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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 03/06/2019	**Recruitment status** Recruiting	[X] Prospectively registered [X] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 14/08/2019	**Overall study status** Ongoing	
Last Edited 19/08/2025	**Condition category** 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

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Clinical Trials Information System (CTIS)
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Integrated Research Application System (IRAS)
249774

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40609

Study information

Scientific Title
PHOENIX Trial: A pre-surgical window of opportunity and post-surgical adjuvant biomarker study of DNA damage response inhibition with or without anti-PD-L1 immunotherapy in patients with neoadjuvant chemotherapy resistant residual triple negative breast cancer

Acronym
PHOENIX

Study objectives
Current study objectives as of 19/08/2025:

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 with or without anti-PD-L1 immunotherapy prior to surgery will demonstrate a signal of anti-tumour biological activity within the residual disease tissue.

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Previous 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.

Primary study design
Interventional

Study design
For cohorts A-D: Interventional randomized controlled trial, For Cohorts E-G : Interventional non-randomized

Study type(s)
Treatment

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

Interventions
Current interventions as of 19/08/2025:

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.

Cohorts A-D have been formally closed for recruitment since 06 August 2024.

Following this and with the update to the trial design, patients are allocated to one of the 3 groups or cohorts according to HRD and germline BRCA1/2 mutation status which forms Part 1, a post-neoadjuvant treatment preoperative WOP component of the trial and a Part 2, post-operative component :

Cohort E: Olaparib
Part 1: Pre-operative exposure to 300mg of Olaparib to be administered orally twice daily on Days 1-14 of the WOP.

Cohort F : Olaparib
Part 1: Pre-operative exposure to 300mg of Olaparib to be administered orally twice daily on Days 1-14 of the WOP.
Part 2: 12 months post-operative exposure to 300mg Olaparib (2 x 150mg tablets) to be administered orally twice daily on a continuous schedule Day 1-28 of a 28 day cycle.

Cohort F: Durvalumab
Part 2 : 12 months post-operative exposure to 1500mg durvalumab to be administered via intravenous (IV) infusion on Day 1 only of a 28 day cycle.

Cohort G: Olaparib
Part 1: Pre-operative exposure to 300mg of Olaparib to be administered orally twice daily on Days 1-14 of the WOP.
Part 2 : 12 months post-operative exposure to 300mg Olaparib (2 x 150mg tablets) to be administered orally twice daily on a continuous schedule Day 1-28 of a 28 day cycle.

Cohort G: Durvalumab
Part 2: 12 months post-operative exposure to 300mg Olaparib (2 x 150mg tablets) to be administered orally twice daily on a continuous schedule Day 1-28 of a 28 day cycle.

On trial registration, patient's archival diagnostic tumour tissue sample and collected blood sample should be sent to the PHOENIX Central Laboratory immediately. This is required in order to allocate patients to the appropriate cohort (E,F or G) based on their HRD and germline BRCA1 /2 mutation status.

PHOENIX, trial-specific imaging, to be performed at least 1 week following day 1 of the final cycle of NACT. Patients with confirmed residual disease ≥ 1cm by imaging, to be approached for trial entry.

No further protocol required assessments, other than those required as part of standard patient care- listed below, which forms part of trial entry screening assessment, should be conducted until the PHOENIX Informed Consent Form for Trial Entry, has been obtained from the eligible patients.
- Written informed consent for Trial Entry
- Medical history
- Physical examination and vital signs (including height, weight, blood pressure (BP), heart rate, temperature)
- ECOG performance status
- Review of concomitant medication
- Safety bloods to confirm adequate haematological, renal and hepatic function as per inclusion criteria for Trial Entry, and assessment of hepatitis serologies (hepatitis B and C mandatory, hepatitis A as per local practice)
- Pregnancy test for women of childbearing potential
- ECG

PART 1 TRIAL ASSESSMENTS
PART 1 Baseline Assessments WOP (All Cohorts)
The following assessments should be performed within 3 days prior to commencing trial treatment in the WOP defined as the 2-week time period (Day 1 – Day 14) starting at least 3 weeks after the first day of the final cycle of NACT and 2 weeks prior to the patients scheduled surgical intervention (taking into account any pre-surgical self-isolation period required according to national COVID-19 guidance):

- Physical examination and vital signs (including weight, blood pressure, heart rate, temperature)
- ECOG performance status
- Assessment of baseline conditions
- Review of concomitant medications
- Safety bloods: Haematology – full blood count, white cell count with differential and ANC, prothrombin time and international normalised ratio (INR); Biochemistry – sodium, potassium, calcium, magnesium, ALT, gamma-glutamyl transferase (GGT), bilirubin, albumin, creatinine, alkaline phosphatase, glucose, urea.
- ECG
- Pregnancy test should be performed for women of child bearing potential on Day 1 prior to commencing trial treatment

Research tissue and blood sample collection pre-treatment on either Day -1 or 1:
- Research tissue collection:
- Mandatory pre-treatment image-guided baseline biopsy – guided by a new distinct radio-opaque marker insertion into residual disease
- Collection of a minimum of four and up to a maximum of eight core biopsies for research purposes. (The number of cores should be decided on a case-by-case basis by the radiologist at the time of collection, with the aim of ensuring that at least 4 high quality tissue cores are

obtained).
- Research blood sample collection as specified in the PHOENIX Investigator Laboratory Manual.

PART 1 WOP Day 14 Assessments (All Cohorts)
The following procedures should be performed on D14 of the WOP:

- Physical examination and vital signs (including weight, blood pressure, heart rate, temperature)
- ECOG performance status
- Review of concomitant medications
- Safety bloods: Haematology – full blood count, white cell count with differential and ANC, prothrombin time and international normalised ratio (INR); Biochemistry – sodium, potassium, calcium, magnesium, ALT, gamma-glutamyl transferase (GGT), bilirubin, albumin, creatinine, alkaline phosphatase, glucose, urea.
- Assessment of AEs
- Dosing compliance
- Olaparib DDI with anaesthetics prior to surgery.
- Cohorts F & G only: Provision of Patient Information Sheet for PART 2 Trial Treatment to the patient for those allocated to Cohorts F and G if confirmed by the ICR-CTSU trial team prior to this trial visit. If cohort allocation has not been confirmed at the time of this visit the Patient Information Sheet should be shared as soon as possible and ahead of the 30-day post surgery visit but only once cohort allocation has been confirmed.

Research tissue and blood sample collection:
- Research tissue collection:
- Mandatory post-treatment image-guided core biopsy – taken from the same site as the pre-treatment biopsy guided by the distinct radio-opaque marker inserted pre-treatment
- Collection of a minimum of four and up to a maximum of eight core biopsies for research purposes. (The number of cores should be decided on a case-by-case basis by the radiologist at the time of collection, with the aim of ensuring that at least 4 high quality tissue cores are obtained).
- In exceptional cases when the collection of the biopsy on Day 14 is not feasible then image-guided research biopsy cores can be collected on the day of surgery or taken by the surgeon intraoperatively, with the time from the Day 14 assessments to biopsy minimised and recorded.
- Research blood sample collection as specified in the PHOENIX Investigator Laboratory Manual.

PART 1 Surgery (All Cohorts)
Research tissue collection:
- Provision of Surgical Resection blocks (must include primary breast with or without involved lymph node tissue).

PART 1 - 30 Day Post-Surgery Follow-up Assessments (All Cohorts)

The following assessments should be performed 30 days (±5 days) post-surgical resection:
- Physical examination and vital signs (including weight, blood pressure, heart rate, temperature)
- ECOG performance status
- Review of concomitant medications
- Safety bloods: Haematology – full blood count, white cell count with differential and ANC, prothrombin time and international normalised ratio (INR); Biochemistry – sodium, potassium, calcium, magnesium, ALT, gamma-glutamyl transferase (GGT), bilirubin, albumin, creatinine, alkaline phosphatase, glucose, urea.
- Pregnancy test for women of childbearing potential
- ECG

- Assessment of AEs
- Assessment for any surgical complications including wound healing assessment.
- Cohorts F & G only: patient invited to consent to further trial treatment in Part 2 using the Part 2 Trial Treatment Patient Information sheet and consent form

Research blood sample collection:
- Research blood sample collection as specified in the PHOENIX Investigator Laboratory Manual.

SELECTION OF PATIENTS FOR TRIAL TREATMENT IN PART 2

All patients consent to follow-up after surgery at the time of Trial Entry. Trial pathway in Part 2 is dependent on cohort allocation i.e. HRD and gBRCA1/2 mutation status, and whether a patient is eligible and consents to further trial treatment in Part 2:

- Patients allocated to Cohort E (gBRCA1/2m negative and non-HRD), and patients allocated to either Cohort F or G who are ineligible for or non-consenting to further trial treatment, will receive SOC adjuvant treatment of Physician's Choice with 3 monthly follow-up and ctDNA blood sampling visits
- Patients allocated to either Cohort F or Cohort G, who consent to and are eligible for trial treatment in Part 2 will receive Olaparib and durvalumab in combination for 12 months with 4 weekly safety and ctDNA blood sampling visits. This will be followed by a further 12 months of 3 monthly follow-up and ctDNA blood sampling visits . Patients who are found to be ineligible for durvalumab treatment will receive Olaparib only.

Part 2 trial treatment for patients ineligible for durvalumab treatment:
Patients who do not fulfil eligibility criteria above for durvalumab treatment, and who remain eligible for olaparib, should receive olaparib monotherapy for 12 months (13 cycles) during Part 2.

Only patients allocated to Cohorts F and G who have consented to trial treatment in Part 2 can commence trial treatment post-surgery. The following pre-treatment assessments should be performed prior to commencing trial treatment in PART 2:

Assessments to be conducted within 28 days prior to commencing treatment:
- ECG
- Pre-treatment conditions
- Assessment for any surgical complications including wound healing assessment

Assessments to be conducted within 3 days prior to Cycle 1 Day 1:
- Physical examination and vital signs (including weight, blood pressure, heart rate, temperature)
- ECOG performance status
- Review of concomitant medications
- Safety bloods: Haematology – full blood count, white cell count with differential and ANC, prothrombin time and international normalised ratio (INR); Biochemistry – sodium, potassium, calcium, magnesium, ALT, gamma-glutamyl transferase (GGT), bilirubin, albumin, creatinine, alkaline phosphatase, glucose, urea.
- Pregnancy test for women of childbearing potential

For patients who received pembrolizumab as SOC, and who discontinued this following consent to trial treatment in Part 2, the above assessments required within 3 days of Cycle 1 Day 1 should only be conducted once the required washout period of 30 days has been completed .

Research blood sample collection:
- Research blood sample collection as specified in the PHOENIX Investigator Laboratory Manual.

PART 2 On-Treatment Assessments Cycle 2, Day 1 Pre-Treatment

The following assessments should be performed as close to as possible and within 3 days prior

to treatment administration:
- Physical examination and vital signs (including weight, blood pressure, heart rate, temperature)
- ECOG performance status
- Dosing compliance
- Review of concomitant medications
- Safety bloods: Haematology – full blood count, white cell count with differential and ANC, prothrombin time and international normalised ratio (INR); Biochemistry – sodium, potassium, calcium, magnesium, ALT, gamma-glutamyl transferase (GGT), bilirubin, albumin, creatinine, alkaline phosphatase, glucose, urea. In addition for patients receiving durvalumab: TSH
- ECG
- Review of AEs
- Pregnancy test for women of childbearing potential

Research blood sample collection:
- Research blood sample collection as specified in the PHOENIX Investigator Laboratory Manual (taken pre-dose for each cycle).

PART 2 On-Treatment Assessments Cycle 3 Onwards, Day 1 Pre-Treatment
The following assessments should be performed as close to as possible and within 3 days prior to treatment administration:
- Physical examination and vital signs (including weight, blood pressure, heart rate, temperature)
- ECOG performance status
- Dosing compliance
- Review of concomitant medications
- Safety bloods: Haematology – full blood count, white cell count with differential and ANC, prothrombin time and international normalised ratio (INR); Biochemistry – sodium, potassium, calcium, magnesium, ALT, gamma-glutamyl transferase (GGT), bilirubin, albumin, creatinine, alkaline phosphatase, glucose, urea. In addition for patients receiving durvalumab: TSH
- ECG
- Review of AEs
- Pregnancy test for women of childbearing potential

Research blood sample collection:
- Research blood sample collection as specified in the PHOENIX Investigator Laboratory Manual (taken pre-dose for each cycle).

PART 2 Treatment Discontinuation Assessments
The following assessments should be performed at the time of discontinuation of trial treatment for any reason:
- Physical examination and vital signs (including weight, blood pressure, heart rate, temperature)
- ECOG performance status
- Dosing compliance
- Review of concomitant medications
- Safety bloods: Haematology – full blood count, white cell count with differential and ANC, prothrombin time and international normalised ratio (INR); Biochemistry – sodium, potassium, calcium, magnesium, ALT, gamma-glutamyl transferase (GGT), bilirubin, albumin, creatinine, alkaline phosphatase, glucose, urea. In addition for patients receiving durvalumab: TSH
- ECG
- Review of AEs

Research blood sample collection:
- Research blood sample collection as specified in the PHOENIX Investigator Laboratory Manual.

PART 2 30 Days (and 90 Days for patients receiving durvalumab) Post-Treatment Discontinuation Assessments
The following assessments should be performed 30 (± 7) days (and 90 [± 7] days for patients receiving durvalumab) post-treatment discontinuation:
- Physical examination and vital signs (including weight, blood pressure, heart rate, temperature)
- ECOG performance status
- Review of concomitant medications
- Safety bloods: Haematology – full blood count, white cell count with differential and ANC, prothrombin time and international normalised ratio (INR); Biochemistry – sodium, potassium, calcium, magnesium, ALT, gamma-glutamyl transferase (GGT), bilirubin, albumin, creatinine, alkaline phosphatase, glucose, urea. In addition for patients receiving durvalumab: TSH
- ECG
- Review of AEs
- Pregnancy test for women of childbearing potential (30 day post-treatment discontinuation visit

PART 2 Post-Treatment Follow Up Assessments
All patients should be followed up at 3 monthly intervals (+/-2 weeks) from the end of trial treatment for 12 months or for a total of 24 months from the Part 2 pre-treatment assessment visit in case trial treatment is stopped earlier than 12 months; assessment should be in line with standard practice and should include:
- Survival and disease recurrence
- Further treatment

Research blood sample collection:
- Research blood sample collection as specified in the PHOENIX Investigator Laboratory Manual.

A recurrence tumour tissue sample should be provided at relapse for each patient who has tissue available from a biopsy or from surgery performed routinely as part of standard patient care.

PART 2 TRIAL ASSESSMENTS for Cohort E (and patients from Cohorts F & G who do not consent trial treatment in Part 2), should receive adjuvant treatment of physician's choice as clinically indicated and according to national and local guidance for dosing schedule, preparation, handling, warnings, precautions and contraindications. Treatment of physician's choice should be limited to only currently approved, and NHS available, therapies given as SOC in the trial eligible population. There are no protocol restrictions for treatment of physician's choice in terms of dose reductions permitted or treatment discontinuation, which will be based on Investigator's judgment. Details of treatment received should be documented on the appropriate eCRF within the trial database.

PART 2 Follow Up for patients allocated to Cohorts F and G who have consented to trial treatment in Part 2:
All patients should be followed up as per standard guidelines, including any investigation that is deemed clinically indicated, every 3 months (+/-2 weeks), with ctDNA blood sampling, for a total of 24 months post-surgery visit.

Assessment should be in line with standard practice and should include:
- Survival and disease recurrence
- Further treatment

An assessment for any surgical complications including wound healing assessment should be performed at the 3-month post-surgery visit only.

A recurrence tumour tissue sample should be provided at relapse for each patient who has tissue available from a biopsy or from surgery, performed routinely as part of standard patient care.

Research blood sample collection:
- Research blood sample collection as specified in the PHOENIX Investigator Laboratory Manual.

PART 2 Follow Up for patients allocated to Cohort E (and patients from Cohorts F & G who do not consent trial treatment in Part 2):
All patients should be followed up as per standard guidelines, including any investigation that is deemed clinically indicated, every 3 months (+/-2 weeks), with ctDNA blood sampling, for a total of 24 months post-surgery visit.

Assessment should be in line with standard practice and should include:
- Survival and disease recurrence
- Further treatment
-Assessment for any surgical complications including wound healing assessment

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.

Cohorts F-G:
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.
AND/OR
3. Changes in the plasma ctDNA (D0-D14) post WOP intervention compared to pre-treatment.

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Previous 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(s)
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.

Key secondary outcome(s)
Current secondary outcome measures as of 19/08/2025:

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.

1. Cohort E: Change in proliferation index and/or changes in proliferation gene expression signature and/or change in plasma ctDNA defined as per the primary endpoint for cohorts F-G.
2. Incidence of adverse events (AEs) during trial treatment (including surgical complications) by treatment cohort at 1 month post-surgery.
3. Methylation status of BRCA1 and RAD51C on diagnostic and pre- and post-WOP tumour samples and changes in methylation levels between these timepoints.

Previous 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.

Completion date
01/05/2029

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)

(added 19/08/2025):
Inclusion Criteria for Trial Registration (cohorts E-G)
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) Patients currently receiving SOC pembrolizumab, or having previously received SOC pembrolizumab but subsequently discontinued treatment, in combination with NACT are eligible for Trial Registration;
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;
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 participation in the trial.
10.Patients with clinical stage II or III disease or clinical suspicion of metastatic disease must have staging studies to exclude metastatic disease if this is standard of care, and staging methods should be used as per standard of care (axillary lymph nodes or internal mammary node involvement will not be regarded as evidence of metastatic disease);
11. 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;
12. 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;
13. Patients must be a) surgically sterile (i.e. if female have undergone a hysterectomy, bilateral salpingectomy or bilateral oophorectomy; if male have undergone a bilateral orchidectomy); b) have a sterilised sole partner; or c) be post-menopausal; or d) must agree to practice total/true abstinence; or e) use a condom and one highly effective form 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.
Post-menopausal is defined by at least one of the following criteria:
a. Amenorrhoeic for 1 year or more following cessation of exogenous hormonal treatments
b. Luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in the post-menopausal range for the institution for women < 50 years of age not using hormonal contraception or hormonal replacement therapy. Please note: in absence of amenorrhea for 1 year, a single LH and/or FSH measurement is insufficient.
c. Radiation-induced oophorectomy with last menses >1 year ago
d. Chemotherapy-induced menopause with >1 year interval since last menses
e. Surgical sterilisation (hysterectomy, bilateral salpingectomy or bilateral oophorectomy)

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) Patients currently receiving SOC pembrolizumab, or having previously received SOC pembrolizumab but subsequently discontinued treatment, in combination with NACT are eligible for Trial Registration;
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;
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 participation in the trial.
10.Patients with clinical stage II or III disease or clinical suspicion of metastatic disease must have staging studies to exclude metastatic disease if this is standard of care, and staging methods should be used as per standard of care (axillary lymph nodes or internal mammary node involvement will not be regarded as evidence of metastatic disease);
11. 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;
12. 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;
13. Patients must be a) surgically sterile (i.e. if female have undergone a hysterectomy, bilateral salpingectomy or bilateral oophorectomy; if male have undergone a bilateral orchidectomy); b) have a sterilised sole partner; or c) be post-menopausal; or d) must agree to practice total/true abstinence; or e) use a condom and one highly effective form 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.
Post-menopausal is defined by at least one of the following criteria:
a. Amenorrhoeic for 1 year or more following cessation of exogenous hormonal treatments
b. Luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in the post-menopausal range for the institution for women < 50 years of age not using hormonal contraception or hormonal replacement therapy. Please note: in absence of amenorrhea for 1 year, a single LH and/or FSH measurement is insufficient.
c. Radiation-induced oophorectomy with last menses >1 year ago
d. Chemotherapy-induced menopause with >1 year interval since last menses
e. Surgical sterilisation (hysterectomy, bilateral salpingectomy or bilateral oophorectomy)

Inclusion Criteria for Trial Entry (cohorts E-G):
1. Signed Informed Consent Form (ICF) for Trial Entry;
2. Residual disease is confirmed as at least one viable disease focus ≥1cm on trial-specific imaging performed at least 1 week following day 1 of the final cycle of NACT.
3. Provision of acceptable archival diagnostic tumour tissue sample prior to Trial Entry as defined in the Investigator Laboratory Manual.

4. Recovery from all acute adverse events of prior NACT or pembrolizumab 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.
5. Patients must have adequate haematological, renal and hepatic function as defined by:
- Haemoglobin (Hb) ≥ 10 g/dL (≥ 100 g/L) with no blood transfusion in the past 28 days
- Absolute neutrophil count (ANC) ≥ 1500/mm3 (≥ 1.5 x 109/L)
- Platelet count ≥100,000/mm3 (≥ 100 x 109/L)
- Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
- Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT)) ≤ 2.5 x institutional ULN
- Calculated creatinine clearance ≥51 mL/min using the Cockcroft-Gault equation (please refer to Appendix 4) or based on a 24 hour urine test or another validated test as per local practice
6. 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 on the day of planned trial treatment.
7. Confirmation that all Trial Registration inclusion criteria listed above, remain satisfied.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

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.

(added 19/08/2025):
Exclusion Criteria for Trial Registration (Cohorts E-G)
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:
a. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease;
b. 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 indicating uncontrolled, potentially irreversible cardiac conditions, as judged by the investigator (e.g., unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >470 msec, electrolyte disturbances, etc.), or patients with congenital long QT syndrome;
7. Patients unable to swallow orally administered medication;
8. Patients receiving therapeutic anti-coagulation treatment (including warfarin and novel oral anti-coagulants).
9. Patients with gastrointestinal disorder affecting absorption (e.g. gastrectomy, active peptic ulcer disease within last 3 months);
10.History of seizure or any condition that may predispose to seizure.
11. Other non-malignant systemic disease that would preclude trial treatment or would prevent required follow-up;
12. Pregnant or breast-feeding;
13. Prior exposure to PARP inhibitor, including olaparib, anti-PD-1 or anti-PDL1 immunotherapy (including durvalumab) except for pembrolizumab if received as standard of care in combination with neoadjuvant chemotherapy;
14.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;
15. Patients with a known hypersensitivity to pembrolizumab, durvalumab or olaparib or any excipients of the products;
16.Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT);
17. Active infection including tuberculosis (TB) (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (HBV; known positive HBV surface antigen (HBsAg) result), hepatitis C (HCV), or human immunodeficiency virus (HIV; positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA;

The following exclusion criteria will apply prior to Trial Entry. These criteria should be considered prior to Trial Registration with the expectation that the patient would not be excluded from Trial Entry based on these points:

1. History of clinically significant or uncontrolled cardiovascular disease including:
- Myocardial infarction within 6 months prior to Trial Entry;
- Uncontrolled angina within 3 months prior to Trial Entry;
- Congestive heart failure New York Heart Association (NYHA) class III or IV, or patients with history of congestive heart failure NYHA class III or IV in the past, unless an echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan performed within 3 months prior to Trial Entry results in a left ventricular ejection fraction that is 45%;

- History of clinically significant ventricular arrhythmias (e.g. ventricular tachycardia, ventricular fibrillation, torsades de pointes);
- History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place;
- Consistent evidence of hypotension as indicated by systolic blood pressure < 90 millimeters of mercury (mm Hg) prior to Trial Entry;
- Consistent evidence of bradycardia as indicated by a heart rate of < 50 beats per minute on the ECG prior to Trial Entry;
- Consistent evidence of uncontrolled hypertension as indicated by systolic blood pressure > 170 mm Hg or diastolic blood pressure > 105 mm Hg prior to Trial Entry.
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 the National Cancer Institute (NCI)'s Common Terminology Criteria for Adverse Events Version 5.0 (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 (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) within 2 weeks prior to first dose of trial treatment. The required washout period prior to commencing trial treatment is 2 weeks;
7. Concomitant use of known strong (e.g. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John’s Wort) or moderate (e.g. bosentan, efavirenz, modafinil) CYP3A inducers. The required washout period prior to commencing trial treatment is 5 weeks;
8. Whole blood infusion or erythropoietin within 28 days prior to trial entry (packed red blood cells and platelet transfusions are acceptable).
9. Receipt of live attenuated vaccine within 30 days prior to commencing trial treatment.

Date of first enrolment
01/11/2019

Date of final enrolment
01/02/2027

Locations

Countries of recruitment
United Kingdom

England

Wales

Study participating centre

Royal Bournemouth Hospital
Bournemouth
United Kingdom
BH7 7DW

Study participating centre
Christie Hospital NHS Trust
Manchester
United Kingdom
M20 4BX

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

ROR
https://ror.org/043jzw605

Funder(s)

Funder type
Industry

Funder Name
AstraZeneca

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

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

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	version 10.0		28/06/2023	No	No

Protocol file	23/04/2025	13/08/2025	No	No