ISRCTN47127434 https://doi.org/10.1186/ISRCTN47127434

# A trial to look for markers in the tumour cells and blood which signal that trial treatments are working in a patient with triple negative breast cancer, for whom upfront chemotherapy has not provided the maximum expected benefit: PHOENIX

| | | |
|---|---|---|
| **Submission date**<br>03/06/2019 | **Recruitment status**<br>Suspended | [X] Prospectively registered<br>[ ] Protocol<br>[ ] Statistical analysis plan<br>[ ] Results<br>[ ] Individual participant data<br>[ ] Record updated in last year |
| **Registration date**<br>14/08/2019 | **Overall study status**<br>Completed | |
| **Last Edited**<br>20/09/2021 | **Condition category**<br>Cancer | |

**Plain English summary of protocol**
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-using-markers-to-help-work-out-how-well-new-treatments-work-for-triple-negative-breast

## Contact information

**Type(s)**
Public

**Contact name**
Ms Hannah Johnson

**Contact details**
The Institute of Cancer Research Clinical Trials and Statistics Unit
15 Cotswold Road
Sutton
United Kingdom
SM2 5NG
0203 437 6712
Phoenix-icrctsu@icr.ac.uk

## Additional identifiers

**EudraCT/CTIS number**

2018-002077-21

### IRAS number

### ClinicalTrials.gov number
NCT03740893

### Secondary identifying numbers
40609

# Study information

### Scientific Title
PHOENIX Trial: A pre-surgical window of opportunity and post-surgical adjuvant biomarker study of DNA damage response inhibition and/or anti-PD-L1 immunotherapy in patients with neoadjuvant chemotherapy resistant residual triple negative breast cancer

### Acronym
PHOENIX

### Study objectives
PHOENIX aims to assess whether, in patients who have moderate to significant residual disease remaining following neo-adjuvant chemotherapy (NACT), short exposure to trial treatment with a DNA damage response (DDR) inhibitor and/or anti-PD-L1 immunotherapy prior to surgery will demonstrate a signal of anti-tumour biological activity within the residual disease tissue

### Ethics approval required
Old ethics approval format

### Ethics approval(s)
Approved 17/04/2019, London-South East Research Ethics Committee (Health Research Authority, Skipton House, 80 London Road, London, SE1 6LH; 0207 104 8340; NRESCommittee.London-SouthEast@nhs.net), ref: 19/LO/0127.

### Study design
Randomised; Interventional; Design type: Treatment, Drug, Immunotherapy

### Primary study design
Interventional

### Secondary study design
Randomised controlled trial

### Study setting(s)
Not specified

### Study type(s)
Treatment

### Participant information sheet

Not available in web format, please use the contact details below to request a patient information sheet

## Health condition(s) or problem(s) studied
Breast cancer

## Interventions
Patients confirmed eligible will be randomly allocated to one of four groups or cohorts:
Cohort A - standard care: no trial treatment
Cohort B - AZD6738: tablets taken twice daily for 10 days
Cohort C - olaparib: tablets taken twice daily for 14 days
Cohort D - durvalumab: an infusion on day 1
Patients will be allocated in a 1:1:1:1 ratio into Cohorts A-D until 9 patients have been recruited into cohort A. Following this, patients will be allocated in a 1:1:1 ratio to Cohorts B-D.

If it is available, the hospital research team will provide the PHOENIX researchers with tumour tissue collected from the original breast cancer diagnosis.

PRE-TREATMENT SAMPLE COLLECTION DAY -1 TO 1 (OR DAY -1 TO 5 FOR COHORT B)
Prior to the start of the 2-week window between completing chemotherapy and surgery (and to commencing trial treatment for those allocated to a treatment cohort), patients will have a new marker inserted into the tumour, in order to guide the research biopsies collected in PHOENIX. A research biopsy will be collected during the same procedure and 4 cores will be collected guided by the new marker via ultrasound scan. A blood sample will also be collected at this time point.

TRIAL TREATMENT BEFORE SURGERY
Patients allocated to a treatment cohort will receive trial treatment in the 2-week window between completing chemotherapy and having breast cancer surgery.

ON-TREATMENT ASSESSMENTS DAY 7 (COHORT C ONLY)
Patients in Cohort C will have an additional visit on Day 7 of trial treatment:
- Discussion about changes in health or medications since the previous visit

DAY 14 ASSESSMENTS
On the final day of the 2-week window before surgery, patients will have:
- Discussion about changes in health or medications since the previous visit
- Physical examination
- Blood test for routine safety checks
- Pre-operative sample collection, as described below

PRE-OPERATIVE SAMPLE COLLECTION DAY 14
On Day 14 of the window of opportunity and prior to surgery, a second biopsy guided by the marker inserted at baseline via ultrasound scan and research blood samples will be collected. Patients in cohort A will not receive trial treatment in the window between completing chemotherapy and surgery but the research biopsies and blood samples described above will still be collected. Cohort A is important as it will help to work out whether any changes we see in cohorts B, C or D are due to the trial treatment, due to the biopsies, or due to another reason.

SURGERY
All patients will proceed to breast cancer surgery as planned. The research team at site will provide the PHOENIX researchers with tumour tissue collected during surgery.

30-DAY POST SURGERY FOLLOW UP
All patients will be seen 30 days after surgery for a safety follow up visit. Assessments carried out in this visit will be:
- Discussion about changes in health or medications since the previous visit
- A physical examination
- An electrocardiogram
- Blood test for routine safety checks
- Patients will also donate a research blood sample during this 30-day post-surgery follow up visit.

3-MONTH POST-SURGERY FOLLOW UP
All patients will be seen 3 months after surgery for a safety follow up visit. Assessments carried out in this visit will be:
- Discussion about changes in health or medications since the previous visit
- A physical examination
- An electrocardiogram
- Blood test for routine safety checks

At the 3-month post-surgery follow up visit, patients will find out from their trial doctor or nurse whether they are suitable for continuation to PHOENIX PART 2.

PATIENTS NOT CONTINUING TO PART 2:
This will include all patients in Cohort A, patients for whom a trackable mutations has not been identified in their tumour tissue provided in PART 1, and patients who for any reason do not wish to continue with the trial further. No further visits will be required for these patients for PHOENIX, but we will collect follow up information on how patients are doing every 3 months for a period of 2 years, including any relapses or further treatment received.

INFORMED CONSENT FOR PART 2
If patients are suitable for continuation to PHOENIX PART 2, they will receive a verbal explanation of the next part of the trial, together with the cohort specific Patient Information Sheet for Continuation to PART 2, which they can take home with them. Patients will be given sufficient time to consider whether they want to continue in the trial and will have the opportunity to raise any questions before deciding whether to continue. Should they choose to continue to PART 2, they will be asked to sign a consent form to record their informed consent.

ctDNA SCREENING:
A blood sample for ctDNA screening will be collected from all patients consenting for continuation to PART 2.

FOLLOW UP OF PATIENTS WITH A ctDNA NEGATIVE RESULT:
If ctDNA is not found to be present in the blood sample provided for ctDNA screening or tests show that the cancer has not spread to other parts of the body but the patient is not suitable to resume trial treatment in PART 2 for any other reason, we will continue to collect blood samples from the patient every 3 months for a period of 24 months. We will also collect information on how the patients are doing during this time, including any relapses or further treatment received.

PATIENTS WITH A ctDNA POSITIVE RESULT:
If ctDNA is found to be present in the blood sample provided for ctDNA screening patients will undergo an imaging assessment to see whether the cancer has spread to other parts of the body. The imaging will be either a CT scan and bone scan, or an FDG PET-CT scan, depending on the hospital's usual process.

If the scan shows the cancer has spread to other parts of the body, patients will not be able to resume trial treatment within PHOENIX. Instead, their trial doctor will discuss treatment options available outside of the PHOENIX trial. No further visits will be required for these patients for PHOENIX, but we will collect information on how the patients are doing every 3 months for a period of 2 years, including any relapses or further treatment received.
If the scan does not show any evidence that the cancer has spread to other parts of the body, patients may be able to resume trial treatment for 12 months within PART 2, provided that pre-treatment assessments show they are suitable to resume treatment.

PART 2 PRE-TREATMENT ASSESSMENTS:
The following pre-treatment assessments will be conducted on Day -28 to -1 prior to resuming trial treatment:
- Scan, as described above, to confirm no evidence on imaging that the cancer has spread
- Electrocardiogram
- Discussion about changes in health since the previous visit
The following pre-treatment assessments will be conducted on Day -3 to -1 prior to resuming of trial treatment:
- Discussion about changes in medication since the previous visit
- Physical exam
- Blood test for routine safety checks
- A pregnancy test (for all women who are able to get pregnant)

PART 2 TRIAL TREATMENT - ADJUVANT SETTING FOR 12 MONTHS:
Patients confirmed as suitable to resume trial treatment in PART 2 will receive the same trial treatment as received in PART 1 in 4-weekly cycles for 12 months (13 cycles) with ctDNA blood samples collected every 4 weeks:
- CohortB - AZD6738: tablets taken twice daily, for the first 2 weeks of each cycle
- Cohort C - Olaparib: tablets to be taken twice daily, every day of each cycle
- Cohort D - durvalumab: an infusion on day 1 of each cycle

PART 2 ON-TREATMENT ASSESSMENTS:
The following assessments will be conducted on Day 1 of each cycle (cycles 2 -13), before the first dose is taken:
- Discussion about changes in health or medications since the previous visit
- A physical examination
- Electrocardiogram
- A pregnancy test (for all women who are able to get pregnant)
- Blood test for routine safety checks
- Blood samples taken for research

END OF TREATMENT ASSESSMENTS:
The following assessments will be conducted at the time of treatment discontinuation:
- Medication and symptoms review
- Physical examination
- Electrocardiogram
- Blood test for routine safety checks
- Blood samples taken for research

POST-TREATMENT SAFETY FOLLOW UP - 30 DAYS (AND 90 DAYS FOR COHORT D ONLY) POST-TREATMENT
DISCONTINUATION:
The following assessments will be conducted at the post-treatment safety follow up visit 30

days (and 90 days for Cohort D only) after treatment discontinuation:
- Discussion about changes in health or medications since the previous visit
- Physical exam
- Electrocardiogram
- A pregnancy test (for all women who are able to get pregnant)
- Blood test for routine safety checks (30 days only)
FOLLOW UP:
Patients will be followed up for a further 12 months after treatment discontinuation (or total of 24 months from the 3 month post-surgery visit if treatment is discontinued earlier than 12 months) with a research blood sample collected every 3 months and information collected on how the patient is doing during this time, including any relapses or further treatment received.

## Intervention Type
Drug

## Phase
Phase II

## Drug/device/biological/vaccine name(s)
AZD6738 Olaparib Durvalumab

## Primary outcome measure
Cohorts B and C:
1. Change in mean proliferation index (as measured by tumour cell Ki67 staining) post WOP intervention within the post-treatment biopsy compared to pre-treatment baseline biopsy. AND /OR
2. Changes in the proliferation gene expression signature post WOP intervention within the post-treatment biopsy compared to pre-treatment baseline biopsy.
Cohort D:
1. Change in CD8+ tumour infiltrating lymphocyte (TIL) frequency post anti-PD-L1 immunotherapy within the post-treatment biopsy compared to pre-treatment baseline biopsy. AND/OR
2. Changes in the Interferon Gamma-positive (IFNγ+) signature post WOP intervention within the post-treatment biopsy compared to pre-treatment baseline biopsy. Cohort A (standard care reference cohort) will allow assessment of any biopsy effect on all co-primary endpoints assessed in treatment cohorts B, C and D.

## Secondary outcome measures
1. Incidence of adverse events (AEs) during trial treatment (including surgical complications) by treatment cohort at 1 month post-surgery.
2. Changes in phosphorylation of ATR and its downstream effectors (Chk1, γH2AX, TAO upon drug exposure: including but not limited to levels of phosphorylation of p53, p38, p21/p27, cyclin dependent kinases (CDC25)).
3. Changes in biomarkers of DDR and adaptive and innate response, including but not limited to 53BP1, RAD51, RPA, RPA32, pRPA, BRCA1/2, PARP expression and immune checkpoint ligands and receptors and adaptive and innate immune response markers (IFNg, cGAS-STING pathway, NKG2D receptors, ligands and cell markers) in the post treatment biopsy compared to pre-treatment baseline biopsy using gene expression profiling.
4. Assessment of associated expression of coinhibitory immune checkpoint receptors using immune cell markers and high content image de-convolution.
5. Assessment of associated expression of coinhibitory immune checkpoint ligands using

immune cell markers and high content image de-convolution.
6. Assessment of frequency and function of tumourinfiltrating lymphocyte subsets using immune cell markers and high content image de-convolution.
7. Assessment of frequency and function of tumourinfiltrating myeloid cells subsets using immune cell markers and high content image de-convolution.
8. Change in the levels of Th1/IFNg response measured by transcriptional and proteomic profiling.
9. Immune cell population sub-set characterisation using appropriate and T and B cell receptor DNA sequencing methodologies.
10. Assess change in Ki67+:CD8+ ratio within the post-treatment biopsy sample compared to pre-treatment baseline biopsy.

### Overall study start date
01/02/2019

### Completion date
01/08/2023

## Eligibility

### Key inclusion criteria
INCLUSION CRITERIA FOR TRIAL REGISTRATION:
1. Signed Informed Consent Form (ICF) for Trial Registration;
2. Aged > = 18 years old;
3. Histologically confirmed invasive triple negative breast cancer (TNBC). TNBC defined as ER negative, PgR negative (ER and PgR negative as defined by Allred score 0/8, 1/8 or 2/8 or stain in < 1% of cancer cells) or PgR unavailable, and HER2 negative (immunohistochemistry 0/1+ or negative in situ hybridization) as determined by local laboratory and recorded in the patients notes;
4. Planned definitive surgical treatment after at least 6 cycles of neoadjuvant chemotherapy (NACT);
5. Radiographically measurable tumour mass assessable for new distinct radio-opaque marker insertion and repeated biopsies on the NACT mid-assessment standard of care imaging modality (MRI or US); or clinically thought to be > 5cm in diameter (T3);
6. Eastern Oncology Cooperative Group (ECOG) performance status 0-1;
7. Considered fit enough to have breast cancer surgery with curative intent;
8. Considered fit to complete at least 2 weeks of pre-operative trial treatment in the WOP;
9. Patients must be suitable for a mandatory pre-treatment baseline biopsy performed Day -1 or 1 of the window of opportunity (WOP) and a post-treatment biopsy performed on Day 14 of the WOP. Registered patients who are approached for Trial Entry will be required to consent to the pre- and post- WOP treatment biopsy. If it is deemed unsafe to proceed with biopsy upon Trial Entry the patient will not be eligible for Trial Registration.
10. Patients with clinical stage II disease or clinical suspicion of metastatic disease must have staging studies as per standard of care to exclude metastatic disease (axillary lymph nodes or internal mammary node involvement will not be regarded as evidence of metastatic disease);
11. Patients with stage III disease must have staging studies as per standard of care at any point after diagnosis but before Trial Registration, to exclude metastatic disease (axillary lymph nodes or internal mammary node involvement will not be regarded as evidence of metastatic disease), even if asymptomatic.
12. Patients with previous invasive cancers (including breast cancer) are eligible if the treatment was completed > 5 years prior to Trial Registration, and there is no evidence of recurrent disease;

13. Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the trial protocol and follow-up schedule; those conditions should be discussed with the patient before Trial Registration;
14. Patients must be:
14.1 Surgically sterile (i.e. if female have undergone a hysterectomy, bilateral salpingectomy or bilateral oophorectomy; if male have undergone a bilateral orchidectomy);
14.2 Have a sterilised sole partner; or
14.3 Be post-menopausal; or
14.4 Must agree to practice total/true abstinence; or
14.5 Use two highly effective forms of contraception in combination during the period of trial treatment and be willing to do so for a period of at least 6 months following the end of trial treatment.

INCLUSION CRITERIA FOR TRIAL ENTRY:
1. Signed Informed Consent Form (ICF) for Trial Entry;
2. Residual disease is confirmed as at least one viable disease focus > = 2cm on trial-specific dynamic contrast enhanced MRI scan performed 1 week following day 1 of the final cycle of NACT.
3. Recovery from all acute adverse events of prior NACT to baseline or NCI CTCAE Grade < = 1, except for alopecia. Patients with irreversible toxicity not reasonably expected to be exacerbated by trial treatment may be included only after consultation with the CI or Coordinating Investigator.
4. Patients must have adequate haematological, renal and hepatic function.
5. Women of childbearing potential must have a confirmed menstrual period and a negative urinary or serum pregnancy test prior to Trial Entry. This should be repeated as applicable to ensure a negative pregnancy test is performed within 3 days prior to commencing trial treatment (or on the day of planned trial treatment for Cohort C)

## Participant type(s)
Patient

## Age group
Adult

## Lower age limit
18 Years

## Sex
Both

## Target number of participants
Planned Sample Size: 81; UK Sample Size: 81

## Key exclusion criteria
EXCLUSION CRITERIA FOR TRIAL REGISTRATION:
1. Definitive evidence of metastatic disease (axillary lymph nodes or internal mammary node involvement will not be regarded as evidence of metastatic disease);
2. Patients with bilateral tumours;
3. History of another primary malignancy within the last 5 years prior to Trial Registration, except for:
3.1. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of

disease;
3.2 Adequately treated carcinoma in situ without evidence of disease;
4. Patients with myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) or with features suggestive of MDS/AML;
5. Severe concurrent disease, infection or co-morbidity that, in the judgment of the local Investigator, would make the patient inappropriate for Trial Registration;
6. Resting ECG with QTc > 470msec for females and > 450 msec for men on 2 or more time points within a 24 hour period, factors which increase the risk of QTc prolongation or family history of long QT syndrome;
7. A diagnosis of ataxia telangiectasia;
8. Patients unable to swallow orally administered medication;
9. Patients receiving formal anti-coagulation treatment;
10. Patients with gastrointestinal disorder affecting absorption;
11. History of seizure or any condition that may predispose to seizure;
12. Other non-malignant systemic disease that would preclude trial treatment or would prevent required follow-up;
13. Pregnant or breast-feeding;
14. Prior exposure to ATR inhibitor (including AZD6738), PARP inhibitor (including olaparib), anti-PD-1 or anti-PDL1 immunotherapy (including durvalumab);
15. Any other disease(s), psychiatric condition, metabolic dysfunction, or findings from a physical examination or clinical laboratory test result that in the investigators opinion would cause reasonable suspicion of a disease or condition, that contraindicates the use of trial treatment, that may increase the risk associated with trial participation, that may affect the interpretation of the results, or that would make this trial inappropriate for the patient;
16. Patients with a known hypersensitivity to the trial treatments or any excipients of the products;
17. Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT);
18. Active or prior documented autoimmune or inflammatory disorders
19. Active infection including tuberculosis (TB), hepatitis B, hepatitis C (HCV), or human immunodeficiency virus (HIV)

EXCLUSION CRITERIA FOR TRIAL ENTRY:
1. History of clinically significant or uncontrolled cardiovascular disease
2. History of loss of consciousness or transient ischemic attack within 12 months prior to Trial Entry;
3. Patients with Grade > = 2 neuropathy, as defined by NCI CTCAE v5.0 will be evaluated on a case-by-case basis after consultation with the CI or Coordinating Investigator;
4. Major surgery (excluding minor procedures, e.g. placement of vascular access) within 2 weeks prior to Trial Entry. Patients must have recovered from any effects of any major surgery prior to commencing trial treatment.
5.Use of any investigational agent within 30 days prior to commencing trial treatment.
6. Concomitant use of known strong CYP3A inhibitors.
7. Concomitant use of known strong CYP3A inducers. The required washout period prior to commencing trial treatment is 5 weeks;
8. Whole blood transfusions in the last 4 months prior to commencing trial treatment (packed red blood cells and platelet transfusions are acceptable, with no blood transfusion or erythropoietin in the past 28 days prior to trial entry);
9. Current or prior use of immunosuppressive medication within 14 days prior to commencing trial treatment, with the exception of intranasal and inhaled corticosteroids or systemic

corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisolone, or an equivalent corticosteroid.
10. Receipt of live attenuated vaccine within 30 days prior to commencing trial treatment.

### Date of first enrolment
01/11/2019

### Date of final enrolment
01/06/2021

## Locations

### Countries of recruitment
England

Northern Ireland

United Kingdom

Wales

### Study participating centre
**Royal Bournemouth Hospital**
Bournemouth
United Kingdom
BH7 7DW

### Study participating centre
**Bristol Haematology and Oncology Centre**
Bristol
United Kingdom
BS2 8ED

### Study participating centre
**King's College Hospital**
London
United Kingdom
SE5 9RS

### Study participating centre

**Christie Hospital NHS Trust**
Manchester
United Kingdom
M20 4BX

**Study participating centre**
**Belfast City Hospital**
Belfast
United Kingdom
BT9 7AB

**Study participating centre**
**Velindre Cancer Center at Velinde Hospital**
Cardiff
United Kingdom
CF14 2TL

**Study participating centre**
**Queen Elizabeth Hospital, University Hospitals Birmingham NHS Trust**
Birmingham
United Kingdom
B15 2TH

**Study participating centre**
**Guy's and St Thomas' Hospital NHS Foundation Trust**
London
United Kingdom
SE1 9RT

**Study participating centre**
**Weston Park Hospital**
Sheffield
United Kingdom
S10 2SJ

# Sponsor information

**Organisation**
Institute of Cancer Research

**Sponsor details**
15 Cotswold Road
Belmont
Sutton
United Kingdom
SM2 5NG

**Sponsor type**
Research organisation

**ROR**
https://ror.org/043jzw605

# Funder(s)

**Funder type**
Industry

**Funder Name**
AstraZeneca

**Alternative Name(s)**
AstraZeneca PLC, Pearl Therapeutics

**Funding Body Type**
Government organisation

**Funding Body Subtype**
For-profit companies (industry)

**Location**
United Kingdom

**Funder Name**
NIHR Biomedical Research Centre, Royal Marsden NHS Foundation Trust/Institute of Cancer Research

**Alternative Name(s)**
Royal Marsden BRC, Biomedical Research Centre, Biomedical Research Centre for Cancer, NIHR BRC at The Royal Marsden and the ICR, NIHR Royal Marsden Biomedical Research Centre, National Institute for Health Research Biomedical Research Centre, NIHR Biomedical Research Centre at The Royal Marsden and The Institute of Cancer Research, NIHR Biomedical Research

Centre at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, NIHR Biomedical Research Centre at The Royal Marsden and the ICR, BRC, NIHR BRC

### Funding Body Type
Government organisation

### Funding Body Subtype
Research institutes and centers

### Location
United Kingdom

## Results and Publications

### Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

### Intention to publish date
01/08/2024

### Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

### IPD sharing plan summary
Available on request

### Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| HRA research summary | | | 28/06/2023 | No | No |