancer Institute (NCI). PMB policy requires that olaparib/placebo be shipped directly to the institution where the patient is to be treated.

Study supplies are packaged in "kits." Each kit contains 2 bottles of olaparib or matching placebo tablets. The label instructions on each bottle read "Take 1 tablet by mouth twice a day." This consistency of dosing instructions among dose levels is intended to avoid dosing errors for patients receiving 250 mg.

Note: Kits are to be dispensed intact. Do not separate the bottles. Instruct patients to take 1 tablet from each bottle in the kit twice a day.

No blinded starter olaparib/placebo will be available for this study. Blinded, patient-specific olaparib/placebo will be sent to the registering investigator at the time of randomisation and should arrive within approximately 5 business days. Once a patient has been randomised, the NRG Oncology SDMC will electronically transmit a clinical drug request for that patient to the PMB. The request will be processed by the PMB the next business day and shipped the following business day. Shipments will be sent by FedEx Ground (up to 5 business days for delivery but can be expedited by the provision of an express courier account name and number to the NRG Oncology SDMC at the time the patient is randomised. Please note that additional processing time is required for QA/QC checks on patient-specific/blinded orders and next day delivery is not available.

The initial shipment will contain 8 kits (16 bottles) of olaparib or placebo, enough olaparib or placebo to complete 16 weeks of therapy (2 tablets twice a day for 28 days per cycle).

Subsequent orders for blinded, patient-specific supplies must be requested by the Principal Investigator (or his/her authorized designee[s]) for NSABP B-55/BIG 6-13 at each participating institution using the PMB On-line Agent Order Processing (OAOP) program. The assigned patient ID number (e.g., E999999) and the patient initials (e.g., "LFM") should be entered in the "Patient or Special Code" field. A separate order is required for each patient ID number (e.g., E999999) being ordered. All drug orders should be shipped directly to the physician responsible for treating the patient. Requests can be placed **12 weeks after the last shipment is received.** It is recommended that 6 kits (12 bottles) be requested at each order. **The recommended ordering schedule is Weeks 11, 23, and 35.**

Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator

at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees must submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB at any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

5.5.6 Special ordering procedures for patients requiring a dose reduction

If the patient is **dose reduced** from 300 mg b.i.d. to 250 mg b.i.d. (or 250 mg b.i.d. to 200 mg b.i.d.), an agent request must be submitted by the site through the OAOP application.

- For each 250 mg kit, request 1 bottle of 100 mg tablets and 1 bottle of 150 mg tablets.
- For each 200 mg kit, request 2 bottles of 100 mg tablets.

The number of kits included in the initial shipment will depend on the patient's place on the treatment calendar.

5.5.7 Agent inventory records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

5.5.8 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://eapps-ctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

5.5.9 Transfer of olaparib/placebo

Kits/bottles may ***not*** be transferred from one patient to another patient or from one protocol to another protocol. PMB does not permit the transfer of agents between institutions (unless prior

approval from PMB is obtained). Olaparib/placebo may not be used outside the scope of this protocol, nor can olaparib/placebo be transferred or licensed to any party not participating in this clinical study. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 240-276-7893) a Transfer Investigational Agent Form available on the NCI home page (http://ctep.cancer.gov) or call the PMB at 240-276-6575. The participating institution should also inform the NRG Oncology SDMC of the transfer.

5.5.10 Return of olaparib/placebo

At the completion of accrual and treatment, all unused (unopened) bottles of olaparib/placebo must be returned to the PMB. When it is necessary to return study drug (e.g., unused bottles remaining when the protocol is closed to accrual and treatment at a participating clinical site or unopened expired bottles), investigators should return the olaparib/placebo to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov) or call the PMB at 240-276-6575.

Tablets remaining from dispensed bottles should be documented on the patient-specific NCI Investigational Agent Accountability Record Form for Oral Agents. On the correct dispensing row, document the date returned and the quantity, then destroy on site in accordance with institutional policy.

5.5.11 Labelling

For **BLINDED (olaparib or placebo) THERAPY**, each bottle will be labeled with:

- the protocol number (i.e., "NSABP-B-55")
- the bottle number (i.e., "Bottle 1 of 2, 2 of 2")
- the number of tablets (i.e., "32 tablets")
- the patient ID number (e.g., "E999999", where "E999999" represents a unique patient identifier assigned by NRG Oncology at registration)
- the patient initials (i.e., last initial, first initial, middle initial [e.g., "L, FM"])
- the agent identification (i.e., "Olaparib 150 mg or Placebo")
- a blank line for the pharmacist to enter the patient's name
- administration instructions (i.e., "Take 1 tablet by mouth twice a day. Discard contents after 90 days")
- storage instructions (i.e., "Store below 30°C (86°F).")
- emergency contact instructions
- a Julian date

The Julian date indicates the day the bottle was labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2013 = 13, 2014 = 14) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a bottle labeled and shipped on January 1, 2013, would have a Julian date of '13001' and a bottle labeled and shipped on December 31, 2014, would have a Julian date of '14365'. The Julian date will be used by PMB for recalls. When a lot expires,

PMB will determine the last date the expired lot was shipped and will recall all bottles (i.e., both Olaparib and Placebo) shipped on or before that date thus eliminating any chance of breaking the blind. The combination Julian Date – Order Number, located in the in the upper right hand corner of the bottle label, should be recorded in the lot number field on the Oral DARF.

Each **BLINDED (olaparib or placebo) KIT BOX** will be labeled with:

- the protocol number (i.e., "NSABP-B-55")
- the patient ID number (e.g., "E999999", where "E999999" represents a unique patient identifier assigned by NRG Oncology at registration)
- the patient initials (i.e., last initial, first initial, middle initial [e.g., "L, FM"])
- the agent identification (i.e., "Olaparib 300 mg or Placebo Kit")
- a blank line for the pharmacist to enter the patient's name
- administration instructions (i.e., "Take 1 tablet from each bottle twice a day.")
- storage instructions (i.e., "Store below 30°C (86°F).")
- emergency contact instructions
- a Julian date

5.5.12 Management of toxicity of study treatment

General instructions

- The CTCAE v4.0 must be used to grade the severity of AEs.
- All dose modifications should be based on the AE requiring the greatest modification.
- Therapy should be held until the AE returns to ≤ grade 1 unless specified otherwise in the dose modification instructions.
- ***If study drug must be held for more than 4 weeks due to an AE or for any other reasons, permanently discontinue olaparib/placebo.***
- Once a dose has been reduced, dose escalation is not permitted.
- If olaparib/placebo must be permanently discontinued, patient follow-up continues to be required as described on Table 2 and Table 3.
- If any investigational treatment is administered, olaparib/placebo must be discontinued.

5.5.12.1 Study therapy following breast cancer recurrence or second primary cancer

Olaparib/placebo must be discontinued following diagnosis of breast cancer recurrence or diagnosis of a second primary malignancy (i.e., excluding new in situ carcinomas of any site and squamous or basal cell skin cancers). Further therapy is at the investigator's discretion.

5.5.12.2 Olaparib/placebo dose levels

All olaparib/placebo dose reductions are based on the dose levels listed in Table 6.

Any toxicity observed during the course of the study should be managed by guidelines as outlined in Table 7 Table 8 and Table 9. Once a dose has been reduced, dose re-escalation to a higher dose is not permitted.

Table 6 Olaparib/placebo dose levels

	Dose Level (mg) twice daily				
	Starting Dose	**Dose levels for AEs (no re-escalation)**		**Temporary dose levels due to CYP3A inhibitor exposure**	
Olaparib/placebo	300	250	200	150	100

Table 7 Mandatory treatment for hematologic toxicity and treatment guidance for other olaparib/placebo toxicities

Important table instructions: • Dose modifications must be based on the AE requiring the greatest modification.			
	Adverse Event	**CTCAE (v 4.0) Grade**	**Action to be Taken**
Hematologic Toxicity **Mandatory**	Anaemia	2 (8.0-9.5 g/dL)	*Hold study therapy until > 9.5 g/dL:* If recovery without packed red blood cells transfusion takes: 1-2 weeks – maintain dose; 3-4 weeks – ↓ one dose level If packed red blood cells transfusion given: reduce one dose level
		3, 4	*Hold study therapy until > 9.5 g/dL:* 1st appearance – ↓ 1 dose level 2nd appearance – ↓ 2 dose levels or discontinuation
	Neutrophil count decreased (incl. febrile neutropenia)	3	*Hold study therapy until ≥ 1200/mm3* ↓ one dose level
		4	*Hold study therapy until ≥ 1200/mm3* ↓ two dose levels
	Platelet count decreased	2	*Hold study therapy until ≥ 75,000//mm3* ↓ one dose level
		3,4	*Hold study therapy until ≥ 75,000//mm3* ↓ two dose levels
Other toxicity deemed to be attributable to study treatment **Guidance**	Diarrhea *(if attributable to olaparib/placebo)*	2	Maintain dose or ↓ one dose level
		3	↓ one dose level
		4	Discontinuation
	Mucositis – oral	2	Maintain dose or ↓ one dose level
		3	↓ one dose level
		4	Discontinuation

Table 7 Mandatory treatment for hematologic toxicity and treatment guidance for other olaparib/placebo toxicities

Important table instructions: • Dose modifications must be based on the AE requiring the greatest modification.			
	Adverse Event	**CTCAE (v 4.0) Grade**	**Action to be Taken**
Other toxicity deemed to be attributable to study treatment **Guidance**	Nausea *(despite antiemetics)*	2	Maintain dose or ↓ one dose level
		3	↓ one dose level
	Vomiting *(despite antiemetics)*	2	Maintain dose or ↓ one dose level
		3	↓ one dose level
		4	↓ one dose level or discontinuation
	Infection	3	*Hold study therapy:* When resolved: Maintain dose or ↓ one dose level Repeat appearance – ↓ one dose level
		4	*Hold study therapy:* When resolved: ↓ two dose levels or discontinuation
	Dyspnea	1, 2, 3	Hold study therapy; rule out pneumonitis Follow instructions in footnote **a**
		4	Discontinuation
	Pneumonitis	2	Follow instructions in footnote **a**
		3, 4	Discontinuation
	Other clinically significant AEs deemed related to study treatment**b**	2	Maintain dose or ↓ one dose level
		3	↓ one dose level
		4	↓ two dose levels or discontinuation

a Hold olaparib/placebo and determine etiology. Unless prohibited based on instructions for other clinical diagnoses (i.e. other AEs), resume olaparib/placebo when grade 0 (if the AE requiring olaparib to be held was dyspnea) or when ≤ grade 1 (if the AE requiring olaparib/placebo to be held was ≥ grade 2).

b Determination of "clinically significant" AEs is at the investigator's discretion.

Table 8 Dose reduction for study treatment to manage moderate renal impairment

Initial dose	**Moderate renal impairment (calculated creatinine clearance by Cockcroft -Gault equation or based on a 24 hour urine test between 31 and 50 ml/min): Dose reduction**
300 mg twice daily	200 mg twice daily

Table 9 Dose reduction for study treatment with concurrent use of a strong or moderate CYP3A inhibitor

Initial dose	Strong CYP3A inhibitor	Moderate CYP3A inhibitor
300 mg twice daily	100 mg twice daily	150 mg twice daily

For guidance on dose reductions for management of renal impairment refer to Section 5.5.12.3,

For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided see section 5.6.2.

5.5.12.3 Renal impairment

If subsequent to study entry and while still on study therapy, a patient's estimated creatinine clearance falls below the threshold for study inclusion (>51 ml/min), retesting should be performed promptly.

A dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation or based on a 24 hour urine test of between 31 and 50 ml/min) for any reason during the course of the study: the dose of study treatment should be reduced to 200 mg b.i.d.

Because the creatinine clearance determination is only an estimate of renal function, in instances where the creatinine clearance falls between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

Olaparib has not been studied in patients with severe renal impairment (creatinine clearance <30 ml/min) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that study treatment be discontinued.

5.5.12.4 Management of haematological toxicity

If blood transfusion support is required to maintain haemoglobin levels above 9.5 g/dL at Dose Level -2 with no alternative explanation for the recurring anaemia, study treatment should be permanently discontinued and the patient referred for haematological evaluation.

If a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF may be given according to local hospital guidelines. If grade 3 or 4 anaemia, neutropenia or thrombocytopenia occurs, weekly differential blood counts including reticulocytes and peripheral blood smear should be performed until Hgb is > 9.5 g/dL, ANC is > 1200/mm^3 and platelets are > 75,000/mm^3. If persistent haematological toxicities lead to discontinuation of study therapy, the patient should be referred to a haematologist for further investigations. Differential blood counts including reticulocytes and peripheral blood smear should be performed at least every 2 weeks until resolution or stabilization.

Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice. Clinical notes and results from further testing should be submitted.

Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE.

Administration of blood cell products and platelet transfusions must be recorded in eCRF.

5.5.12.5 Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g., dyspnoea) or radiological abnormality occurs, study treatment should be held and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Protocol Officer (see Section 13.1).

5.5.12.6 Management of nausea and vomiting

No routine prophylactic anti-emetic treatment is required at the start of study treatment; however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. As per international guidance on antiemetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered.

5.5.12.7 Interruptions for intercurrent non-toxicity related events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease recurrence or toxicity, the case should be discussed with the Protocol Officer (see Section 13.1). All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded according to the eCRF guidelines. Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered. Because the AEs related to olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.

5.6 Concomitant and subsequent treatment(s)

Any concomitant medications (exceptions described in Table 10) which are considered necessary for the patient's welfare, and which will not interfere with the study medication (in the opinion of the treating physician), may be given at the discretion of the investigator, providing the medications, the doses, dates and reasons for administration are recorded on the appropriate eCRF page in Medidata Rave.

Bisphosphonates or denosumab are allowed during study treatment phase and follow-up.

In addition, any relevant unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded. This includes any blood transfusions.

The reasons for the use, doses and dates of treatment should be recorded in the patient's medical records and appropriate sections of the eCRF.

All medications (prescriptions or over the counter medications) continued at the start of study or started during the study or until 30 days from the end of the last protocol treatment and different from the study medication must be documented.

Information on endocrine therapies should be collected and recorded in the clinical database until IDFS endpoint is met due to breast cancer related distant relapse.

The receipt of other anti-neoplastic medications (with the exception of hormonal therapies as addressed in Section 5.6.1) and other investigational medication is prohibited during study treatment and follow-up.

Subsequent anti-cancer treatment is expected to be initiated following breast cancer recurrence; if subsequent anti-cancer treatment needs to be initiated during the 1-year treatment phase, study treatment must be stopped. Information on first line treatment for first breast cancer recurrence and any subsequent regimens containing PARP inhibitors or platinum received by the patient at any time must be recorded in the clinical database.

5.6.1 Administration of endocrine therapy

Patients should receive adjuvant endocrine therapy per local policy and/or international guidelines. Information on endocrine therapies should be collected and recorded in the eCRF until IDFS endpoint is met due to breast cancer related distant relapse.

5.6.2 Restricted concomitant medications

The use of any natural/herbal products or other traditional remedies should be discouraged but use of these products, as well as any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Table 10 Restricted concomitant medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
Strong CYP3A inhibitors: itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir Moderate CYP3A inhibitors: ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil	Strong or moderate CYP3A inhibitors should not be taken with study treatment. If there is no suitable alternative concomitant medication then the dose of study treatment should be reduced for the period of concomitant administration. The dose reduction of study treatment should be recorded in the CRF with the reason documented as concomitant CYP3A inhibitor use. • Strong CYP3A inhibitors — reduce the dose of study treatment to 100 mg b.i.d for the duration of concomitant therapy with the strong inhibitor and for 5 half-lives afterwards. • Moderate CYP3A inhibitors - reduce the dose of study treatment to 150 mg b.i.d for the duration of concomitant therapy with the moderate inhibitor and for 3 half-lives afterwards. • After the washout of the inhibitor is complete, the study treatment dose can be re-escalated.
Strong CYP3A inducers: phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort Moderate CYP3A inducers: bosentan, efavirenz and modafinil	Strong or moderate CYP3A inducers should not be taken with study treatment. If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib. If a patient requires use of a strong or moderate CYP3A inducer then they must be monitored carefully for any change in efficacy of study treatment.

Table 10 Restricted concomitant medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
• CYP3A4 substrates: hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine • CYP2B6 substrates: bupropion, efavirenz • OATP 1 B1 substrates: bosentan, glibenclamide, repaglinide, statins and valsartan • OCT1, MATE1 and MATE2K substrates: metformin • OCT2 substrates: serum creatinine • OAT3 substrates: furosemide, methotrexate	Effect of olaparib on other drugs Based on limited in vitro data, olaparib may increase the exposure to substrates of CYP3A4, OATPIB1, OCT1, OCT2, OAT3, MATE1 and MATE2K. Based on limited in vitro data, olaparib may reduce the exposure to substrates of 2B6. Caution should be observed if substrates of these isoenzymes or transporter proteins are co-administered.
Anticoagulant therapy	Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalised ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low molecular weight heparin are permitted.
Administration of other anti-cancer agents	Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or denosumab.

5.6.3 Anti-emetics/Anti-diarrheals

Should a patient develop nausea, vomiting and/or diarrhea, then these symptoms should be reported as AEs (see Section 6.4.9) and appropriate treatment given.

5.6.4 Live virus and bacterial vaccines

Live virus and bacterial vaccines should not be administered whilst the patient is receiving study treatment and during the 30-day follow-up period. An increased risk of infection by the

administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

5.7 Treatment compliance

The administration of all study drugs during the 1-year treatment phase of the study should be recorded in the appropriate sections of the eCRF.

Patients should be given clear instructions on how and when to take their study treatment. Patients will self-administer study treatment. Study site staff should do a tablet count at regular intervals during treatment. Compliance will be assessed by the tablet count and the information should be recorded in the appropriate section of the eCRF. The number of tablets returned is to be noted in the return column of the Oral Drug Accountability Record (DARF) then destroyed per the institution's standard operating procedures. All patients must return their bottle(s) of study treatment at the appropriate scheduled visit, when a new bottle will be dispensed. Patients should be instructed to notify study site personnel of missed doses. Site staff will then complete the relevant eCRF pages to document the drug actually given.

Patients should return all containers and tablets at the next scheduled visit or at the End of Treatment visit.

5.7.1 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the patient.

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all olaparib/placebo received from the PMB according to good clinical practices and NCI guidelines using the NCI Investigational Agent Accountability Record for Oral Agents available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. Refer to the NCI Investigator's Handbook for procedures for Drug Accountability and Storage http://ctep.cancer.gov/investigatorResources/docs/InvestigatorHandbook.pdf). Certificates of delivery, destruction and return should be signed and retained. Any discrepancies must be accounted for on the appropriate forms.

A separate Oral NCI Investigational Agent Accountability Record must be maintained for patient ID number (e.g., E999999) and tablet strength (e.g., 100 mg, 150 mg) on this protocol. The combination Julian Date – Order Number, located in the in the upper right hand corner of the bottle label, should be recorded in the lot number field on the Oral DARF.

5.8 Discontinuation of study treatment

Patients may be discontinued from the study treatment in the following situations:

- Patient decision. The patient is free at any time to discontinue study treatment, without prejudice to further clinical care
- Adverse Event

- Completion of 12 months treatment period
- Confirmed pregnancy during treatment
- Severe non-compliance with study protocol
- Loco-regional breast cancer recurrence (ipsilateral invasive breast cancer recurrence, regional invasive breast cancer recurrence)
- Distant breast cancer recurrence
- Contralateral invasive breast cancer or second primary non-breast invasive cancer
- Death
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML)

5.8.1 Procedures for discontinuation of a patient from study treatment

A patient that decides to discontinue study treatment should always be asked about the reason(s) and the presence of any adverse events. If possible, he/she will be seen and assessed by an investigator(s). Adverse events will be followed up (See Sections 6.4.9 and 6.4.10); questionnaires and all study drugs should be returned by the patient.

If a patient is withdrawn from study, see Section 5.9.

If patients discontinue study treatment early, the NRG Oncology SDMC must be informed immediately.

Any patient discontinuing study treatment prior to completing 52 weeks should attend the treatment discontinuation visit, if possible. Thereafter the patient should be seen at 30 days post discontinuation for the evaluations outlined in the study schedule.

After premature discontinuation of study treatment, the principal investigator/sub-investigator will continue to provide appropriate clinical care and, as far as possible, follow the study visit schedule. Only the visits where efficacy assessments are scheduled should be performed i.e., week 12, 24, 38, and 52 (as applicable) in Year 1 and all visits in Year 2 onwards. Only the following assessments should be done: recurrent/new cancers assessment, mammogram and/or breast MRI, and Quality of Life questionnaires.

Collection of vital signs, AEs, haematology/clinical chemistry results and concomitant medications is no longer required. Information on endocrine therapies should be collected and recorded in the clinical database until IDFS endpoint is met due to breast cancer related distant relapse. The date of discontinuation, the reasons, and details of these specific cancer therapies (first line treatment for first breast cancer recurrence and any subsequent regimens containing PARP inhibitors or platinum received by the patient at any time) should also be recorded on the eCRF.

Samples should be collected at disease recurrence per protocol: blood biomarker samples (mandatory) and tumour sample (optional). If a recurrent/new cancer assessment is scheduled

within 4 weeks of the study treatment discontinuation visit, it can be performed at 30-day follow-up visit.

Patients who meet the IDFS endpoint while on study therapy should attend the treatment discontinuation visit and follow-up visit 30 days after the last dose of study treatment. See Section 3 for guidelines on subsequent study visits, which are dependent on which IDFS endpoint has been met.

After discontinuation of study treatment at any points in the study, all ongoing AEs or SAEs must be followed until resolution unless, in the investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow-up (see Sections 6.4.9 and 6.4.10). All new AEs and SAEs occurring during the 30 calendar days after the last dose of study medication must be reported (if SAEs, they must be reported as described in Section 6.4.10) and followed to resolution as above. Patients should be seen at least 30 days after discontinuing study medication to collect and/or complete AE information.

5.9 Withdrawal from study

Patients are at any time free to withdraw from the study (study treatment and assessments), without prejudice to further clinical care (withdrawal of consent). Such patients should always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (See Sections 6.4.9 and 6.4.10); questionnaires (e.g. for patient reported outcomes) and all study drugs should be returned by the patient.

Withdrawn patients will not be replaced.

Reasons for withdrawal from the study:

- Voluntary withdrawal by the patient who is at any time free to discontinue their participation in the study, without prejudice to further treatment*
- Incorrectly enrolled patients i.e., the patient does not meet the required inclusion/exclusion criteria for the study – this option is only applicable to patients not randomised into the study (i.e. screen failures identified prior to randomisation)
- Patient lost to follow-up
- Death

*If a patient decides at any point in the trial that they do not wish to continue with the full study schedule of assessments but are still willing to provide important study information (e.g. disease recurrence information and/or survival status information) then the patient should continue in the study and information should continue to be collected in the eCRF. However, if a patient does not wish to have any further data collected, only then should they be considered as withdrawing consent from the study. To minimise the number of cases of early withdrawal the investigator should discuss the options with the patient to see if they would still be willing to provide

information on the important study endpoints (disease recurrence and overall survival), in which case they would remain in the study.

If a patient withdraws consent (i.e. nor further assessment or collection of their data), he/she should be specifically asked if they are also withdrawing consent to the use of any of their samples (tumour and blood) taken during the trial (see Sections 6.6, 6.7 and 6.8).

Data obtained prior to withdrawal of consent will be maintained in the clinical database and used in the study reporting.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

6.1.1 Instructions for completion of B-55/6-13 forms and materials

Data form worksheets are available on the CTSU Member Web site, https://www.ctsu.org. A generic transmittal form can be created through the "Study Management" link located in Coordinator Online on the Members' Area of the NSABP Web site. Contact the Support Desk at support@nrgoncology.org for an account to access the NSABP Web site.

6.1.2 Instructions for submission of B-55/6-13 data, forms, and materials

- B-55/6-13 will use Medidata Rave for remote data capture of all data including routine adverse event reporting. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided. Query generation and resolution for B-55/6-13 are part of the Rave program. All queries will be issued and responded to electronically within Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam>) and the appropriate Rave role (Rave CRA, Rave Read-Only, CRA [Lab Admin], SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

  Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

  Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU

website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU Members' website under the Rave tab at https://www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement.

The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

- Exceptions to submission of data through Medidata Rave are the signed and dated informed consent form, the BAHO questionnaire, and required source documents which should be faxed to the NRG Oncology SDMC according to the instructions on the form worksheet. When submission of supporting documentation to the NRG Oncology SDMC is required, fax to 412-622-2111. Remove patient names and identifiers such as social security number, address, telephone number, etc. from reports and supporting documentation. Do not include a cover sheet for faxed data.

6.1.3 Data monitoring for CTEP

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. CTEP has assigned abbreviated CDUS reporting: no AE reporting (routine or expedited) is required via any of the CDUS mechanisms. Cumulative CDUS data will be submitted quarterly by the NRG Oncology SDMC to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

Note: B-55/6-13 has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS, but expedited adverse events are still required to be submitted via CTEP-AERS.

6.2 Study procedures

A schedule for the tests and evaluations to be conducted in this study is contained in this section and in Table 1, Table 2, and Table 3.

6.2.1 Screening procedures

The following assessments, procedures, and data collection should be performed during screening as per Figure 1 and Table 1.

- Provision of informed consent
- Assessment of eligibility against inclusion/exclusion criteria
- Date of birth
- Collect data on race and ethnicity
- Current and concomitant medications including previous cancer therapies

- Medical and surgical history including previous cancer and radiotherapy and history of blood transfusions in previous 120 days
- Family history of cancer
- Physical examination
- Vital signs (blood pressure and pulse; body temperature), body weight, height
- ECG (within 28 days prior to randomisation)
- Haematology/Clinical chemistry/Coagulation (see Section 6.4.11.2)/Urinalysis
- ECOG Performance Status
- If a patient with conservative surgery does not have a mammogram or breast MRI within 12 months prior to Screening PART 1, then this assessment must be performed prior to randomisation. Breast imaging should be performed on any remaining intact breast. Radiological tests to exclude a second primary breast cancer (either ipsilateral and/or contralateral) are mandatory before enrolment (within 12 months prior to Screening PART 1) for patients with any remaining intact breast tissue. The preferred tests are mammograms or MRI (MRI preferred for patients below 50 years of age). For patients who underwent a bilateral mastectomy, with no remaining breast tissue, a physical examination is sufficient and radiological tests are not mandatory. For patients who underwent a bilateral mastectomy, as well as for male patients, clinical exam may be supplemented by ultrasound exams at investigator's discretion.
- Pregnancy tests on serum or urine samples will be performed for women of childbearing potential within 28 days prior to randomisation and on Day 1 of the study prior to commencing treatment.
- CPS+EG score (Clinical stage (CS), estrogen receptor status (E), nuclear grade (G), and post-treatment pathologic stage (PS)) for the non-pCR patients who received prior neoadjuvant chemotherapy (Mittendorf et al 2011; Jeruss et al 2008). Instructions on how to calculate the CPS&EG score are provided in Appendix H.
- Patient Reported Outcomes and Quality of life questionnaire: FACIT-Fatigue and EORTC QLQ-C30 will be collected prior to randomisation once eligibility is confirmed.
- Germline *BRCA1/2* mutation status determination
    - All patients must have a known deleterious or suspected deleterious germline *BRCA* mutation to be randomised; this may have been determined by local genetic testing prior to enrolment into the study or may be assessed as part of the enrolment procedure for the study which requires a central laboratory test at Myriad Genetics, Inc.

- Two blood samples are mandated for all patients, one sample will be used to test for *BRCA* mutations using the current commercial Myriad BRCAnalysis test, and the second sample is required for a bridging study to validate the companion diagnostic test for olaparib.

- Patients with unknown *BRCA* status must have a central test performed by Myriad prior to randomisation into the study. Patients will need to have met the locally agreed guidelines for *BRCA* testing with genetic counselling arranged as appropriate. When the result from the Myriad test indicates the patient does have a deleterious or suspected deleterious *BRCA* mutation, and the patient meets all other eligibility criteria, the patient can be randomised into the study. Specimen collection and results disclosure to the potential subject will be conducted using local ethical procedures.

- It is recommended that, where required, the Myriad g*BRCA* test is undertaken during adjuvant or neoadjuvant chemotherapy to allow time for necessary counselling and for the return and discussion of the test result.

- Patients with known deleterious or suspected deleterious *BRCA* mutation/s prior to enrolment into the study can be randomised into the study based on this local result provided they meet all other eligibility criteria. The specific *BRCA1/2* mutation must be reported in the clinical database by selecting the appropriate value from the drop down menu. At screening, reconfirmation of the *BRCA* mutation from a blood sample will be undertaken by a central laboratory (Myriad Genetics, Inc.). Should the result from the central Myriad test indicate that the patient does not have a deleterious or suspected deleterious *BRCA* mutation, this information will be available to the study investigator and the decision as to whether or not the patient continues study treatment should be made between the patient and study investigator.

- If the discordance is based on the absence of the alteration identified in the local laboratory by the central laboratory, then analysis of a second specimen, collected independently from the patient and sent to Myriad Genetics, Inc. for re-analysis of the presence or absence of the mutation specified in the original test or otherwise as discussed with Myriad laboratory staff, may be performed under the protocol, to eliminate sample mislabelling and similar errors. These errors are expected to be uncommon. If the discordance is based on interpretation of the pathogenicity of an alteration identified by both laboratories (i.e., Myriad classifies the alteration as neither deleterious nor suspected deleterious), a repeat test will not be indicated. The OlympiA trial Genetic Advisory Committee can be consulted if needed.

See Section 6.6.2 for g*BRCA* Myriad samples collection.

- Adverse events must be captured from time of main consent. Any medical condition (new or worsening of a pre-existing condition) that occurs post Screening PART 2 and is continuing at randomisation should be recorded in Medical History in the eCRF as a medical condition current at randomisation. If the condition worsens post randomisation, this should be recorded as an AE/SAE in the eCRF with start date as the date the grade worsened and the new grade should be reported on the AE form. The AE/SAE would be

considered to have resolved when it resolves to the baseline grade, not to zero. Any medical condition considered of clinical relevance (new or worsening of a pre-existing condition) that occurs post consent for PART 2 and resolves prior to randomisation should also be recorded as medical history. In Screening PART 1 of the study only SAEs related to study mandated procedures (i.e., blood draw) will be collected. In Screening Part 2 all SAEs will be collected. For the patients who experienced an SAE in either Screening PART 1 or PART 2 that were eventually randomised, the SAE should be reported in the eCRF retrospectively in addition to paper reporting as described in Section 6.4.9 and Section 6.4.10.

- Check availability of an archival paraffin embedded tumour tissue sample (see Section 6.6.3). (The sample will only be submitted to the study bio-repository once the patient has been randomised.)

- Check availability of an archival paraffin embedded post neoadjuvant tumour tissue sample (see Section 6.6.4). (The sample is required from neoadjuvant patients only and will only be sent to the study bio-repository once the patient has been randomised.)

The Principal Investigator/Sub-Investigator should adhere to the study plan, procedures and perform tests/observations in accordance with the protocol.

6.2.2 On-treatment assessments

Patients will attend the clinic on day 1 (1st day of treatment) and, following the commencement of 300 mg b.i.d twice daily dosing, every 2 weeks during the first month, every 4 weeks for the following 5 months and 3 monthly for the remaining 6 months of study treatment plus 30 days after its discontinuation.

The following assessments will be performed at time points specified in the study schedule (see Section 3.1, Table 1 and Table 2):

- Physical examination (data need not be entered in the eCRF, however any clinically significant changes from baseline must be reported as an AE or an event) – e.g. any signs of recurrence of disease should be reported

- ECOG performance status: if assessed within 7 days of randomisation, it should not be assessed again at day 1 of study treatment

- Vital signs (blood pressure and pulse rate, body temperature, body weight): if assessed within 7 days of randomisation, are not required to be assessed again at day 1 of 1st day of study treatment

- Haematology and clinical chemistry: Safety blood samples do not need to be repeated on Day 1 of study treatment if there have been separate assessments within 7 days before randomisation and at least 3 weeks after last dose of chemotherapy, unless the investigator believes that it is likely to have changed significantly

- Race and ethnicity unless collection of this data is not allowed by local regulation
- Pregnancy tests on serum or urine samples will be performed for women of childbearing potential. If the test is positive the patient is ineligible/must be discontinued from study treatment immediately.
- AE and concomitant medications (including any blood transfusions) at every visit
- Patient Reported Outcomes and Quality of life questionnaire: FACIT-Fatigue and EORTC QLQ-C30 will be collected at 6 months, 12 months, 18 months and 24 months
- An optional pharmacogenetic sample will be obtained from consenting patients and stored for future exploratory pharmacogenetic analysis (Section 6.7.1). The blood sample will preferably be taken after randomization on day 1 of study treatment. If this is not possible, it should be obtained at a later visit.
- Optional pharmacokinetic samples will be obtained from consenting patients on day 29 (see Section 6.8). PK sampling not being done in the US.
- Optional tumour biopsy at disease recurrence (Section 6.6.5)
- Mandatory blood sample for biomarker analysis (e.g. cfDNA) on day 1 prior to first dose of study treatment, 30 days post study treatment and disease recurrence (Section 6.6.6)
- Radiological tests to exclude a second primary breast cancer (ipsilateral and/or contralateral) are mandatory during study participation (starting at week 24 and yearly thereafter) for patients with any remaining intact breast tissue. The preferred tests are mammogram or MRI (MRI preferred for patients below 50 years of age). For patients who underwent a bilateral mastectomy, with no remaining breast tissue, a physical examination is sufficient and radiological tests are not mandatory. For patients who underwent a bilateral mastectomy, as well as for male patients, clinical exam may be supplemented by ultrasound exams at investigator's discretion.
- Dispensing of and return of unused study treatment

Within this study, patients will not be provided olaparib post discontinuation of study treatment. Patients and investigators will not be unblinded to study treatment prior to the final overall survival (OS) analysis.

6.2.3 Efficacy follow-up assessments

Assessments for disease recurrence, new cancers and overall survival will be performed based on signs and symptoms, clinical assessment (i.e. physical exam), mammograms and/or breast MRI and vital status.

Following randomisation, during the first 2 years patients will be assessed for disease recurrence and new cancers every 3 months. During years 3, 4 and 5 patients will be assessed every

6 months and then annually until approximately 10 years from randomisation if an IDFS endpoint due to a distant breast cancer relapse has not been met.

Mammograms and/or MRI (MRI preferred for patients younger than 50 years) (ipsilateral and/or contralateral) will be performed annually in patients with retained breast tissue beginning 6 months after the first day of treatment for approximately 10 years if an IDFS endpoint due to a distant breast cancer relapse has not been met.

Once a patient has received clinical follow-up for efficacy for approximately 10 years, or an IDFS endpoint due to a distant breast cancer relapse has been met, the patient will then enter the annual survival follow-up phase of the study. During the survival follow-up phase, no clinic visits will be required; information may be collected via telephone, medical records or death registries. Vital status information, as well as other information specified in footnote g of Table 2, will be collected until 10 years after the last patient is randomised.

In addition to disease status and vital status, information on first line treatment for first breast cancer recurrence and any subsequent regimens containing PARP inhibitors or platinum received by the patient at any time, including those received during the survival follow-up phase, will be collected. Information on endocrine therapies should be collected and recorded in the eCRF until IDFS endpoint is met due to breast cancer related distant relapse. The therapy type and start and stop dates of therapy will be collected.

6.2.4 Safety follow-up assessments 30 days after last dose of olaparib/placebo

A follow-up visit should be conducted 30 days after the last dose of olaparib/placebo. Any serious and/or non-serious AEs ongoing at the time of discontinuation of study treatment or which have occurred during the defined 30-day follow-up period must be followed-up (in accordance with Section 6.4.9). Appropriate safety evaluations should be repeated and/or additional tests performed at any time when clinically indicated, or at the discretion of the investigator, until resolution, unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. If the patient is lost to follow-up, then this should be noted in the eCRF. The assessments to be carried out at the 30-day follow up visit are detailed in the study schedule (Table 2).

See Section 6.4.9 for details of long term safety collection.

6.2.5 Patient management post-primary analysis

The data cut off (DCO) for the primary analysis for IDFS will occur once 330 IDFS events have been reported. Once this data is fully validated the primary analysis will be conducted and reported.

At the time of the DCO for the primary analysis patients will continue in the study as per the protocol following the outlined study plan assessments. Patients who have completed treatment and all relevant safety assessments will continue to have regular efficacy assessments as detailed in the study plan. All ongoing patients will continue to be followed for recurrence, new cancers and overall survival irrespective of treatment status.

It is anticipated that further analysis of the efficacy data, particularly the secondary endpoints, will be conducted with more mature follow up. Any further available safety data will also be reported.

6.2.6 Patient management post-final analysis

Study follow up will continue until approximately 10 years after the last patient is randomised. After this time no further data collection is anticipated.

Patient management post the final analysis will be according to local clinical practice. All patients will have completed study treatment by the time of the final analysis.

6.3 Efficacy

6.3.1 Tumour evaluation

All treatment decisions and analysis for this study will be based on investigator evaluation of assessments. Following randomisation, all patients will be assessed regularly for signs, symptoms and evidence of disease recurrence by reviewing medical history, performing physical examination and mammogram and/or breast MRI (MRI preferred for patients younger than 50 years). See Table 2 and Table 3. Efficacy assessments (medical history and physical examination) will be performed on a 3 monthly basis during the first 2 years, followed by 6 monthly assessments for years 3, 4 and 5 and annually thereafter. All patients will have mammogram and/or breast MRI (ipsilateral and/or contralateral) annually for approximately 10 years beginning 6 months after day 1. Evidence of disease recurrence or new primary cancer will require histopathological and/or radiological confirmation.

Patients will be regularly assessed, through clinical visits, for recurrence (local and distant) and new cancers for approximate 10 years follow-up regardless of whether they have discontinued study treatment or started any subsequent anti-cancer therapies. Following completion of approximately 10 years' clinical follow-up assessments, patients will enter a survival follow-up phase, which will continue until 10 years after the last patient is randomised. During the survival contact period information on any known subsequent sites of metastases, new cancers and further subsequent therapies (information on first line treatment for first breast cancer recurrence and any subsequent regimens containing PARP inhibitors or platinum received by the patient at any time) will be captured as well as vital status. Study visits are not required during the survival follow-up phases; contact may be made via telephone, medical records or death registries once per year.

Loco-regional recurrence of the disease (ipsilateral or regional invasive breast cancer) should be cytologically/histologically confirmed. Imaging to assess for distant metastatic disease or any other area as clinically indicated should be performed at the time of local recurrence to ensure that any further spread of the disease is detected. Isolated loco-regional recurrence should be managed with curative intent when possible. Suspected distant recurrence should be confirmed by radiological examination and every attempt made to obtain histopathological confirmation when a metastatic lesion is easily accessible for biopsy. Invasive contralateral breast cancer or invasive non-breast secondary primary cancer should be confirmed by histopathology.

Patients who develop loco-regional recurrence should discontinue study treatment (if within the study treatment period) but will continue to be followed for distant recurrence (including subsequent sites of metastases) and all new cancers (local, regional, second primary malignancy or contralateral breast cancer), subsequent therapies and survival as per study schedule. The first EVENT (local, regional or distant recurrence, second primary malignancy or contralateral breast cancer) should be recorded in the eCRF. The following additional information should also be recorded in the eCRF along with the results of the confirmatory tests.

- First distant relapse (if not the first EVENT);
- CNS metastases, that should always be reported regardless of any prior recurrences;
- Local regional relapses, occurring after the first event;
- Contralateral breast cancer, at any time;
- Any second primary malignancies, at any time.

Patients who develop distant recurrence should discontinue study treatment (if within the study treatment period) but will continue to be followed for development of additional sites of metastatic disease, new cancers, subsequent therapies and survival as per the survival follow-up schedule.

Disease recurrence or new cancers should be reported in the eCRF as soon as possible after they are discovered. This includes events diagnosed during study visits but also any event diagnosed during non-study visits.

Once known, death information should also be recorded in the eCRF as soon as possible.

6.4 Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

6.4.1 Investigational agents

The investigational agent administered in B-55/6-13 is olaparib, which is being made available under an IND sponsored by NRG Oncology, Inc. Expectedness of adverse events is based on the current IB.

6.4.2 Commercial agents

There are no commercial supply agents in B-55/6-13.

6.4.3 Double-blind study drug

This is a double-blind study and includes an investigational agent with placebo. When an AE occurs that is expected for the investigational agent, the AE should be considered expected for the blinded study therapy. Conversely, when an adverse event occurs that is not listed for the investigational agent, the AE should be considered to be unexpected for the blinded therapy.

6.4.4 Adverse event characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. CTCAE version 5.0 is being utilized for SAE reporting as of April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0 and the CTCAE version 5.0. A copy of the CTCAE version 4.0 and CTCAE version 5.0 can be downloaded from the CTEP Web site (http://ctep.cancer.gov).

6.4.5 Definition of adverse events (AE)

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, electrocardiogram).

The term AE is used to include both serious and non-serious AEs.

6.4.6 Definitions of serious adverse event (SAE)

A serious adverse event is an AE occurring during any study phase (i.e. from the time a patient signs a study specific consent form, treatment, and follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of an SAE, see Appendix A to the Clinical Study Protocol.

6.4.7 Common adverse events associated with olaparib

Following is a list of common AEs associated with olaparib. Refer to the current IB for complete toxicity information.

- *Blood and Lymphatic System Disorders* – Anemia
- *Gastrointestinal Disorders* – Abdominal pain; Bloating; Diarrhea; Dyspepsia; Mucositis oral; Nausea; Vomiting
- *General Disorders and Administration Site Conditions* – Edema limbs; Fatigue, Fever
- *Immune System Disorders* – Allergic reaction

- *Investigations* – Creatinine increased; Investigation – Other, mean corpuscular volume; Lymphocyte count decreased; Platelet count decreased
- *Metabolism and Nutrition Disorders* – Anorexia
- *Neoplasms benign, malignant and unspecified (incl cysts and polyps* - Leukemia secondary to oncology chemotherapy; Myelodysplastic syndrome; Treatment related secondary malignancy
- *Nervous System Disorders* – Dizziness; Dysgeusia; Headache
- *Respiratory, Thoracic, and Mediastinal Disorders* – Cough; Dyspnea; Pneumonitis
- *Skin and Subcutaneous Tissue Disorders* – Dermatitis; Rash maculo-papular

6.4.8 Expedited reporting of adverse events

NRG Oncology follows procedures for centralized reporting of adverse events, which requires that adverse events/serious adverse events be reported to the NRG Oncology SDMC. NRG Oncology forwards reports to the appropriate regulatory agencies and the pharmaceutical company involved in the trial.

All serious adverse events that meet expedited reporting criteria defined in Table 11 will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers. NRG Oncology is identified in CTEP-AERS as the Lead Group for CTEP-AERS reporting.

Submitting a report via CTEP-AERS serves as notification to the NRG Oncology Statistics and Data Management Center (SDMC) and satisfies NRG Oncology requirements for expedited adverse event reporting.

In the rare event when Internet connectivity is disrupted, a 24-hour notification is to be made to the NRG Oncology SDMC by telephone at 412-383-2557. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

For questions concerning expedited AE reporting, contact the B-55/6-13 AE reporting nurse (see Information Resources).

6.4.8.1 Expedited reporting methods

- Per CTEP NCI Guidelines for Adverse Events Reporting Requirements, a **CTEP-AERS 24-Hour Notification** must be submitted to the NCI **within 24 hours** of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a CTEP-AERS 3 Calendar Day Report (see Table 11).
- **CTEP-AERS 3 Calendar Day Report** requires that a complete report is electronically submitted to the NRG Oncology Lead Group **within 3 calendar days** of submission of the CTEP-AERS 24-hour notification (see Table 11).
- **CTEP-AERS 5 Calendar Day Report** requires that a complete report is electronically submitted to the NRG Oncology Lead Group **within 5 calendar days** of learning of the AE (see Table 11).
- Reports submitted via CTEP-AERS 24-hour notification are available for review by both the NCI and NRG Oncology after submission. **All other CTEP-AERS reports are first sent to the NRG Oncology Lead Group and then are forwarded to the NCI.** The timelines in

Table 11 have been set so that the information can be forwarded to the NCI in a timely manner per the NCI's/CTEP's guidelines.

- **Supporting documentation** is requested by the IND sponsor for this study (NRG Oncology) as needed to complete adverse event review. **All CTEP-AERS documentation is faxed to NRG Oncology SDMC at 412-622-2113.** When submitting supporting source documentation, remove all identifiers and include the protocol number, patient ID number, and CTEP-AERS ticket number on each page.

6.4.8.2 Protocol-specific expedited reporting requirements

Protocol-specific expedited reporting requirements: For this study, the following adverse events require expedited reporting via CTEP-AERS to the NRG Oncology Lead Group **within 5 calendar days** (or sooner if required based on other Table 11 instructions) of learning of the event:

Expedited reporting via CTEP-AERS is required for the following from the first dose of study therapy until the end of the patient's follow-up irrespective of the timing of the event in relation to study therapy):

- ***Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])***
- ***Myelodysplastic syndrome (MDS)***
- ***Second primary malignancy***
- Pneumonitis

Supporting documentation, including pathology and cytogenetics reports which confirm the second malignancy, must be faxed to the NRG Oncology SDMC expedited fax at 412-622-2113. Each page of supporting documentation must include the NCI protocol number, the CTEP-AERS ticket number, and the protocol-specific Patient ID number provided during trial registration.

Any second malignancy (including AML/MDS) should also be reported within the B-55/6-13 Follow-up folder in Medidata Rave. Fax supporting documentation that confirms the secondary malignancy diagnosis with the transmittal form to 412-622-2111.

Table 11 Late Phase 2 and Phase 3 Studies: Expedited reporting requirements for adverse events that occur on studies under an IND within 30 days of the last administration of the investigational agent (olaparib/placebo)[1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NRG Oncology) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect
6) Important Medical Events (IME) that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI and NRG Oncology via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	5 Calendar Days			24-Hour, 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		5 Calendar Days	

NOTE: ***See Section 6.4.8.2 for protocol-specific expedited reporting requirements and exceptions.***

Expedited AE reporting timelines are defined as**:**

- "24-Hour, 3 Calendar Days" – The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report submitted to the NRG Oncology Lead Group within 3 calendar days of the initial 24-hour report.
- "5 Calendar Days" – A complete expedited report on the AE must be submitted within 5 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report with 3 calendar days for:

- All Grade 4 and Grade 5 AEs

Expedited 5 calendar days reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

Effective Date: May 5, 2011

6.4.9 Recording of adverse events

Time period for collection of adverse events

Adverse events will be collected from time of signature of main informed consent* throughout the treatment period up to and including the 30-day follow-up period (see Section 6.2.4). All ongoing and any new AEs/SAEs identified during the 30 calendar day follow-up period after the last dose of study medication must be followed to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up or in survival follow-up. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary. Any medical condition (new or worsening of a pre-existing condition) that occurs post Screening PART 2 and is continuing at randomisation should be recorded in medical history in the eCRF as a medical condition current at randomisation. If the condition worsens post randomisation, this should be recorded as an AE/SAE in the eCRF with start date as the date the grade worsened and the new grade should be reported on the AE form. The AE/SAE would be considered to have resolved when it resolves to the baseline grade, not to zero. Any medical condition considered of clinical relevance (new or worsening of a pre-existing condition) that occurs post consent for PART 2 and resolves prior to randomisation should also be recorded as medical history. Any AE happening from randomisation to the 30-day follow-up period should be reported on the AE form in the eCRF. If an Investigator learns of any SAEs, including death, at any time after a patient has completed the 30 days post treatment follow-up period, and he/she considers there is a reasonable possibility that the event is causally related to the study treatment, the investigator should report the SAE via CTEP-AERS (see Sections 6.4.9 and 6.4.10 and Table 11).

Any case of MDS/AML or new second primary malignancy occurring at any time from signature of informed consent for the entire participation of the patient in the study including the follow-up period should be reported as a SAE via CTEP-AERS, regardless of the investigator's assessment of causality, knowledge of the treatment arm, and irrespective of the timing of the event in relation to study therapy. All non-melanoma invasive skin cancers and all carcinoma in situ cases need to be reported as a non-serious AE unless at least one of the seriousness criteria is met and then it must be reported as an SAE (see Section 6.4.6). If a patient develops MDS/AML, full diagnostic details and classification should be provided e.g. bone marrow and cytogenetic analysis reports, see Sections 5.5.12.4 and 6.4.11.5. A questionnaire will be sent to any investigator reporting MDS/AML or new primary malignancy so that relevant details can be reported.

*In Screening PART 1 of the study only SAEs related to study mandated procedures (i.e. blood draw) will be collected. In Screening PART 2 all SAEs will be collected (see Table 1). For the patients who experienced an SAE in either Screening PART 1 or PART 2 that were eventually randomised, the SAE should be reported in the eCRF retrospectively in addition to reporting the SAE via CTEP-AERS as described in Sections 6.4.9 and 6.4.10 and Table 11)

Adverse events after the 30-day follow up period

For pharmacovigilance purposes and characterisation, any SAE of MDS/AML, new second primary malignancy (with the exception of non-melanoma skin cancers and carcinoma in situ), or pneumonitis occurring after the 30-day follow up period should be reported as a SAE via CTEP-AERS regardless of investigator's assessment of causality, knowledge of the treatment arm, and irrespective of the timing of the event in relation to study therapy (see Section 6.4.8.2).

At any time after a patient has completed the study, if an investigator learns of any SAE including sudden death of unknown cause, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the SAE should be reported via CTEP-AERS.

Otherwise, after study treatment completion (i.e. after any scheduled post treatment follow-up period has ended) there is no obligation to actively report information on new AEs or SAEs occurring in study patients. This includes new AEs/SAEs in patients still being followed up for survival but who have completed the post treatment follow up period (30 days).

Follow-up of unresolved adverse events

Any SAEs or non-serious adverse event that is still ongoing during the 30-day follow-up visit must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up. AstraZeneca may request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if necessary.

Reporting routine adverse events through Medidata Rave

- Reporting of routine adverse events is done through Medidata Rave.
- **All ≥ grade 1 adverse events** that occurred during study therapy must be reported on the B-55/6-13 Adverse Event forms (the Listed Adverse Event form or the Other Adverse Event form) through Medidata Rave, regardless of whether these adverse events are expected or unexpected.
- All adverse events reported via CTEP-AERS must also be reported on the B-55/6-13 Adverse Event forms through Medidata Rave.
- Supporting documentation for each AE reported on either of the B-55/6-13 Adverse Event forms through Medidata Rave must be maintained in the patient's research record. When submission of supporting documentation to the NRG Oncology SDMC is required, fax with a transmittal form to 412-622-2111. Remove patient names and identifiers such as social security number, address, telephone number, etc., from reports and supporting documentation.

Variables

The following variables will be collected for each AE;

- AE description (verbatim)
- The dates when the AE started and stopped

- CTCAE grade and changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the study treatment (yes or no)
- Action taken with regard to study treatment
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date that the AE met criteria for serious AE
- Date Investigator became aware of serious AE
- Reason for AE being considered serious
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study treatment or procedure(s)
- Causality assessment in relation to Other medication
- Description of AE.

Severity of AE

For each episode of an adverse event, all changes to the CTCAE grade attained as well as the highest attained CTC grade should be reported.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.6. An AE of severe intensity should not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

The grading scales found in the National Cancer Institute (NCI) CTCAE version 4.0 will be utilised for all events with an assigned CTCAE grading. For those events which do not fall under any of the CTCAE defined categories, the investigator should assess them as mild, moderate severe, or life-threatening, or, if the patient dies, as an event leading to the patient's death.

A copy of the CTCAE version 4.0 can be downloaded from the NCI Cancer Therapy Evaluation Program website http://ctep.cancer.gov/.

Causality collection

The Investigator will assess causal relationship between study treatment and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the study treatment?'

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix A to the Clinical Study Protocol.

Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the eCRF and submitted. When collecting AEs, the recording of diagnoses is preferred (when possible) rather than recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse events based on examinations and tests

The reporting of laboratory/vital signs/ECG abnormality as an AE should be avoided unless one of the following is met:

- Any criterion for an SAE is fulfilled
- Causes study treatment discontinuation
- Causes study treatment interruption
- Causes study treatment dose reduction
- The investigator believes that the abnormality should be reported as an AE

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported and submitted as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g. anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported and submitted as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease recurrence, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported and submitted as an AE.

NB. Cases where a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs, please refer to Appendix D 'Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law', for further instructions.

Disease recurrence

The development of loco-regional recurrence or distant metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease recurrence, should not be reported as an AE during the study.

Report breast cancer recurrence within the B-55/6-13 Follow-up folder in Medidata Rave. Fax supporting documentation that confirms the breast cancer recurrence with the transmittal form to 412-622-2111.

New primary cancers (second malignancy)

The development of a new primary cancer (second malignancy) should be reported as a SAE. New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease recurrence. New primary cancers are considered as IDFS events and must also be reported on the endpoint CRF. Patients with new primary cancers that can be adequately treated with surgery only and which do not require any additional (neo)adjuvant treatment of any kind can continue to receive investigational product and be followed for secondary endpoints. Rules regarding temporary interruption due to surgery apply (see Section 5.5.12.7). Patients with new primary cancers which require (neo)adjuvant treatment of any kind for appropriate management must be discontinued from study treatment.

Deaths

All deaths that occur during the study (see Section 6.4.9) must be reported as follows:

- Death that is clearly the result of breast cancer recurrence or progression should be reported in the DEATH eCRF but should not be reported as an SAE
- Where death that occur within 30 days of the last dose of study treatment is not due (or not clearly due) to breast cancer recurrence or progression of the disease under study, the cause of death must be reported via CTEP-AERS as a SAE within 24 hours (see Section 6.4.10 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information should be captured in the relevant eCRF.

- Deaths with an unknown cause that occur within 30 days of the last dose of study treatment must be reported via CTEP-AERS. A post mortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to the NRG Oncology SDMC within the usual timeframes.

- A copy of the death certificate should be forwarded to the NRG Oncology SDMC if it is readily available or if it contains important cause-of-death information that is not documented elsewhere.

- Please submit the last clinical/office note made before the death or the investigator's note summarizing events resulting in death.

Olaparib adverse events of special interest

Adverse events of special interest (AESI) are events of scientific and medical interest specific to the further understanding of olaparib's safety profile and require close monitoring and reported via CTEP-AERS. Adverse Events of Special Interest for olaparib are MDS/AML, new second primary malignancy (other than MDS/AML) and pneumonitis.

A questionnaire will be sent to any investigator reporting an AESI as an aid to provide further detailed information on the event. During the study there may be other events identified as AESIs that require the use of a questionnaire to help characterise the event and gain a better understanding regarding the relationship between the event and study treatment.

6.4.10 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the study treatment or to the study procedure(s). All SAEs will be reported via CTEP-AERS and Medidata Rave (see Section 6.4.8, Section 6.4.9, and Table 11).

The NRG Oncology site AE reporter works with the investigator to ensure that all the necessary information is provided **within one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

If CTEP-AERS is not available, refer to Section 6.4.8 for reporting instructions.

6.4.11 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the times indicated in the Study Schedule (see Table 1 and Table 2).

These tests will be performed by the hospital’s local laboratory. Additional analyses may be performed if clinically indicated.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF.

The following laboratory variables will be measured:

6.4.11.1 Full haematology assessments for safety

- haemoglobin
- red blood cells [RBC]
- platelets
- mean cell volume [MCV]
- mean cell haemoglobin concentration [MCHC]
- mean cell haemoglobin [MCH]
- white blood cells [WBC]
- absolute differential white cell count
    - (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and absolute neutrophil count or segmented neutrophil count and Band forms should be performed at each visit and when clinically indicated. If absolute differentials not available please provide % differentials

6.4.11.2 Coagulation

- activated partial thromboplastin time (APTT) will be performed at baseline and if clinically indicated
- international normalised ratio (INR) will be performed at baseline and if clinically indicated unless the patient is receiving warfarin. Patients taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable

6.4.11.3 Clinical chemistry assessments for safety

- sodium
- potassium
- calcium
- creatinine
- total bilirubin
- alkaline phosphatase [ALP]

- aspartate transaminase [AST]
- alanine transaminase [ALT]
- urea or blood urea nitrogen [BUN]
- total protein
- albumin

NB. If a patient has AST **or** ALT ≥ 3xULN **or** total bilirubin ≥ 2xULN please refer to Appendix D 'Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law', for further instructions.

For blood volume see Section 7.1.

6.4.11.4 Urinalysis

Urinalysis by dipstick should be performed at baseline and then only if clinically indicated. Microscopic analysis should be performed by the hospital's local laboratory if required.

6.4.11.5 Bone marrow or blood cytogenetic samples

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged haematological toxicities as defined in Section 5.5.12.4.

Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. Full reports must be provided by the investigator for documentation on the Patient Safety database.

6.4.12 Physical examination

For timing of individual measurement refer to study schedule (Table 1, Table 2, and Table 3). A physical examination will be performed according to site's local practice.

Clinical signs and symptoms of disease recurrence should be further investigated as appropriate (please refer to Section 6.3).

6.4.13 ECG

6.4.13.1 Resting 12-lead ECG

ECGs are required during screening within 28 days prior to randomisation.

Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes. The investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs.

ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the investigator will record it as an AE on the eCRF. The original ECG traces must be stored in the patient medical record as source data.

6.4.14 Vital signs

Height will be assessed at screening only.

Weight will be assessed at screening and as clinically indicated at any other time.

Any changes in vital signs should be recorded as an AE, if applicable.

The date of collection and measurement will be recorded on the appropriate eCRF.

6.4.14.1 Pulse and blood pressure

Blood pressure and pulse rate will be measured preferably using a semi-automatic BP recording device with an appropriate cuff size. For timings of assessments refer to the Study Schedule (see Table 1 and Table 2).

The date of collection and measurement will be recorded on the appropriate eCRF.

6.4.14.2 Body temperature

Body temperature will be measured in degrees Celsius at the times indicated in the Study Schedule (see Table 1 and Table 2).

The date of collection and measurement will be recorded on the appropriate eCRF.

6.4.15 Other safety assessments

6.4.15.1 Serum or urine pregnancy test

Pregnancy tests on serum or urine samples will be performed for women of childbearing potential within 28 days prior to randomisation (Table 1), on Day 1 of the study prior to commencing treatment, at the time points shown in Table 2 during study treatment and at the 30 day follow up visit. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued from study treatment immediately. Details of the pregnancy tests must be recorded in the patient's medical records.

6.5 Patient reported outcomes (PRO)

6.5.1 FACIT-Fatigue

The Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F Scale) is a 13-item questionnaire that assesses patient self-reported fatigue and its impact upon daily activities and function (Yellen et al 1997). Response options for each item range from 0 (Not at all) to 4 (Very much), where higher scores indicate greater patient-reported fatigue. The FACIT-F scale was originally developed to evaluate fatigue associated with anaemia in cancer patients and has been used as an endpoint in clinical trials in various cancer populations including breast cancer

and non-small cell lung cancer. Content validity of the FACIT-F has been demonstrated in a large sample of mixed cancer patients (n>300). Reliability (internal consistency, test-retest reliability, criterion validity, and responsiveness/sensitivity to change) of the FACT-F has also been documented (Yellen et al 1997).

6.5.2 EORTC QLQ-C30

In this study patient-reported disease related symptoms and health-related quality of life (HRQoL) will be evaluated using the validated EORTC QLQ-C30 questionnaire (Aaronson et al 1993). The EORTC QLQ-C30 questionnaire was developed to assess HRQoL and is the most commonly used cancer-specific tool in oncology. It has undergone extensive testing and validation as well as detailed cross-cultural testing and validation and has been used in breast cancer trials.

The EORTC QLQ-C30 comprises 30 questions designed for all cancer types. Questions can be grouped into the following subscales:

- 5 multi-item functional scales (physical, role, emotional, cognitive and social functioning)
- A 2-item global health status scale
- Symptom scales/items
  - 3 multi-item symptom scales (fatigue, pain, nausea vomiting)
  - Dyspnoea
  - Insomnia
  - Appetite loss
  - Constipation
  - Diarrhoea
  - Financial difficulties

6.5.3 Administration of PRO questionnaires

FACIT-Fatigue and EORTC QLQ-C30 questionnaires will be collected at baseline (within screening period after eligibility confirmed but prior to randomisation) and then 6 months, (24 weeks), 12 months (52 weeks), 18 months and 24 months following randomisation.

Questionnaires shall be administered to a patient by delegated site personnel (e.g., a research nurse, study coordinator) adequately trained and listed on Site's Delegation Log. Site shall assign a trained back-up person to cover if that individual is absent. The significance and relevance of the data need to be explained carefully to participating patients so that they are motivated to comply with data collection.

The instructions for completion of the PRO questionnaires are as follows:

- They must be completed at the clinical visit prior to any other study procedures (following informed consent) and before discussion of disease progress to avoid biasing the patient's responses to the questions. They must be completed in private by the patient

- The patient should be given sufficient time to complete at their own speed

- The patient should not receive help from relatives, friends or clinic staff to answer the questionnaire. However, if the patient is unable to read the questionnaires (e.g., is blind or illiterate) the questionnaires may be read out by trained clinic staff and responses recorded

- On completion of the questionnaires they should be handed back to the person responsible for questionnaires who should check for completeness

- Only one answer should be recorded for each question.

Completed questionnaires must be faxed to the NRG Oncology SDMC (see Information Resources).

After the baseline, questionnaires are to be administered at follow-up visits, so that when a follow-up visit is delayed, completion of the questionnaire may also be delayed. Patients who experience disease recurrence or diagnosis of a second primary cancer will not be expected to continue with the PRO assessments. Patients who discontinue study drug for other reasons will be expected to continue the PRO assessments per protocol schedule if they have not indicated study withdrawal. Patients who never initiate study medication should not continue to complete PRO assessments. If a patient declines to complete a scheduled PRO assessment or if the questionnaire is not completed for any other reason (and cannot be completed by phone or mail), a Quality of Life Missing Data form should be submitted by the institution instead.

6.5.4 Reimbursement

All sites will receive reimbursement for the PRO study from funding provided by AstraZeneca. Cancer Control credits will not be available.

6.6 Biomarkers

Tumour and blood samples will be collected for mandated and optional biomarker work as detailed in the B-55/6-13 Pathology and Correlative Science Instructions.

For blood volume see Section 7.1

6.6.1 Biomarker samples

The archival diagnostic tumour sample is mandated* and the screening blood samples for *BRCA* mutation status are mandated.

Table 12 Samples for Biomarker Research

Sample Type	Visits	Optional or Mandatory
Whole blood sample for prospective germline *BRCA* testing at central laboratory for patients with unknown *BRCA* status and for confirmation of *BRCA* status for those with previous results	Screening	Mandatory
Whole blood sample for assessment of current and future *BRCA* mutation assay(s)	Screening	Mandatory
Archival tumour sample Surgical tumour samples for adjuvant patients	Screening	Mandatory* for all randomised patients
Pre-treatment diagnostic core biopsy for neoadjuvant patients	Screening	Required* for all randomised patients
Surgical tumour sample post neoadjuvant chemotherapy	Screening	Required* for all randomised neoadjuvant patients
On-study disease recurrence tumour biopsy	At disease recurrence	Optional
Blood samples (plasma and serum) for biomarker analysis	Day 1 prior to first dose of study treatment, 30 days post study treatment discontinuation, disease recurrence	Mandatory
Blood for optional exploratory pharmacogenetics	Day 1 or at a later visit	Optional

*For adjuvant patients, this refers to the surgical specimen; for neoadjuvant patients, both the pre-treatment core biopsy and the surgical specimen with residual disease are requested but only one is mandatory. If the surgery tumour blocks are available, but cannot be submitted, sites may submit a portion of invasive tumour from the original block, either by taking at least one core of at least 3 mm in diameter, or by splitting the original block in two parts, and re-embedding one in a new block for central submission. If blocks containing pre-neoadjuvant treatment core biopsies are available but cannot be submitted, sections mounted on glass slides prepared from the block can be provided. If tumour sample can't be provided as requested above or if it's not available, approval by Study Team for patient's entry into the trial is required.

The tumour and blood samples collected in this study will be used for studies specified in the B-55/6-13 protocol and for studies to be conducted in the future related to the purposes of the B-55/6-13 study and not currently described in the protocol document.

Detailed protocols for the genomics work described in this protocol will be developed as separate protocols to include analytical and statistical methodologies and will be submitted for review and approval of these methodologies in accordance with the National Clinical Trials Network. Studies conducted in the future related to the purposes of the B-55/6-13 study and not currently

described in the protocol document will be submitted for review and approval in accordance with the National Clinical Trials Network.

The samples and data from this research will be coded and not identified with any personal details. Each sample will be identified with the B-55/6-13 Patient ID number. In this way biomarker data may be correlated with clinical data, samples destroyed in the event of withdrawal of consent and regulatory audit enabled. However, only the investigator will be able to link the biomarker sample to the individual patient. Research biomarker data may be generated in real time during the study or retrospectively and will have unknown clinical significance. The study investigative team will not provide research biomarker results to patients, their family members, any insurance company, an employer, clinical study investigator, general physician or any other third party unless required to do so by law. The patient's samples will not be used for any purpose other than those described in the protocol.

The *gBRCA* status result from the Myriad assessment for patients with unknown *BRCA* status will be provided to the investigator and will be collected as part of the patient's demography and medical history details.

6.6.2 Collection of blood sample for Myriad germline *BRCA1* and *BRCA2* testing

Two blood samples are mandated for all patients. One sample will be used to test for *BRCA* mutations using the current commercial Myriad BRCAnalysis test. This result will confirm or determine patient eligibility. The second sample is required for a bridging study to validate the companion diagnostic test for olaparib (see Section 6.6.2.1 below).

All patients must have a known deleterious or suspected deleterious germline *BRCA* mutation to be randomised; this may have been determined by local genetic testing prior to study entry or may be assessed as part of the enrolment procedure for the study (via a central testing by Myriad), see Section 6.2.1. The specific g*BRCA* alteration on which eligibility is based must be entered into the trial database by selecting the appropriate value from the drop down menu. If the central laboratory analysis does not confirm a local g*BRCA* determination, that information should also be entered in the eCRF, along with indication of whether or not the patient was enrolled into the trial.

Residual blood (or its derivatives) may be used to evaluate future BRCA companion diagnostic tests and for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, and improve the understanding of disease recurrence (including BRCA mutation status and its role in response).

For blood volume see Section 7.1.

6.6.2.1 Collection of a blood sample for assessment of current and future *BRCA* mutation assay(s)

At the time that the sample is collected for shipment to Myriad for central testing, all patients will be required to provide a second mandatory 9 ml blood sample that will be stored for subsequent assessment of current and future *BRCA* mutation assay(s).

Samples may also be used to investigate future *BRCA* mutation assays as well as mutations in other genes known/predicted to have a role in breast cancer.

Please refer to the B-55/6-13 Pathology and Correlative Science Instructions for further details of archival tumour collection, shipping and storage.

6.6.3 Exploratory Biomarker Research on Archival Tumour Samples (Mandatory*)

These samples will be collected from the site pathologist during the screening period. Collection of archival samples is mandated* for all randomised patients for the assessment of tissue *BRCA* mutation status, however further exploratory work is planned on surplus tissue. This material may be used for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, and improve the understanding of disease recurrence (including tumour *BRCA* mutation status and its role in response).

Retrospective testing of ER, PgR and HER2 status shall be performed at a central laboratory. The results of such tests shall be used for exploratory purposes in the context of the trial and shall not be routinely reported back to the site.

Please refer to the B-55/6-13 Pathology and Correlative Science Instructions for further details of archival tumour collection, shipping and storage.

*For adjuvant patients, this refers to the surgical specimen; for neoadjuvant patients, both the pre-treatment core biopsy and the surgical specimen with residual disease are requested but only one is mandatory. If the surgery tumour blocks are available, but cannot be submitted, sites may submit a portion of invasive tumour from the original block, either by taking at least one core of at least 3 mm in diameter, or by splitting the original block in two parts, and re-embedding one in a new block for central submission. If blocks containing pre-neoadjuvant treatment core biopsies are available but cannot be submitted, sections mounted on glass slides prepared from the block can be provided. If tumour sample can't be provided as requested above or if it's not available, approval by Study Team for patient's entry into the trial is required.

6.6.4 Exploratory Biomarker Research on Post Neoadjuvant Tumour Samples (Mandatory* for neoadjuvant patients only)

These samples will be collected from the site pathologist following neoadjuvant therapy. A formalin fixed paraffin embedded tissue block which is truly representative of the area of the tumour should be provided.

This material may be used for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, and improve the understanding of disease recurrence (including tumour *BRCA* mutation status and its role in response).

Please refer to the B-55/6-13 Pathology and Correlative Science Instructions for further details of post neoadjuvant tumour collection, shipping and storage.

*For adjuvant patients, this refers to the surgical specimen; for neoadjuvant patients, both the pre-treatment core biopsy and the surgical specimen with residual disease are requested but only

one is mandatory. If the surgery tumour blocks are available, but cannot be submitted, sites may submit a portion of invasive tumour from the original block, either by taking at least one core of at least 3 mm in diameter, or by splitting the original block in two parts, and re-embedding one in a new block for central submission. If blocks containing pre-neoadjuvant treatment core biopsies are available but cannot be submitted, sections mounted on glass slides prepared from the block can be provided. If tumour sample can't be provided as requested above or if it's not available, approval by Study Team for patient's entry into the trial is required.

6.6.5 Exploratory Biomarker Research on Disease Recurrence Tumour Biopsy Samples (Optional)

When a patient presents with a recurrent tumour suitable for biopsy (recurrent lesion may be either in the breast or axilla (loco-regional recurrence) or elsewhere in the body distant metastases), a tumour biopsy sample should be obtained, only in patients who have agreed to the optional tumour biopsy in the consent form). Tumour tissue collected during the study should be immediately frozen, and if collection of a frozen sample is not possible, biopsy samples should be immediately fixed and processed to a FFPE block. If a whole block can't be provided, sections mounted on glass slides prepared from the block can be provided instead.

Please refer to the B-55/6-13 Pathology and Correlative Science Instructions for further details of on-study tumour tissue collection, shipping, and storage.

6.6.6 Exploratory Blood samples for biomarker analysis (e.g. cfDNA) (Mandated)

All consenting patients will be required to provide blood samples on day 1 prior to the first dose of study treatment, 30 day safety follow-up and disease recurrence for exploratory biomarker research.

Patients will be required to provide:

- 1 x 6 ml blood sample for preparation of serum on day 1 prior to the first dose of study treatment, 30 days post study treatment and at disease recurrence.

- 1 x 6 ml blood sample for preparation of plasma on day 1 prior to the first dose of study treatment, 30 days post study treatment and at disease recurrence.

Please refer to the B-55/6-13 Pathology and Correlative Science Instructions for further details of sample collection and shipping.

6.7 Pharmacogenetics

6.7.1 Collection of pharmacogenetic samples

An optional pharmacogenetic sample (9 mL) will be obtained from consenting patients and stored for future exploratory pharmacogenetic analysis. The blood sample will preferably be taken after randomisation on day 1 of treatment. If this is not possible, it should be obtained at a later visit. Patients do not have to consent to this sample in order to participate in the study.

Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn on Day 1, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Please refer to the B-55/6-13 Pathology and Correlative Science Instructions for further details of blood sample collection and shipping.

For blood volume see Section 7.1.

6.8 Pharmacokinetics (Optional)

PK sampling will not be done in the US.

PK sampling (optional) is to be performed in a subset of patients. Each patient participating in this component of the study will be asked to provide 5 blood samples, one from each of the pre-defined time windows below, preferably on visit 4, day 29. Nevertheless, the samples can also be taken at a later treatment visit, provided that PK consent was obtained beforehand.

- Pre-dose (before morning dose)
- Between 0 and 0.5 hours post-dose
- Between > 0.5 and 1.5 hours post-dose
- Between 3 and 6 hours post-dose
- Between > 6 and 12 hours post dose (before evening dose)

6.8.1 Pharmacokinetic samples (Subset of patients)

Approximately 150 patients randomised to olaparib/placebo, at pre-agreed sites will have PK assessment samples taken. PK sampling will not be done in the US.

6.8.2 Collection of samples

PK samples are to be taken as a blood sample (2 mL) for determination of olaparib concentrations in plasma. It is essential that PK blood sampling is conducted within the protocol sample collection windows indicated above.

To ensure that the assessments are carried out in the correct order, and that PK sampling is conducted within the required sampling window, it will be necessary to arrange the assessment procedures so that the PK assessments fall on/around the correct timing (see Section 6.8). The actual time of dosing and collection of all PK samples must be recorded as described below:

It is essential that the time of all 5 PK samples is recorded and that the times of the morning and evening dose on the day of PK sampling and the time of dose the evening before is recorded.

For blood volume see Section 7.1.

6.8.3 Determination of drug concentration

Samples for determination of olaparib concentrations in plasma will be analysed by Covance on behalf of Clinical Bioanalysis Alliance, AstraZeneca R&D, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report. Placebo samples will not be analyzed unless specified.

6.9 Health economics

6.9.1 Resource use (serious adverse events)

Resource use for serious adverse events (including hospitalisations) will be captured through the adverse reporting procedures described in Section 6.4.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The volume of blood that will be drawn from each patient will vary, dependent upon the length of time that the patient remains in the trial and if the patient is in the subset having PK samples taken. However, the total volume of blood to be drawn from each patient in the study (including for PK samples), assuming they complete screening, 12 months of treatment, a treatment discontinuation visit and the 30-day follow-up visit, should not exceed 208 mL.

Safety laboratory assessments will be performed locally at each centre's laboratory by means of their established methods. The number of samples/blood volumes is therefore subject to site-specific change.

Extra blood samples may also be collected if, for example, additional samples are required for repeat safety assessments or *BRCA* testing.

The total volume of blood that will be drawn from each patient in this study is as follows:

Table 13 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	5	13	65
	Haematology	5	13	65
	Coagulation	5	1	5
Whole blood sample for Myriad *BRCA* test (retrospective/prospective)		9	1	9
Whole blood sample for assessment of current and future *BRCA* mutation assay(s)		9	1	9
Pharmacogenetics (optional)		9	1	9

Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
Serum Pregnancy test	Site dependent	Site may use urine instead	
Serum sample for exploratory biomarkers, day 1 (mandatory)	6	1	6
Plasma sample for exploratory biomarkers, day 1 (Mandatory)	6	1	6
Serum sample for exploratory biomarkers, 30 days post study treatment discontinuation (Mandatory)	6	1	6
Plasma sample for exploratory biomarkers, 30 days post study treatment discontinuation (Mandatory)	6	1	6
Plasma sample for exploratory biomarkers, disease recurrence (Mandatory)	6	1	6
Serum sample for exploratory biomarkers, disease recurrence (Mandatory)	6	1	6
Pharmacokinetic (Blood samples processed to plasma & frozen) (Optional)	2	5	10
Total			208

7.2 Handling, storage and destruction of biological samples

The samples may be used up, disposed of after analyses or retained for further use as described here.

Biological samples for future research will be retained at the study bio-repository for a maximum of 15 year*s* following the Last Patient's Last Visit in the study. The results from future analysis will not be reported in the Clinical Study Report but separately in a Scientific Report.

Biosamples collected for this study will be stored in study specific bio-repositories that are under the guardianship of BIG (non-US samples) and NRG Oncology and NCI (US samples) on behalf of the study Steering Committee.

7.2.1 Pharmacogenetic samples

The processes adopted for ensuring confidentiality of samples for genetic analysis are important. Samples will be stored for a maximum of 15 years, from the date of the Last Patient's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample

and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analysed.

7.2.2 Pharmacokinetic samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses will be reported separately from the Clinical Study Report (CSR).

Sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report. Anonymised samples will be retained for no longer than 12 months after the Bioanalytical Report is finalised.

7.3 Labeling and shipment of biohazard samples

The Principal Investigator should ensure that samples are labelled and shipped in accordance with the B-55/6-13 Pathology and Correlative Science Instructions and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix B 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials should not be shipped and no further samples will be taken from the patient unless agreed with AstraZeneca/NRG Oncology/BIG or partners and appropriate labelling, shipment and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre is responsible for ensuring full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate).

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca/NRG Oncology/BIG and their Partners keep oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Biosamples collected for this study will be stored in study specific bio-repositories that are under the guardianship of BIG (non-US samples) and NRG Oncology and NCI (US samples) on behalf of the study Steering Committee.

Samples retained for further use are registered in the bio-repositories systems during the entire sample life cycle.

If required, the remaining biological samples are returned to the site, according to local regulations or at the end of the retention period, whichever is the sooner.

7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca/NRG Oncology/BIG and their Partners are not obliged to destroy the results of this research.

BRCA sample: As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

Archival tumour sample: Although mandatory*, the patient may continue in the study if the patient is already randomised.

*For adjuvant patients, this refers to the surgical specimen; for neoadjuvant patients, both the pre-treatment core biopsy and the surgical specimen with residual disease are requested but only one is mandatory. If the surgery tumour blocks are available, but cannot be submitted, sites may submit a portion of invasive tumour from the original block, either by taking at least one core of at least 3 mm in diameter, or by splitting the original block in two parts, and re-embedding one in a new block for central submission. If blocks containing pre-neoadjuvant treatment core biopsies are available but cannot be submitted, sections mounted on glass slides prepared from the block can be provided. If tumour sample can't be provided as requested above or if it's not available, approval by Study Team for patient's entry into the trial is required.

Tumour samples at relapse: As collection of the biological samples is an optional part of the study, then the patient may continue in the study.

Pharmacokinetic samples: As collection of the pharmacokinetic samples is an optional part of the study, then the patient may continue in the study.

Blood samples for biomarker analysis (e.g. cfDNA): Collection of the biological samples is a mandatory part of the study, however, the patient may continue in the study despite withdrawing consent for analysis of the biomarker samples.

Blood sample for pharmacogenetic analysis: As collection of the biological samples is an optional part of the study, then the patient may continue in the study.

The Principal Investigator/site staff:

- Should ensure that NRG SDMC is notified immediately of a patients' withdrawal of informed consent for the use of donated samples
- Should ensure that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Should ensure that the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Should ensure that the patient and study representative are informed about the sample disposal.

The study representative ensures that the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, a study medical representative or an investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

The exception to the above is the result of the Myriad g*BRCA* test. This will be made available to the Investigator and patient.

8.3 Ethics and regulatory review

An IRB must approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable IRB, and to the study site staff.

The opinion of the IRB should be given in writing. The investigator should submit the written approval to the CTSU before enrolment of any patient into the study.

The IRB should approve all advertising used to recruit patients for the study.

AstraZeneca/BIG/Partners (and NRG Oncology/CTEP for US centres) should approve major modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form must be approved by a local IRB or the NCI Central Institutional Review Board (CIRB), according to local regulations.

NRG Oncology will handle the distribution of these documents to the national regulatory authorities.

AstraZeneca/BIG/Partners will provide Regulatory Authorities, IRBs/Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), outside the United States, where relevant. NRG Oncology will determine distribution of safety updates/reports as appropriate, in the United States.

Each Principal Investigator is responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product according to local requirements. If applicable, AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

8.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided

- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study

- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File

- Ensure a copy of the signed Informed Consent Form is given to the patient

- Ensure that any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an IRB.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator, National Co-ordinating Investigator, and the Principal Investigator and AstraZeneca/BIG/NRG Oncology/Partners and the study Steering Committee.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

Any protocol amendment must be approved by the relevant IRB and if applicable, should obtain the national regulatory authority approval, before implementation. Local requirements are to be followed for amended protocols.

NRG Oncology will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to IRBs see Section 8.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca/BIG/Partners, NRG Oncology/CTEP for US centres, and the centre's IRB are to approve the revised Informed Consent Form before the revised form is used.

If required by local regulations, any administrative changes will be communicated to or approved by each IRB.

8.6 Audits and inspections

Authorised representatives of NRG Oncology may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator/site staff should contact the Protocol Officer immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT

9.1 Pre-study activities

Qualification visits are not performed by NRG Oncology. NRG Oncology Member Institutions must determine that the sites are appropriate for the study. NRG Oncology distributes the approved protocol to its member institutions which are in good standing. Those sites which are confident that they have significant investigator interest and available patients proceed by seeking local (or central) Institutional Review Board approval. Upon receipt of the approval, a database of site IRB approvals is maintained through the NCI CTSU. Patient entry cannot proceed unless an up-to-date IRB approval is in this database.

9.2 Training of study site personnel

The Principal Investigator should ensure that appropriate training relevant to the study is given to all site staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.3 Monitoring of the study

The study will be monitored by site audit visits, submission of copies of source documents for centralized review, and communication with the investigator and appropriate staff by NRG Oncology to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the B-55/6-13 Pathology and Correlative Science Instructions and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification that the appropriate version of the consent form was used and that it was signed and dated prior to any study procedures. This will require direct access to all original records for each patient (e.g. clinic charts)
- If relevant, ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The investigator will provide direct access to source data/documents for audits, IRB review, and regulatory inspections. NRG Oncology will be available between visits if the investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.4 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The study is expected to start in Q1 2014 and to end by 2028.

The study will end approximately 10 years following the randomisation of the last patient. Patients will be followed up until 10 years after the randomisation of the last patient.

The study may be prematurely terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely upon recommendations of the study IDMC if concerns for safety arise within this study or in any other study with olaparib.

10. DATA MANAGEMENT

Data management will be performed by the NRG Oncology SDMC.

The data collected through third party sources will be obtained and reconciled against study data by Frontier Science.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. Coding will be done by Frontier Science.

Additional details of data management procedures can be found in the Data Management Plan for the Study. This document will be continuously updated through the life of the study.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also document the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

The results from genetic research may be reported in the CSR for the main study, or in a separate report as appropriate. Refer to Appendix C.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of efficacy variable(s)

11.1.1 Primary endpoint

The primary endpoint of the trial is invasive disease free survival (IDFS), defined as the time from randomisation to date of first recurrence, where recurrence is defined as loco-regional, distant recurrence, new cancer or death from any cause. IDFS is further detailed according to the standardised STEEP system definition (Hudis et al 2007) as one of the following:

- Ipsilateral invasive breast tumour recurrence (IIBTR): Invasive breast cancer involving the same breast parenchyma as the original primary.
- Regional invasive breast cancer recurrence: Invasive breast cancer in the axilla, regional lymph nodes, chest wall, and skin of the ipsilateral breast.
- Distant recurrence: Metastatic disease-breast cancer that has either been biopsy confirmed or radiologically diagnosed as recurrent invasive breast cancer.
- Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause.
- Contralateral invasive breast cancer.
- Second primary non-breast invasive malignancies (i.e., excluding new in situ carcinomas of any site). Second primary non-breast invasive malignancies include hematologic malignancies and MDS. Squamous or basal cell skin cancers will not be counted as primary endpoint events.

Loco-regional recurrence of the disease (ipsilateral or regional invasive breast cancer) should be cytologically/histologically confirmed. Appropriate imaging (CT, MRI bone and/or PET scan) of the chest/abdomen/pelvis or any other area as clinically indicated should be performed at the time of local recurrence to exclude further spread of the disease. Distant recurrence should be diagnosed by radiological examination and/or histopathological confirmation when metastatic lesion is easily accessible for biopsy.

For confirmed local recurrence events, the earliest date of diagnosis based on an objective finding (physical exam, radiological/imaging assessment, cytological/histopathological assessment) will be used to determine the time to event for the analysis but not the date of the first symptoms or blood analysis abnormality. For example if a physical exam results in 'suspected' disease recurrence and disease recurrence is then confirmed by cytology/histology then the date of the physical exam will be used to derive the time to event.

For confirmed distant recurrence the date of the earliest radiological/imaging examination or cytological/histopathological assessment linked to the diagnosis will be used to determine the time to event for the analysis (i.e. physical exam will not be considered within the derivation of time to distant recurrence nor will be symptoms or blood analysis).

Invasive contralateral breast cancer or invasive non-breast secondary primary cancer should be confirmed by histopathological report. The date of the earliest objective finding related to diagnosis of the new cancer will be used as the date of new cancer for the analysis.

If two recurrence events (local and distant) are reported within 2 months of each other then this is referred to as a simultaneous event and will be considered as a single event. In this situation the worst case will be taken as the event 'type' but the date of recurrence will be the earliest date of the two events. For example if local and distant recurrence are reported within a 2 month period then for the analysis and reporting of IDFS the event type will be distant recurrence but the date of recurrence will be the earliest date of the two events.

If two recurrence events are reported but more than 2 months has elapsed between the events then the events will be regarded as two separate recurrence events and the earliest event and corresponding date of event will be used in the derivation of IDFS (i.e. IDFS is based on the first recurrence event).

If a patient dies during the study with no documented disease recurrence or invasive contralateral breast cancer or invasive non-breast secondary primary cancer then death will be regarded as an event and the date of death will be used to determine the patients IDFS time.

Patients who have not had a recorded IDFS event at the time of the analysis will be censored at the date of their last disease evaluation. Disease evaluation includes mammogram and/or breast MRI (MRI preferred for patients younger than 50 years), other radiological/imaging examination or clinical examination (e.g. physical exam).

11.1.2 Secondary endpoints

11.1.2.1 Overall Survival

Overall survival is defined as the time from the date of randomisation until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

11.1.2.2 Distant disease free survival (DDFS)

DDFS will be defined as the time from randomisation until documented evidence of first distant recurrence of breast cancer. Distant recurrence will include the following events:

- Distant recurrence: Metastatic disease-breast cancer that has either been biopsy confirmed or radiologically diagnosed as recurrent invasive breast cancer.
- Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause.
- Second primary non-breast invasive cancer.

Evidence of distant recurrence should be provided by either radiological examination or preferably by histopathological examination when metastasis is easily accessible for biopsy.

Second primary non-breast invasive cancer should be confirmed by histopathological report.

For the analysis of DDFS, the date of the confirmed DDFS event will use the earliest assessment date from the radiological and/or histological or cytological assessment. For example if a patient has distant recurrence suspected by radiological examination which is later confirmed by biopsy then the date of the radiological examination will be used as the date of event.

Patients who do not have documented evidence of DDFS at the time of the analysis of DDFS will be censored at the date of their last clinical examination (i.e. last physical exam or radiological evaluation).

The first site of distant recurrence will be recorded and used in the analysis. Information on subsequent sites of recurrence will also be collected during follow-up assessments to ensure as complete as possible information on distant recurrence is obtained.

11.1.2.3 Incidence of contralateral invasive breast cancer, contralateral non-invasive breast cancer, new primary ovarian cancer, new primary fallopian tube cancer and new primary peritoneal cancer

The incidence of contralateral invasive breast cancer, contralateral non-invasive breast cancer, new primary ovarian cancer, new primary fallopian tube cancer and new primary peritoneal cancer will each be considered separately and be defined as the number and percentage of patients with documented evidence of contralateral invasive breast cancer, contralateral non-invasive breast cancer, new primary ovarian cancer, new primary fallopian tube cancer and new primary peritoneal cancer regardless of when this occurs (i.e. does not need to be their first recurrence event).

All patients should be followed for evidence of new primary breast cancers and all other cancers. This includes patients with a first event of local or distant recurrence as they may go on to develop new cancers in the future. All new cancers will be collected for all patients not just the first new cancer.

Data analyses of new contralateral breast cancer (invasive and non-invasive) will exclude patients who have had bilateral mastectomy prior to randomisation.

Data analyses of new ovarian cancers will exclude patients who have had both ovaries removed prior to randomisation.

Data analyses of new fallopian tube cancers will exclude patients who have had both fallopian tubes removed prior to randomisation.

Data analyses of new peritoneal cancer will include all patients in the ITT populations.

11.2 Calculation or derivation of safety variable(s)

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data and vital signs. These will be collected for all patients. Appropriate summaries of these data will be presented as described in Section 12.

11.2.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

11.3 Calculation or derivation of patient reported outcome variables

Patient reported outcomes will be assessed based on the FACIT-Fatigue symptoms and the EORTC QLQ-C30 questionnaires. Further details are given in Section 12.2.3 and full details will be provided in the statistical analysis plan.

11.4 Calculation or derivation of pharmacokinetic variables

The pharmacokinetic (PK) analysis of the plasma concentration data for olaparib will be performed at AstraZeneca R&D or by a CRO identified by AstraZeneca R&D. The actual sampling times will be used in the PK calculations. For each patient providing a complete set of PK samples, non-linear mixed effects modelling (NONMEM) will be used to estimate steady state C_{max}, AUC and C_{min}.

11.5 Calculation or derivation of pharmacodynamic variable(s) - not applicable

11.6 Calculation or derivation of pharmacogenetic variables

Any data summaries that will be reported in the main clinical study report will be detailed within the statistical analysis plan. Additional exploratory analyses or data summaries that may be produced outside of the main study report will be defined in an exploratory analysis plan, if appropriate.

11.7 Calculation or derivation of health economic variables –not applicable

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

A comprehensive statistical analysis plan (SAP) will be prepared before first subject in (FSI).

Table 14 gives a summary of outcome variables and analysis populations.

12.1.1 Full analysis set

Intention to treat (ITT): The primary statistical analysis of the efficacy of olaparib will include all randomised patients and will compare the treatment groups on the basis of randomised

treatment, regardless of the treatment actually received. Patients who were randomised but did not subsequently go on to receive study treatment are included in the Full Analysis Set (FAS).

For the interim analysis two efficacy populations will be defined.

1. ITT population: This will include all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. Note: it is anticipated that all patients will be randomised by the time of the interim analysis.
2. Mature cohort ITT population: This will include the first 900 randomised patients only and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received.

12.1.2 Safety analysis set

All patients who received at least one dose of randomised study treatment, olaparib or placebo, will be included in the safety analysis set. If a patient receives at least one dose of olaparib he/she will be summarised in the olaparib arm for safety summaries (e.g. olaparib arm will include patients randomised to olaparib who receive at least one dose of olaparib or placebo patients who receive at least one dose of olaparib in error at any time). If a patient randomised to olaparib receives only placebo treatment then he/she will be summarised as part of the placebo arm.

Table 14 Summary of Outcome Variables and Analysis Populations

Outcome Variable	Populations
Efficacy Data - Interim	
IDFS	FAS (ITT), Mature cohort ITT
Other efficacy variables	FAS (ITT)
Efficacy data- Final	FAS (ITT)
IDFS, OS, DDFS, incidence of contralateral breast cancers, new primary ovarian, new primary fallopian tube cancers and new primary peritoneal cancer and symptom/HRQoL endpoints	
Demography	FAS (ITT)
Pharmacokinetics data	PK
Safety Data	
Exposure	Safety
Adverse Events	Safety
Lab measurements	Safety
Vital Signs	Safety

12.1.3 PK Analysis set

PK data will be analysed according to treatment received. This population will comprise all randomised to olaparib patients who receive at least one dose of study treatment and have at least one PK sample collected.

12.2 Methods of statistical analysis

12.2.1 Analysis of primary endpoint

12.2.1.1 Primary analysis

The primary analysis of IDFS will occur when a minimum of 330 IDFS events have been observed (to provide at least 90% power to detect a hazard ratio of 0.7). Based on the event rate from the 10 November 2017 database, the number of IDFS events required to trigger the primary analysis is expected to be accrued by November 2020 (80% CI: March 2020 to September 2021). The maturity rate will be 18.3%, where maturity is defined as the number of events divided by the total number of randomised patients.

IDFS will be compared across two treatment arms using a log rank test stratified by the stratification factors at randomisation, and the corresponding p-value will be reported as the primary analysis result. In addition, IDFS will be analysed using a stratified Cox proportional hazard model stratified by the stratification factors at randomisation and using the Efron approach for handling ties. The point estimate of the treatment effect, i.e., the hazard ratio of IDFS (olaparib vs. placebo) will be obtained by maximizing the Cox partial likelihood function, which is the product of the partial likelihood of each stratum. The 95% confidence interval will be estimated using the profile likelihood approach.

A Kaplan-Meier plot of IDFS will be presented by treatment group. Summaries of the number and percentage of patients experiencing an IDFS event, and the type of event (recurrence or death) will be provided for each treatment.

The estimated 3 year IDFS will be summarised (using estimates from the KM curve) and presented by treatment group.

12.2.1.2 Sensitivity analysis

If applicable, an analysis will be performed for IDFS using the same model as described above but based on all randomised patients confirmed to have *gBRCA* mutations by the central test. This analysis is only required if the analysis population differs from the primary ITT population.

Any patients mis-stratified in the randomisation system (i.e. incorrect details are entered at the time of randomisation) will be included in the primary stratified log rank test and Cox proportional hazard model using the baseline data collected from the randomisation system (Registration and Randomisation System). If > 5% of randomised patients are incorrectly stratified (i.e., randomisation system data does not match baseline data), then a sensitivity analysis will be performed for IDFS based on the (correct) baseline data collected in the eCRF. If the results of ER and PgR status from the local and central labs differ in >5% of randomised

patients, a sensitivity analyses will also be performed based on ER and/or PgR positive/HER2 negative and TNBC subsets as defined by the central laboratory testing.

The assumption of proportionality will be assessed. Proportionality will be tested firstly by producing plots of complementary log-log (event times) versus log (time) and, if these raise concerns, a time dependent covariate would be fitted to assess the extent to which this represents random variation. Note that in the presence of non-proportionality, the HR will be interpreted as an average HR over the observed extent of follow-up.

As patients will be randomised, imbalances in demographic factors between the treatment groups are not anticipated. However if any imbalances should occur, these additional demographic variables may be fitted into the stratified Cox model. The HR and associated confidence interval would be presented.

12.2.1.3 Subgroup analysis

Subgroup analyses will be conducted to assess consistency of treatment effect across potential or expected prognostic factors, including the baseline stratification factors.

If there are too few results available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 5 events in either treatment group), the relationship between that subgroup and IDFS will not be formally analysed. In this case, only descriptive summaries will be provided.

The following subgroups are of primary interest:

- Hormone receptor status (ER and/or PgR positive and HER2 negative; TNBC)
- Neoadjuvant chemotherapy; adjuvant chemotherapy
- Prior platinum therapy for current breast cancer (Yes; No)
- BRCA mutation type (BRCA1; BRCA2; BRCA1/2 both)
- Hormone receptor status by prior chemotherapy setting (if there are sufficient events to split into the four groups)
  - ER and/or PgR positive with neoadjuvant chemotherapy
  - ER and/or PgR positive with adjuvant chemotherapy
  - ER and PgR negative with neoadjuvant chemotherapy
  - ER and PgR negative with adjuvant chemotherapy
- *BRCA* status by prior platinum therapy setting
  - *BRCA1* with prior platinum therapy for current breast cancer

- BRCA1 with no prior platinum therapy for current breast cancer
- BRCA2 with prior platinum therapy for current breast cancer
- BRCA2 with no prior platinum therapy for current breast cancer

The following additional subgroups will also be analysed to assess consistency in treatment effect across a broader set of baseline characteristics known before start of study medication:

- Type of prior Neo/Adjuvant chemotherapy (anthracycline; taxane; anthracycline plus taxane)
- Type of breast surgery prior to randomisation (breast conservation; unilateral mastectomy; bilateral mastectomy)
- Bilateral Oophorectomy (Yes; No)
- Axillary nodal status at surgery prior to randomisation (Positive or negative for the post adjuvant patients only)
- CPS+EG score baseline (2, 3 or 4; 5 or 6 for the post neoadjuvant group only)
- Age at randomisation (< 50; 50-64; ≥ 65)
- Race
- Sponsor (AZ; NRG Oncology)

Other baseline variables may also be assessed if there is clinical justification. These would be pre-defined within the SAP.

For each subgroup, the HRs (olaparib: placebo) and associated CIs will be calculated from a Cox proportional hazards model (using the Efron approach for handling ties) that contains the treatment term, factor and treatment-by-factor interaction term. The treatment effect HRs for each treatment comparison along with their confidence intervals will be obtained for each level of the subgroup from this single model. The HRs and 95% CIs will be presented on a forest plot including the HR and 95% CI from the overall population (using the primary analysis).

No adjustment to the significance level for testing subgroups will be made since all these subgroup analyses will be considered exploratory. The results would be used as supportive data for the primary analysis of IDFS based on all randomised patients.

12.2.1.4 Analysis of interaction

The presence of quantitative interactions will be assessed by means of an overall global interaction test. This will be performed in the overall population by comparing the fit of a Cox proportional hazards model including treatment, all covariates (including stratification factors), and all covariate-by-treatment interaction terms, with one that excludes the interaction terms and will be assessed at the 2-sided 10% significance level. If a covariate does not have more than 20

events per level (of the covariate) it will be included as a covariate in the model, but the covariate-by-treatment interaction term will be omitted. If the fit of the model is not significantly improved then it will be concluded that overall the treatment effect is consistent across the subgroups.

If the global interaction test is found to be statistically significant, an attempt to determine the cause and type of interaction will be made. Stepwise backwards selection will be performed on the saturated model, whereby (using a 10% level throughout) the least significant interaction terms are removed one-by-one and any newly significant interactions re-included until a final model is reached where all included interactions are significant and all excluded interactions are non-significant. Throughout this process all main effects will be included in the model regardless of whether the corresponding interaction term is still present. This approach will identify the factors that independently alter the treatment effect and prevent identification of multiple correlated interactions.

Any quantitative interactions identified using this procedure will then be tested to rule out any qualitative interaction using the approach of Gail and Simon 1985.

12.2.2 Analysis of secondary endpoints

OS and DDFS

OS and DDFS will be analysed at the time of the IDFS analysis as per the multiple testing procedure (MTP) outlined in Section 12.2.5 and will use the same methodology and model as described above for the primary analysis of IDFS.

If applicable, a sensitivity analysis will be performed for DDFS and OS using the same model as described above for IDFS but based on all randomised patients confirmed to have *gBRCA* mutations by the central test. This analysis is only required if the analysis population differs from the primary ITT population Subgroup analyses will also be conducted for DDFS and OS based on the same subgroups described above for IDFS.

DDFS and OS will be analysed at the time of the primary analysis for IDFS (when 330 IDFS events are reported).

The final OS analysis will be conducted once the trial follow up is complete (i.e. 10 years from when the last patient is randomised, estimated 14 years from first patient randomised assuming recruitment of 5 years).

In addition another analysis will be performed half way between the primary IDFS analysis and the final overall survival analysis (estimated around 10 years from first patient randomised but timings will be driven by the primary IDFS analysis once known). At this time point both DDFS and OS will be analysed and some alpha will be reserved for formal hypothesis testing. IDFS may also be updated if more information is available but this would be considered a supportive update of the primary analysis and no alpha will be reserved for IDFS.

For details on alpha spend and how this will be allocated across the planned analyses see Section 12.2.6.

Incidence of contralateral invasive breast cancer, contralateral non-invasive breast cancer, new primary ovarian cancer, new primary fallopian tube cancer and new primary peritoneal cancer

The actual number and percentage of patients with new contralateral breast cancers (invasive and non-invasive), new primary ovarian cancer, new primary fallopian tube cancer and new primary peritoneal cancers will be presented. In addition a table summarising all reported new cancers (i.e. not just breast, ovarian, fallopian tube or peritoneal cancers) will also be produced.

As described in Section 11.1.2.3, patients who have had a bilateral mastectomy prior to randomisation will be excluded from the analysis of new contralateral breast cancers (invasive and non-invasive) and patients who have had a bilateral oophorectomy prior to randomisation will be excluded from the analysis of new ovarian cancers and patients who have had their fallopian tubes removed prior to randomisation will be excluded from the analysis of new fallopian tube cancers.

The cumulative incidence of new primary contralateral invasive breast, new primary contralateral non-invasive breast, new primary ovarian cancers, new primary fallopian tube cancers and new primary peritoneal cancers will be compared between treatment groups using competing risk analysis (Gray test, Fine and Gray 1999). Death will be considered a competing risk for each endpoint. In addition, bilateral mastectomy after randomization will be a competing risk for the contralateral breast cancer analyses, bilateral oophorectomy will be a competing risk for the new primary ovarian cancers analysis and removal of the fallopian tubes will be a competing risk for the new primary fallopian tube cancer analysis. Hazard ratios and 95% confidence intervals from competing risks regression analyses (Fine and Gray 1999) adjusted for treatment and the stratification factors will also be presented – more details of these analyses are given in the SAP (Edition 2).

Safety

Safety data will be summarised descriptively in terms of AEs, vital signs, clinical chemistry & haematology and physical exam and will include data from the treatment and safety follow-up period. Cumulative incidence plots may also be presented for specific adverse events or groups events of interest. Further information on the summary of safety data will be provided in the SAP.

12.2.3 Analysis of patient reported outcomes

12.2.3.1 Hypotheses and objectives

The hypotheses and measurement strategy focus on the fact that patients in the trial will be starting with significant decrements in HRQoL and high rates of symptoms at study entry (baseline) due to previous chemotherapy and local treatments (surgery with or without radiation therapy). All analyses of Patient Reported Outcomes will be conducted on ITT population as listed in Table 14. Therefore, the following hypotheses are proposed, based on the expected toxicities of olaparib.

Primary hypothesis

Patients receiving olaparib may experience greater fatigue severity during treatment than those receiving placebo as measured by the FACIT-Fatigue scale at 6 and 12 months after randomisation.

Secondary hypotheses

- Patients receiving olaparib may experience greater GI symptoms (nausea, vomiting and diarrhea) severity during treatment than those receiving placebo as measured at 6 and 12 months after randomisation but no difference expected by 24 months after randomisation.

- There will be no difference in fatigue post discontinuation of study treatment as measured at 18 and 24 months.

- There will be no difference in QOL between the two treatment arms as measured by the global QOL score and other sub scales from the EORTC QLQ-C30 at 6, 12, 18 and 24 months after randomisation and patients will demonstrate improvements in functioning over time

Primary PRO objective

To determine the effect of olaparib on patient-reported fatigue at 6 and 12 months after randomisation as measured by the FACIT-Fatigue symptoms questionnaire.

Secondary PRO objectives

- To determine the effect of olaparib on patient-reported GI symptoms (nausea, vomiting and diarrhea) over time at 6, 12, 18 and 24 months as measured by the EORTC QLQ-C30 scale.

- To determine the effect of olaparib on patient reported fatigue over time at 6, 12, 18 and 24 months as measured by the FACIT-Fatigue questionnaire.

- To determine if there will be a difference in QOL between the two treatment groups over time as measured by the 2 item global QOL score of the EORTC QLQ-C30 scale at 6, 12, 18 and 24 months and assess if patients demonstrate improvement in scores over time.

- To examine and compare the effect of olaparib over time on different functional sub scale scores as measured by the EORTC QLQ-C30 and assess if patients demonstrate improvement in functioning over time, with particular interest in the physical and emotional sub scales.

12.2.3.2 Statistical considerations for patient reported outcomes

Statistical analyses

Primary endpoint – Fatigue

For the primary hypothesis, the composite fatigue score (FACIT-Fatigue questionnaire) measured at 6 and 12 months after randomisation will be compared between the two treatment arms using analysis of covariance (ANCOVA) with adjustment for the corresponding baseline measurement. Separate analyses will be done for patients who have received prior neoadjuvant chemotherapy and patients who have received standard post-surgical adjuvant chemotherapy. Separate analyses are preferable because the timing of chemotherapy is expected to impact the fatigue outcome directly. Each comparison will be performed at the significance level of 0.05. No multiple comparisons adjustment will be employed since these outcomes evaluate the toxicity of the study treatment.

To further assess the effect of olaparib on fatigue over time (study treatment period and the year following) the composite fatigue score (FACIT-Fatigue questionnaire) measured at 6, 12, 18 and 24 months after randomisation will be compared between the two treatment arms using a mixed model for repeated measures (MMRM) analysis of all of the post baseline scores. The model will include treatment, time and treatment by time interaction as explanatory variables and baseline score and baseline by time interaction as covariates. The treatment by visit interaction will remain in the model regardless of significance. The adjusted mean change from baseline estimates for each treatment arm, difference in the adjusted mean change from baseline estimates between the arms and corresponding confidence intervals will be presented by time point. Plots of the adjusted means changes over time will also be presented.

Secondary PRO endpoints

A secondary analysis based on GI symptoms (nausea, vomiting and diarrhea) over time from the EORTC QLQ-C30 scale will be performed using the same MMRM model described above. The adjusted mean change from baseline estimates for each treatment arm, difference in the adjusted mean change from baseline estimates between the arms and corresponding confidence intervals will be presented by visit. Plots of the adjusted means changes over time will also be presented for nausea, vomiting and diarrhea.

To assess if there are any difference in HRQoL, the 2 item global QOL score assessed by EORTC QLQ-30 measured at 6, 12, 18 and 24 months after randomisation will be compared between the two treatment arms using the same MMRM model described above. Plots over time will also be produced for the global QOL score.

In addition, other subscales of the EORTC QLQ-C30 will be analysed using the MMRM model described above with particular interest in the emotional and physical subscales. Plots over time will also be produced.

All secondary analyses are considered exploratory and therefore no adjustments for multiplicity will be made. For each comparison, p-values (along with CIs) will be generated to help aid interpretation of the results using a nominal significance level of 0.05 (2-sided).

Because this trial is being conducted internationally, responses to patient reported outcomes may be influenced by differences between country/language categories (Bernhard J et al 2007). Therefore, analyses will be stratified by country/language groups. Further details will be provided in the SAP.

Adjustment for previous treatment exposures (radiation, type of chemotherapy, and surgery) may also be considered as part of the secondary analyses. Further details will be given in the SAP.

Sample size consideration

We assume that half of triple negative patients and a quarter of hormone receptor positive patients will have received neoadjuvant chemotherapy and we anticipate that 95% of patients enrolled in the trial will complete the HRQoL instrument. In addition, adjusting downward to allow for 20% of missing data at the 12 months assessment point, we expect that data from 633 neoadjuvant and 735 adjuvant patients will be available (assuming that 15% of the total 1800 enrolled patients are ER and/or PgR positive HER2 negative). These will be sufficient to provide statistical power of 93% and 96% correspondingly to detect a difference of 3 points on the FACIT-Fatigue scale score between treatment groups assuming a standard deviation of 10.9 (Cella D et al 2002) (estimated SD of mean baseline score) and controlling α-level at 0.05. The 3-point difference is the clinically meaningful difference reported by the developers of the scale (Cella D et al 2002), and we are hypothesizing that the olaparib arm will be worse. A collection of PROs and QOL from all patients enrolled in the main trial will give us sufficient statistical power to detect important differences between two treatment groups.

Missing PRO data

A certain amount of missing data is expected. If data for individual items are missing, imputation will be done as follows: if less than 50% of the subscale items were missing (e.g. at most 2 out of 5 items, etc), the subscale score based on the non-missing items will be divided by the number of non-missing items and multiplied by the total number of items on the subscale. If at least 50% of the items are missing, that subscale will be treated as missing (not evaluable). If the scale is a single-item measure, a missing value will automatically be defined as 'Non-Evaluable'. The information from patients with missing data will be reviewed in order to determine whether data analytic procedures are likely to be biased. Patients with missing data will be reviewed for imbalances in factors such as trial arm, treatment adherence, institution, and reason for non-adherence. When QOL data are missing at a particular time point, data from prior time points will be reviewed in order to investigate whether missing status was preceded by a significant change in QOL scores. In addition, we will investigate whether missing item status is related to other scores on the same questionnaire. If no missing data mechanism can be detected following this review, the data will be analysed assuming the data are missing at random. If, on the other hand, a missing data mechanism appears to be present, we will undertake to develop an appropriate analytic strategy to control for the potential bias and, if possible, to impute the missing values. We will also present sensitivity analyses based on varying assumptions about the missing-data mechanism.

Full details on the analysis and derivation of PRO endpoints will be provided in the statistical analysis plan (SAP).

12.2.3.3 Pharmacokinetic analysis

The plasma concentration-time data will be analysed by non-linear mixed effects modelling in order to evaluate the pharmacokinetic characteristics of olaparib, quantify variability in the pharmacokinetics, identify demographic or pathophysiological covariates which may explain the observed variability and explore exposure-response relationships.

The olaparib plasma concentration data obtained from the samples collected in this study will be included in the listings of the CSR but these data will be pooled with data from other studies in order to perform a population PK analysis. The results of this analysis will be reported in a separate population PK report.

12.2.4 Analysis of exploratory endpoints

Adjusted OS (assessing potential impact of subsequent PARP inhibitors or other active therapies)

Exploratory analyses of OS that make an attempt to adjust for any potential impact of the control arm receiving subsequent PARP inhibitors (including patients taking part in PARP trials where exact treatment allocation may not be known) may be performed if an appropriate proportion of patients on the control arm switch to PARP inhibitors and sufficient data is collected to support such analyses (Note platinum therapies may also be taken into consideration if important imbalances are observed between the treatment arms). Methods such as Rank Preserving Structural Failure Time (RPSFT) (Robins et al 1991), and other methods in development will be explored. The decision on whether to perform these adjusted analyses and final choice of methods will be based on a blinded review of the data and the plausibility of the underlying assumptions as well as the completeness of the data collection on subsequent therapy use. Baseline and time-dependent characteristics will be explored, and summaries of baseline characteristics will be summarised for placebo patients, splitting between those that have and haven't switched to PARP inhibitors at the time of the analyses. Further detail will be provided in the SAP and Payer Analysis Plan. Note: these analyses are intended to support reimbursement applications, where applicable.

Biomarkers

Biomarker data will be summarised descriptively using tables and plots. If the data are available at the time of developing the CSR then the biomarker data will be included in the CSR. Otherwise the biomarker data will be reported in a separate addendum to the CSR (if applicable). Further details on the data summaries and plots for the biomarker data will be provided in the SAP or biomarker analysis plan.

All randomised patients were required to have two blood samples taken in relation to *BRCA* testing. One sample will be used to confirm *BRCA* status for the study patients (using the central Myriad test) and the other will be used to support diagnostic development.

All patients will have their *BRCA* status confirmed via the central test and the results will be summarised, highlighting any patient for whom the central test does not confirm a *BRCA* mutation (i.e. patients who may have entered via a positive local test not confirmed by the central test).

There is expected to be very few patients for whom the g*BRCA* central test result would differ from the local result, however if there are patients in this situation then an analysis of IDFS, DDFS, and OS will be performed which will include only those patients with confirmation of a g*BRCA* mutation by the central Myriad test.

12.2.5 Multiplicity strategy for primary and key secondary endpoints

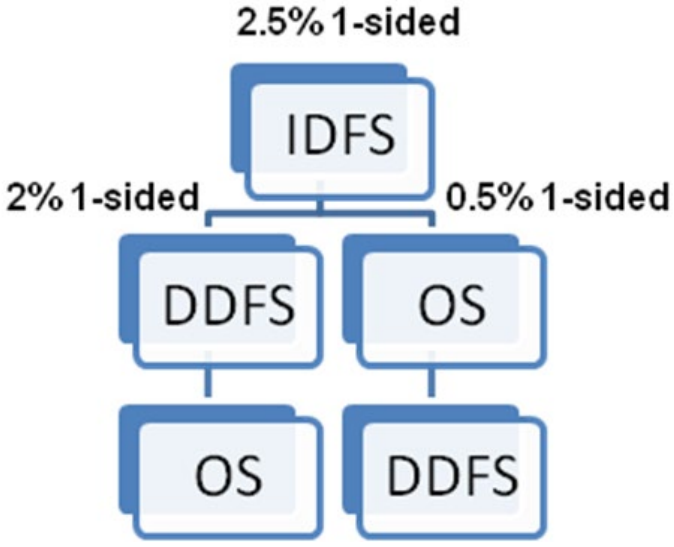
The primary endpoint of the study is IDFS. However, key secondary endpoints will be OS and DDFS.

In order to describe the nature of the benefits of olaparib treatment IDFS, DDFS and OS will be tested at a 2-sided significance level of 5%.

However, in addition, in order to strongly control the overall type I error at 2.5% 1-sided, a multiple testing procedure (MTP) will be employed across the primary endpoint and all key secondary endpoints intended for label claims (DDFS and OS). The MTP will account for any interim analyses on IDFS, DDFS and OS and also planned further analyses post the primary IDFS analysis data cut off.

A hierarchical testing strategy will be employed where IDFS is tested first using the full test mass (i.e. full 2.5%, 1-sided alpha), then DDFS and OS will be tested if IDFS is significant based on a weighted proportion of the test mass (2% for DDFS and 0.5% for OS, 1-sided) which can be recycled to secondary endpoints not yet rejected. Testing stops when the entire test mass is allocated to non-rejected endpoints.

Figure 3 Multiple testing procedure



IDFS is planned to be analysed at the interim and the final analysis (see Section 12.2.6 for further details). If IDFS is significant at the interim based on the ITT population then secondary endpoints will be formally tested at the interim based on the MTP outlined above. To account for multiple analyses on each endpoint a separate alpha spending function will be applied to each

endpoint (Glimm et al 2010). Further analyses of DDFS and OS with more mature follow up may be required for which some alpha will be reserved for significance testing.

12.2.6 Interim analysis

A superiority interim analysis of IDFS will occur when half the events needed for at least 90% power (165 events) have been observed from the first 50% of patients recruited (i.e. from first 900 patients) providing a cohort of patients with a similar level of maturity that is planned for the final analysis. Based on the database at time of amendment, the interim analysis is predicted to be October 2019 (80% CI: March 2019 to August 2020). The predictions will be tracked and monitored as more patients are enrolled in the study and additional data is added to the database. Two populations will be analysed at the interim analysis based on the analysis methods described in Section 12.2.1 for IDFS

1. Primary: ITT population (all patients randomised, estimated 254 events [80% CI: 226 to 289])

2. Supportive: Mature cohort population (first 900 patients randomised, 165 events anticipated)

The inclusion of a mature cohort population at the interim is to provide confidence that any observed treatment effect from the interim ITT population is maintained with longer-term follow-up. It is anticipated, based on the assumed recruitment and event rate that the interim analysis will occur approximately 5.3 years after the first patient is randomised and that all patients will have been randomised. At the time of the interim analysis, median time at risk per patient is expected to be 27 months in the ITT set, and 34 months in the mature cohort. The critical HR value at the interim analysis is 0.701.

Evidence of superiority for IDFS would only be determined at the interim if the results from both analysis populations provide evidence of a sustainable clinically relevant treatment effect for IDFS. More specifically, as a minimum the result in the ITT population would need to have met the statistical threshold defined below. Having met the statistical threshold in the ITT population, the result in the mature cohort (i.e. HR) would need to be of a similar magnitude such that the IDMC would consider it supportive of the ITT result and therefore have added confidence in the result in the ITT population. Statistical significance is not required for the mature cohort population. This analysis will be regarded as supportive, based on a cohort of patients with longer term follow-up, to aid interpretation of the result in the ITT population based on interim data. Other outcome measures such as 3 year IDFS rate will also be presented to aid the interpretation of the HRs (particularly in the case where the assumption of proportional hazards may not hold). KM plots will also be produced for IDFS.

The test mass alpha for IDFS (1 sided 2.5%) will be split between the final and the interim analysis using a bespoke spending function where a fixed significance level will be assigned at the interim and the remaining significance level assigned to the final analysis, taking account of correlation (Stone 2010). A 2-sided significance level of 0.005 will be assigned to the interim analysis so that a highly significant and clinically relevant result will need to be observed to declare superiority on IDFS. As an illustration, if 70% of the total required 330 IDFS events

have occurred in the ITT population at the interim then the observed HR would need to be < 0.7 for superiority to be declared. The HR in the mature cohort would need to be supportive of the ITT result. More detail around the criteria required for the mature cohort will be provided in the IDMC charter or SAP.

If the null hypothesis for IDFS is rejected at the interim for the ITT population then secondary endpoints (DDFS and OS) will be tested based on the MTP procedure outlined in Section 12.2.5 using the significance levels provided in Table 15. If IDFS is not significant at the interim, DDFS and OS will not be tested at the IDFS interim and the significance level allocated to the IDFS interim for DDFS and OS will not be allocated to later timepoints.

Similar to IDFS, a bespoke spending function will be applied to the secondary endpoints OS and DDFS where a fixed significance level will be assigned to each analysis time point and the remaining significance level assigned to the final analysis time point controlling the overall type 1 error at the pre-specified alpha amount (Stone 2010). Provided the last analysis is known in advance of the penultimate one then the remaining alpha can be split to ensure that some alpha is always reserved for the final analysis. This approach allows flexibility in the number of analyses while appropriately controlling the overall type 1 error. Three analyses are planned for DDFS and four for OS for which some alpha will be reserved for significance testing. If additional analyses are required beyond the planned analyses and some alpha is still available for testing then any remaining alpha can be further split to strongly control the type 1 error (based on process described above). If no alpha remains then the additional analyses will be considered supportive updates of the already conducted analyses.

Given the split in alpha between DDFS and OS, if OS is significant based on the assigned significance level then the alpha assigned to OS will be recycled to DDFS and split across the planned analyses (and vice versa if DDFS is significant alpha for DDFS will be recycled to OS and split across analyses). The recycled alpha will be split based on the ratio of the originally assigned alpha split. For example if the original alpha allocation was split 1/3 for each analysis time point then the recycled alpha would also be split 1/3 across each analysis time point. For example, at the first interim analysis, assume IDFS is statistically significant and the secondary endpoint OS is also statistically significant. The significance level for testing DDFS is therefore 0.005 + (alpha assigned to OS recycled to DDFS and split across the planned analyses), i.e. 0.005 + (1% * 0.005/0.04 = 0.00125) = 0.00625, or alternatively thought of as 0.005 * 5/4.

Secondary endpoints will be assessed based on the ITT population. Table 15 shows the different 2-sided significance levels that will be applied to the primary and secondary endpoints across the planned analyses as well as the total alpha spend for each endpoint. Note the significance level for the final analyses of each endpoint will be calculated using the relevant correlation based on the actual number of events for each analysis, the previous alpha spend and the total allocated alpha for that endpoint.

Table 15 Summary of 2-sided significance levels and total alpha spend across the endpoints and analyses

Endpoints	**Interim analysis**	**Final IDFS analysis**	**DDFS and OS analysis**	**Final OS analysis**	
Estimated timings from FSI**	**5.3 years**	**6.5 years**	**10 years**	**14 years**	
	Significance level	Significance level	Significance level	Significance level	Total alpha spend (2-sided)
IDFS	0.005	TBC*	N/A	N/A	5%
If IDFS is statistically significant and alpha is not recycled between secondary endpoints at the analysis					
DDFS	0.005	0.02	TBC*	N/A	4%
OS	0.002	0.003	0.004	TBC*	1%
If IDFS is statistically significant and alpha is recycled between secondary endpoints at the analysis					
DDFS	0.00625	0.025	TBC*	N/A	5%
OS	0.01	0.015	0.02	TBC*	5%

*TBC: to be calculated; significance level to be calculated once relevant correlation based on the actual number of events for each analysis is known taking account of previous alpha spend and total allocated alpha
**FSI: first subject in

The IDMC will review the data from the interim analysis. The boundaries defined by the interim p-values for efficacy will be used as guidelines by the IDMC along with all other relevant trial information, including the safety data, to decide if it is appropriate to make a recommendation other than that to continue the trial as planned.

At the time of the interim analysis for superiority, an assessment of futility will also be performed. This futility assessment will be based on the probability of eventually showing statistical significance for the primary endpoint when the final number of IDFS events (n=330) is reached (Lachin 2005). The determination of this probability will be conditional on the observed data in the ITT population at the time of the interim analysis for superiority and on the assumed hazard ratio for the alternative hypothesis (IDFS HR=0.7). If the probability is less than 0.1, the IDMC will consider the option of declaring futility.

Full details on the process around the interim analysis and the efficacy criteria will be documented in the SAP and IDMC charter.

12.2.7 Sample size justification

The primary endpoint of the study is IDFS and patients will be randomised 1:1 to either olaparib 300 mg b.i.d. (twice daily) or matching placebo.

A total of 1800 patients will be randomised into the study to achieve 330 IDFS events. If the true HR for the comparison of olaparib versus placebo in terms of IDFS is 0.7 then with 330 events, the analysis of IDFS will have 90% power to demonstrate a statistically significant difference in IDFS, assuming a 2-sided 5% significance level. The critical HR value at the primary analysis is 0.805.

The actual accrual pattern between June 2014 and February 2018 is shown in Table 16.

It is estimated that 1800 patients will be randomised by April/May 2019 so that the study will take approximately 5 years to complete recruitment (approximately 230 patients in US and approximately 1570 patients in the Rest of the World countries).

Table 16 Actual accrual between June 2014 and February 2018

Interval since start of randomisation (months)	Number of patients randomized in interval	Cumulative number of patients randomized	Average number of patients randomized per month in interval
0-6	21	21	3.5
6-12	94	115	15.7
12-18	174	289	29
18-24	180	469	33
24-30	229	698	38.2
30-36	249	947	41.5
36-42	234	1181	39
42-45*	118	1299	39.3

*Note: 3-month interval: December 2017 to February 2018 inclusive.

The primary analysis population will be all patients randomised (ITT). A subgroup analysis based on prior chemotherapy (adjuvant or neoadjuvant), prior platinum therapy (yes or no) and hormone receptor status (ER and/or PgR positive/HER2 negative versus TNBC) will be conducted to check for consistency in the treatment effect but this analysis is considered supportive of the primary analysis in the overall population.

During the trial, the Steering Committee will monitor the recruited patient population and actual event rate whilst remaining blinded to treatment. If the data suggests that the original sample size assumptions are incorrect such that achieving the required number of events with the current number of patients does not seem feasible then in consultation with the IDMC a decision may be made to increase the number of patients recruited into the trial to achieve the required 330 events.

12.2.8 Issues relating to racial and ethnic differences in the U.S.

Possible racial and ethnic variation in response to the treatment under consideration is of great concern to. African-Americans. Researchers have noted poorer survival rates for African-American breast cancer patients as compared to Caucasians (Baquet et al 1986, Youn et al 1984). This difference has been attributed to many factors, including more advanced disease at the time of diagnosis (Satariano et al 1986), social and economic factors (Bassett et al 1986), or specific tumour characteristics such as ER positivity (Crowe et al 1986, Mohla et al 1982). Although outcomes tend to be less favorable for African-Americans, significant race-by-treatment interactions have not been previously reported suggesting that, where treatment efficacy exists, both groups appear to benefit. Previous NSABP investigations of the relationship between race and prognosis support these conclusions (Dignam et al 1997, Costantino et al 1987).

Potential for the enrolment of minority patients in this protocol is enhanced by the NRG Oncology's recognition of the importance of increasing minority accrual. To this end, we provide educational opportunities for NRG Oncology investigators and coordinators to increase their awareness and skills related to recruitment of racial and ethnic minority populations. The distributions of ethnicity and race for B-55/6-13 are projected from the NSABP B-40 study. The ethnicity distribution of the NSABP B-40 triple-negative population consists of 11% Hispanic and 89% non-Hispanic. The racial distribution in the triple-negative B-40 population is 84% white; 14% black, not of Hispanic origin; 1% Asian; < 1% Hawaiian or Pacific Islander descent; and < 1% American Indian or Alaskan Native.

The prognostic effect of race/ethnicity will be evaluated using statistical models. Unfortunately, because of power limitations, we will not be able to compare effects separately for the different cultural or racial groups.

Table 17 Expected racial and ethnic composition of NSABP B-55/BIG 6-13

Ethnic Category	Total*
Hispanic or Latino	25
Not Hispanic or Latino	205
Ethnic Category: Total of all subjects	**230**
Racial Category	
American Indian or Alaskan Native	1
Asian	2
Black or African American	32
Native Hawaiian or other Pacific Islander	2
White	193
Racial Category: Total of all subjects	**230**

Totals reflect the estimated accrual for U.S. sites only.

Ethnic Categories:	**Hispanic or Latino** – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race.
	Not Hispanic or Latino
Racial Categories:	**American Indian or Alaskan Native** – a person having origins in any of the original peoples of North, Central or South America, and who maintains tribal affiliations or community attachment.
	Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.
	Black or African American – a person having origins in any of the black racial Groups of Africa.
	Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
	White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

12.3 Independent data monitoring committee

This study will utilise an Independent Data Monitoring Committee (IDMC) whose members include therapeutic area experts and statisticians who are not employed by AstraZeneca and do not have any major conflict of interest. Members of the IDMC will be jointly selected by BIG, AstraZeneca, CTEP and NRG Oncology and the IDMC will report their recommendations to the Steering Committee.

The IDMC will meet approximately every 6 months and will review ongoing study progress including safety and, when appropriate, efficacy data. They will also review the data presented at the time of the protocol-defined interim analysis. The IDMC will have the ability to recommend suspension of enrolment if safety concerns are identified at any of the 6 monthly assessments. At the interim analysis both efficacy and safety will be reviewed and trial recommendations will be based on the totality of the data. The IDMC can recommend changes to the trial, including stopping of the trial, if they have concerns over the benefit risk profile for olaparib.

Reports for the IDMC will be prepared by an Independent Statistical Centre (ISC) and will be presented to the IDMC in closed session. Following review of data, the IDMC will make a recommendation regarding the future conduct of the trial to the Steering Committee. The IDMC recommendation will not contain any unblinded information or any information related to treatment outcomes of the trial.

A separate IDMC Charter will be developed defining the responsibilities and procedures for the IDMC.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.10.**

In the case of a medical emergency the investigator may contact the Protocol Officer. If the Protocol Officer is not available, contact one of the Protocol Chairs.

Name	Role in the study	Address & telephone number
Charles E. Geyer, Jr., MD, FACP (NRG Oncology) Professor of Medicine Harrigan, Haw, Luck Families Chair in Cancer Research	Protocol Chair	Virginia Commonwealth University Massey Cancer Center McGlothlin Medical Education Center Room 12-217 1201 East Marshall St. PO Box 980070 Richmond, VA 23298-0070 Tel: 804-628-6435 Fax: 804-828-5406
Judy E. Garber, MD, MPH (Alliance) Professor of Medicine Harvard School of Medicine Director, Center for Cancer Genetics and Prevention Dana-Farber Cancer Institute Susan F. Smither Center for Women's Cancers	Protocol Chair	Dana-Farber Cancer Institute Susan F. Smither Center for Women's Cancers 450 Brookline Avenue Boston, MA 02215, US Tel: 617-632-5570 Fax: 617-632-2649
Priya Rastogi, MD Associate Professor of Medicine UPMC Cancer Institute Magee-Women's Hospital	Protocol Officer	NRG Oncology Nova Tower 2 Two Allegheny Center – Suite 1200 Pittsburgh, PA 15212-5402 Tel: 412-339-5300

Name	Role in the study	Address & telephone number
Elena Young	Global Safety Physician	AstraZeneca Riverside 2, Granta Park Cambridge, UK Tel: +44 (0) 7469408835
	24-hour emergency cover at NRG Oncology	Tel: 412-339-5300
For routine clinical questions, contact the Clinical Coordinating Department: 1-800-477-7227		

13.2 Overdose

There is currently no specific treatment in the event of overdose with olaparib and possible symptoms of overdose are not established. Study treatment must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose. Any overdose should be reported as a minor protocol deviation. The MTD is 300 mg b.i.d (tablet).

Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then Investigators or other site personnel inform the Protocol Officer immediately, or no later than 24 hours of when he or she becomes aware of it.

The Protocol Officer works with the Investigator to ensure that all relevant information is provided to NRG Oncology.

For overdoses associated with SAE, standard reporting timelines apply (see Section 6.4.10). For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported via CTEP-AERS.

13.3.1 Maternal exposure

If a patient becomes pregnant during the course of the study the investigational product should be discontinued immediately. Call the NRG Oncology Clinical Coordinating Department (see Information Resources).

The outcomes of any conception occurring from the date of the first dose of study medication until 3 months after the last dose of study medication must be followed up and documented.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study medication.

13.3.2 Expedited reporting of pregnancy, pregnancy loss, and death neonatal occurring during study therapy

Any pregnancy, pregnancy loss, or death neonatal occurring while the patient is receiving study therapy or within 3 months following the last dose of study therapy must be reported via CTEP-AERS as a medically significant event. Definitions and reporting instruction for these events are provided in the Cancer Therapy Evaluation Program's (CTEP) revised NCI guidelines for Investigators: Adverse Event Reporting Requirements (Section 5.5.6) located at the following CTEP website:
(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf).

Upon learning of a pregnancy, pregnancy loss, or death neonatal that occurs during study or within 3 months following the last dose of study therapy the investigator is required to:

- Within 5 working days of learning of the event, and as required by the NCI Guidelines for Investigators: Adverse Event Reporting Requirements (Section5.5.6):
  - Create and submit a CTEP-AERS report;
  - Complete the Pregnancy Information Form (located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm); and
  - Fax the completed Pregnancy Information Form with all available supporting documentation to the NRG Oncology SDMC's expedited fax number at 412-622-2113.
- The pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Information Form used for the initial report.
- For questions concerning AE reporting, contact the AE Reporting Nurse (see Information Resources).

13.3.3 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study treatment period and for 3 months following the last dose. Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

The outcome of any conception occurring from the date of the first dose until 3 months after the last dose should be followed up and documented.

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Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalisation

Outsubject treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A Guide to Interpreting the Causality Question

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

Labelling and Shipment of Biohazard Samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are e.g., Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are e.g., Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C Pharmacogenetics Research

1. BACKGROUND AND RATIONALE

AstraZeneca intends to perform genetic research in the olaparib clinical development programme to explore how genetic variations may affect the clinical parameters associated with olaparib and/or agents used in combination or as comparators. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Examples of genes that may be looked at are those encoding metabolising enzymes and transporter proteins. Future research may suggest other genes or gene categories as candidates for influencing not only response to olaparib but also susceptibility to cancer. Thus, this genetic research may involve study of additional un-named genes, but only as related to disease susceptibility, drug reaction and clinical response.

It is emphasised that AstraZeneca will only look for markers within genes relevant to the mode of action of, and response to olaparib and/or agents used in combination or as comparators, and breast cancer under study within the current Clinical Study Protocol. No other research will be performed on the samples.

2. GENETIC RESEARCH OBJECTIVES

The objective of this research is to collect and store DNA for future exploratory research into genes/genetic variation that may influence response (i.e., distribution, safety, tolerability and efficacy) to olaparib and/or agents used in combination and/or as comparators and/or susceptibility to or prognosis of cancer.

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Selection of genetic research population

3.1.1 Study selection record

All subjects will be asked to participate in this genetic research. Participation is voluntary and if a subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

3.1.2 Inclusion criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

3.1.3 Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study.

3.1.4. Discontinuation of subjects from this genetic research

Specific reasons for discontinuing a subject from this genetic research are:

Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 7.5 of the main Clinical Study Protocol.

3.2 Collection of samples for genetic research

The blood sample for genetic research will be obtained from the subjects on day 1 after randomisation. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn on day 1, it may be taken on any day until the last study visit.

Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the B-55/6-13 Pathology and Correlative Science Instructions.

For blood volume, see Section 7.1 of the Clinical Study Protocol.

3.3 Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.).

The samples and data for genetic analysis in this study will be single coded. The link between the subject enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used

to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

4. ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 8 of the main Clinical Study Protocol.

4.1 Informed consent

The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date the consent form for the main study and the genetic component of the study. Copies of the signed and dated consent form must be given to the subject and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue from the genetic aspect of the study at any time.

4.2 Subject data protection

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

5. DATA MANAGEMENT

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze the samples.

The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

7. LIST OF REFERENCES

None

Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with the Protocol Officer, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN

- AST ≥ 3xULN
- TBL ≥ 2xULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Determine whether the subject meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

Follow-Up

Potential Hy's Law Criteria not met

If the subject does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met

If the subject does meet PHL criteria the Investigator will:

- Notify the Protocol Officer

The Protocol Officer contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Protocol Officer) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Protocol Officer contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there **is** an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and submit (see Sections 6.4.9 and 6.4.10 of the protocol)

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') via CTEP-AERS.

  – The 'Medically Important' serious criterion should be used if no other serious criteria apply

  – As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a subject meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. chronic or progressing malignant disease, severe infection or liver disease?

If No: follow the process described in Potential Hy's Law Criteria met of this Appendix

If Yes:

Determine if there has been a significant change in the subject's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required

- If there is a significant change follow the process described in Follow-up of this Appendix

[#]A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Protocol Officer if there is any uncertainty.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

Appendix E Acceptable Birth Control Methods

Olaparib is regarded as a compound with medium/high foetal risk.

Women of childbearing potential who are sexually active, must agree with their partners, to the use of TWO highly effective forms of contraception in combination (as listed below). This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for at least 1 month after the last dose of study drug, or they must totally/truly abstain from any form of sexual intercourse (see below). Please note that in breast cancer patients, hormonal contraception should only be used if considered appropriate by the investigator.

Male patients must use a condom during study treatment and for 3 months after the last dose of study drug when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Male patients should not donate sperm throughout the period of taking study treatment and for 3 months following the last dose of study drug.

Acceptable non-hormonal birth control methods include

- Total/True abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle, this must continue for the total duration of the treatment period and for 1 month after the last dose of study drug for female patients, for 3 months after the last dose for male patients. *[Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception.]*
- Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia
- Tubal occlusion plus male condom
- IUD plus male condom. Provided coils are copper-banded

Acceptable hormonal methods

- Etonogestrel implants (e.g., Implanon, Norplan) PLUS male condom
- Normal and low dose combined oral pills PLUS male condom
- Norelgestromin / EE transdermal system PLUS male condom
- Intravaginal device (e.g., EE and etonogestrel) PLUS male condom
- Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone based pill.
- Hormonal shot or injection (e.g., Depo-Provera) PLUS male condom
- Intrauterine system [IUS] device (e.g., levonorgestrel releasing IUS - Mirena®) PLUS male condom

Appendix F ECOG Performance Status

Example of Performance Status (ECOG SCALE)

DESCRIPTION	ECOG 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 housework, office work.	1
Ambulatory and capable of 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 G Patient Reported Outcomes (FACIT-Fatigue, EORTC QLQ-C30)

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

EORTC QLQ-C30 (version 3)

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

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

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

During the past week:

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

Please go on to the next page

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

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

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

Appendix H CPS & EG Score

Calculation instructions: Add the points for Clinical Stage + Pathologic Stage + ER status + Nuclear grade to derive a sum (CPS&EG score) between 0 and 6.

Table 18 Point assignments for the CPS + EG staging system

Stage/feature		Points
Clinical Stage (AJCC staging[1])	I	0
	IIA	0
	IIB	1
	IIIA	1
	IIIB	2
	IIIC	2
Pathologic Stage (AJCC staging[1])	0	0
	I	0
	IIA	1
	IIB	1
	IIIA	1
	IIIB	1
	IIIC	2
Receptor status	ER negative[2]	1
Nuclear grade[3]	Nuclear grade 3	1

[1] AJCC: American Joint Committee on Cancer (https://cancerstaging.org/Pages/default.aspx)

[2] ER: Estrogen receptor; definitions for ER negativity see eligibility criteria section 4.1.4.a

[3] In the unlikely situation nuclear grade cannot be determined, regular histologic grade should be used; if only Nottingham overall grade is reported, the Nottingham overall grade must be 9 to be scored as 1 point in the CPS&EG score (http://pathology.jhu.edu/breast/grade.php).