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A study to characterise mechanisms of resistance to PARP inhibitors by analysing samples from women with ovarian cancer

Submission date
04/04/2022

Recruitment status
No longer recruiting

Registration date
21/04/2022

Overall study status
Ongoing

Last Edited
13/05/2025

Condition category
Cancer

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-of-parp-inhibitors-for-ovarian-cancer-pairs

Background and study aims
PARP inhibitors are a type of targeted cancer drug. The aim of this study is to collect tumour samples from women who are treated with PARP inhibitors and then analyse them to help us understand why some women benefit from PARP inhibitor therapy while others do not. This would enable us to use PARP inhibitors in the future in a more personalised way, sparing patients unlikely to benefit from the side effects of PARP inhibitors while ensuring those who will benefit receive PARP inhibition therapy.

Who can participate?
Patients aged 16 years and over with a diagnosis of high-grade serous, high-grade endometrioid or carcinosarcoma of the ovary, primary peritoneum or fallopian tube. Trial participants must have an available archival tissue sample from the time of their original diagnosis. They must have had prior treatment with a PARP inhibitor or be about to start maintenance treatment with a PARP inhibitor.

What does the study involve?
This is a sample collection study. Access to participants' archival pre-PARP inhibitor tumour sample will be requested. Blood samples will be taken from participants, alongside their routine blood tests. A biopsy (sample) will be taken if a participant's cancer gets worse during treatment with a PARP inhibitor. Clinical information about participants' cancer will be recorded. The samples will be examined in the laboratory to learn more about markers that predict sensitivity and resistance to PARP inhibitor treatment.

What are the possible benefits and risks of participating?
There is no direct medical benefit to participants. Women diagnosed with ovarian cancer in the future will benefit from an increased understanding of sensitivity and resistance to PARP inhibitors. This increased understanding should spare women who are unlikely to benefit from

PARP inhibitor treatment from the side effects of a PARP inhibitor and develop alternative treatments for those unlikely to benefit and for those who develop resistance to PARP inhibitors.
Participants having a biopsy may suffer from side effects. In general they may have bruising, pain and/or infection at the biopsy site. In order to minimise pain, local anaesthetic may be given prior to the biopsy procedure and painkillers may be prescribed afterwards. If an infection develops, it may require treatment with antibiotics. The risk of infection is estimated to be less than 1 in 100. In very rare cases, biopsy-associated bleeding may require a blood transfusion and /or intervention (radiological or surgical). Other adverse events due to a biopsy will depend on the location the biopsy is taken from. For example, if a lung biopsy is undertaken there would be a risk of pneumothorax (air around the outside of the lung which can sometimes cause shortness of breath). If CT guidance is used, there is a risk of allergic reaction to the contrast given to a patient before the CT to achieve good quality images. In rare cases, patients can suffer from renal impairment as a result of contrast. This CT would be extra to those that participants would have if they did not take part in this study. This procedure uses ionising radiation to form images of the body to aid biopsy. Ionising radiation can cause cell damage that may after many years or decades turn cancerous. In patients with the clinical condition being investigated, the chance of this happening is extremely small.

Where is the study run from?
NHS Greater Glasgow and Clyde (UK)

When is the study starting and how long is it expected to run for?
February 2021 to May 2026

Who is funding the study?
1. Wellbeing of Women (UK)
2. Artios Pharma Limited (UK)

Who is the main contact?
1. Dr Patricia Roxburgh, patricia.roxburgh@glasgow.ac.uk
2. Karen Allan, Karen.Allan.3@glasgow.ac.uk

Contact information

Type(s)
Principal investigator

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Type(s)

Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
297051

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
PAIRS-2021, IRAS 297051, CPMS 51118

Study information

Scientific Title
PArp Inhibitor Resistance Study

Acronym
PAIRS

Study objectives
This study aims to build a cohort of paired tumour samples (pre-PARP inhibitor [PARPi] and post-PARPi) to allow comprehensively assess the mechanisms of PARPi resistance, many of which have only been reported in in vitro studies and report their relative frequencies.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 03/12/2021, West of Scotland REC 5 (West of Scotland Research Ethics Service, Ward 11, Dykebar Hospital, Grahamston Road, Paisley, PA2 7DE, UK; +44 (0)141 314 0213; WoSREC5@ggc.scot.nhs.uk), ref: 21/WS/0128

Study design
Multi-centre non-randomized sample collection study

Primary study design
Observational

Study type(s)
Treatment

Health condition(s) or problem(s) studied
High-grade ovarian cancer

Interventions
Cohort A and B:
Imaging-guided (ultrasound or CT), intra-operative or other suitable biopsies will be taken for research purposes from women who have a tumour progressing on PARPi, meet the eligibility criteria and who give written, informed consent.

Cohorts A, B and C:
Blood will be taken to examine circulating markers of PARPi resistance.
1. Serially (3-4 monthly) for cohort A
2. At progression for cohort B
3. At recruitment for cohort C if the patient is surviving
Archival tissue will be accessed. Associated clinical data will be recorded.

Intervention Type
Other

Primary outcome(s)
Number of PARPi resistant tumours (collected at progression) and matched pre-PARPi tumour samples (collected at baseline) obtained during the recruitment period

Key secondary outcome(s))
1.1. Homologous recombination repair (HRR) gene aberration status using whole exome sequencing (WES) and RNAseq in pre-PARPi tumour samples collected at baseline.
1.2. Homologous recombination (HR) status in pre-PARPi tumour samples collected at baseline, assessed by sequencing of homologous recombinational repair genes
1.3. Status of methylation of HRR genes, assessed by EPIC array in pre-PARPi tumour samples collected at baseline
1.4. HRR gene aberration status in post-PARPi tumour sample collected at progression using WES and RNAseq (where relevant)
1.5. HR status in post-PARPi tumour samples collected at progression for cases previously found to have HRD disease, assessed by sequencing of homologous recombinational repair genes
1.6. Methylation status, assessed by EPIC array in post-PARPi tumour samples collected at progression for cases previously found to have a methylation event in their pre-PARPi tumour.
1.7. Status of other pathways implicated in PARPi resistance as determined by proteomic and

other analysis in pre and post-PARPi tumour samples, collected at baseline and progression respectively.
1.8. Proportion of tumours with each resistance mechanism, determined by statistical analysis at the end of the study
2. Proportion of patients where resistance mechanism can be identified in ctDNA, determined by statistical analysis at the end of the study
3. Proportion of patients where resistance mechanism can be identified in ctDNA prior to detection of disease progression by standard clinical assessments (treatment visits), determined by statistical analysis at the end of the study

Completion date
01/05/2026

Eligibility

Key inclusion criteria
Current inclusion criteria as of 07/04/2025:
All patients:
1. Age ≥16 years
2. Histological diagnosis of high-grade serous, high-grade endometrioid or carcinosarcoma of the ovary, primary peritoneum or fallopian tube
3. Availability of formalin-fixed, paraffin-embedded tissue taken at the time of original diagnosis of high-grade serous ovarian cancer. This may be primary surgical debulking specimen OR core biopsy. For those with only a core biopsy from time of diagnosis, availability of specimen taken at interval debulking surgery is also requested.
4. Prior treatment with a PARP inhibitor or about to commence maintenance PARPi therapy (cohort A). PARPi can be single agent or in combination with bevacizumab. If PARPi is in combination with a different agent as part of a clinical trial, the patient may still be eligible but this should be confirmed with the Cancer Research UK Glasgow Clinical Trials Unit prior to patient registration.

Cohort A:
1. Patients need to be progression-free (defined by no evidence of GCIG Ca125 progression or radiological progression)
2. No contraindication to biopsy
3. Ability to provide written informed consent prior to participating in the study and any study-related procedures being performed
4. Willingness to comply with trial procedures
5. Life expectancy >3 months
6. About to commence, currently receiving PARPi as maintenance therapy or completed PARPi maintenance with no intervening treatment before study entry.

Cohort B:
1. Patients need to have radiologically defined progressive disease on PARPi
2. Patients must have disease deemed suitable for imaging-guided biopsy (ultrasound or CT) by an experienced radiologist or suitable for intra-operative biopsy during secondary debulking surgery as determined by an experienced gynaecological oncology surgeon. Other biopsies, such as skin deposits, are also acceptable. However, this must be confirmed with the Cancer Research UK Glasgow Clinical Trials Unit prior to patient registration (for cohort B).
3. No contraindication to biopsy
4. No systemic anti-cancer treatment (SACT) commenced post PARPi (patients continuing PARPi

after surgical resection of a progressing lesion can be included). Patients who have received 1-2 cycles of SACT whilst awaiting surgery may still be eligible for the study, please contact CTU to discuss prior to registration.
5. Ability to provide written informed consent prior to participating in the study and any study-related procedures being performed
6. Willingness to comply with trial procedures
7. Life expectancy >3 months

Cohort C:
1. Patients need to have had a lesion which radiologically progressed on PARPi
2. Archival tumour of a lesion progressing post PARPi must be available
3. Ability to provide written informed consent prior to participating in the study and any study-related procedures being performed. Patients with available archival pre and post-PARPi tumour samples, who are no longer living may be identified by their clinical team and registered for the study if samples were collected under generic research consent (or equivalent).

Previous inclusion criteria:
All patients:
1. Age ≥16 years
2. Histological diagnosis of high-grade serous, high-grade endometrioid or carcinosarcoma of the ovary, primary peritoneum or fallopian tube
3. Availability of formalin-fixed, paraffin-embedded tissue taken at the time of original diagnosis of high-grade serous ovarian cancer. This may be primary surgical debulking specimen OR core biopsy. For those with only a core biopsy from time of diagnosis, availability of specimen taken at interval debulking surgery is also requested.
4. Prior treatment with a PARP inhibitor or about to commence maintenance PARPi therapy (cohort A). PARPi can be single agent or in combination with bevacizumab. If PARPi is in combination with a different agent as part of a clinical trial, the patient may still be eligible but this should be confirmed with the Cancer Research UK Glasgow Clinical Trials Unit prior to patient registration.

Cohort A:
1. Patients need to be progression-free (defined by no evidence of GCIG Ca125 progression or radiological progression)
2. No contraindication to biopsy
3. Ability to provide written informed consent prior to participating in the study and any study-related procedures being performed
4. Willingness to comply with trial procedures
5. Life expectancy >3 months

Cohort B:
1. Patients need to have radiologically defined progressive disease on PARPi
2. Patients must have disease deemed suitable for imaging-guided biopsy (ultrasound or CT) by an experienced radiologist or suitable for intra-operative biopsy during secondary debulking surgery as determined by an experienced gynaecological oncology surgeon. Other biopsies, such as skin deposits, are also acceptable. However, this must be confirmed with the Cancer Research UK Glasgow Clinical Trials Unit prior to patient registration (for cohort B).
3. No contraindication to biopsy
4. No systemic anti-cancer treatment (SACT) commenced post-PARPi (patients continuing PARPi after surgical resection of a progressing lesion can be included)
5. Ability to provide written informed consent prior to participating in the study and any study-related procedures being performed

6. Willingness to comply with trial procedures
7. Life expectancy >3 months

Cohort C:
1. Patients need to have had a lesion which radiologically progressed on PARPi
2. Archival tumour of a lesion progressing post PARPi must be available
3. Ability to provide written informed consent prior to participating in the study and any study-related procedures being performed. Patients with available archival pre and post-PARPi tumour samples, who are no longer living may be identified by their clinical team and registered for the study if samples were collected under generic research consent (or equivalent).

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
16 years

Sex
Female

Key exclusion criteria
Current exclusion criteria as of 07/04/2025:
1. Ovarian, primary peritoneal or fallopian tube cancer of low-grade serous, grades 1 or 2 endometrioid, clear cell or mucinous subtypes
2. Borderline/low malignant potential tumours
3. Any non-epithelial ovarian malignancy
4. Original diagnosis of high-grade serous cancer made on cytology only
5. Discontinued PARPi for toxicity within 3 months of starting PARPi. (exclusion applies to cohorts B & C only). Patients who are recruited to cohort A at initiation of PARPi and subsequently discontinue within 3 months for toxicity will be replaced. Cohort A patients who progress and discontinue PARPi within 3 months will be included in the analysis and will not be replaced
6. Any other severe concurrent disease which may increase the risk associated with trial participation
7. Any psychological, familial, sociological or geographical considerations potentially hampering compliance with the trial and follow-up schedule

Previous exclusion criteria:
1. Ovarian, primary peritoneal or fallopian tube cancer of low-grade serous, grades 1 or 2 endometrioid, clear cell or mucinous subtypes
2. Borderline/low malignant potential tumours
3. Any non-epithelial ovarian malignancy
4. Original diagnosis of high-grade serous cancer made on cytology only
5. Discontinued PARPi for toxicity within 3 months of starting PARPi
6. Any other severe concurrent disease which may increase the risk associated with trial

participation
7. Any psychological, familial, sociological or geographical considerations potentially hampering compliance with the trial and follow-up schedule

Date of first enrolment
26/07/2022

Date of final enrolment
01/07/2025

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Beatson West of Scotland Cancer Centre
1053 Great Western Road
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Study participating centre
Western General Hospital
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Study participating centre
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Study participating centre

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Study participating centre
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Study participating centre
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Study participating centre
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Sponsor information

Organisation
NHS Greater Glasgow and Clyde

ROR
https://ror.org/05kdz4d87

Funder(s)

Funder type
Charity

Funder Name
Wellbeing of Women

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Funder Name
Artios Pharma Company Ltd

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Cohort A version 1.1	04/11/2021	13/04/2022	No	Yes
Participant information sheet	Cohort B version 1.1	04/11/2021	13/04/2022	No	Yes
Participant information sheet	Cohort C version 1.1	04/11/2021	13/04/2022	No	Yes
Participant information sheet	version 2.0	23/11/2023	07/04/2025	No	Yes
Participant information sheet	version 2.1	12/01/2024	07/04/2025	No	Yes
Participant information sheet	version 2.1	12/01/2024	07/04/2025	No	Yes
Protocol file	version 1	17/09/2021	13/04/2022	No	No
Protocol file	version 2.1	24/05/2024	07/04/2025	No	No