(To be presented on local headed paper)

ATARI

ATr inhibitor in combination with olaparib in gynaecological cancers with **ARI**d1A loss or no loss

PATIENT INFORMATION SHEET FOR REGISTRATION (TISSUE SCREENING)

We are inviting you to be registered for a clinical trial

- We are inviting you to take part in a clinical trial called **ATARI**.
- Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve.
- Please take time to read the following information carefully. Discuss it with friends and relatives and your GP if you want. Take time to decide if you wish to take part.
- You are free to decide if you want to join this research study. If you choose not to take part, this will not affect the care you get from your own doctors in any way.
- You can decide to stop taking part in the study at any time without giving a reason.
- Ask your study doctor if anything is not clear or if you would like more information.

Contents

Important things that you need to know

- The ATARI trial consists of two parts – a tissue screening part and a treatment part.
- This information sheet describes the tissue screening part of the ATARI trial.
- There are separate information sheets to describe the treatment part of the trial. You will be given the relevant information sheet if your tissue screening result means that you could be eligible to consider taking part.
- All of the information you will need to know to make a decision about whether to participate in the screening part can be found in this information sheet.
- You will be able to find further details on why we are doing this trial, why you have been invited and what will be involved if you decide to take part.

How to contact us

If you have any questions about this study, please talk to your doctor at
Hospital Department
Hospital
Address
Address
Tel: XXXX XXX XXX

Research nurse: [name and contact number]
Out of hours contact tel:

1 Why are we doing this study?

ATARI is a clinical trial that has been designed based on laboratory research which shows that cancers with a specific abnormality (mutation) in a gene, a unit of DNA, called **ARID1A** are more likely to be killed by a new class of anti-cancer therapy called **ATR inhibitors**. This molecular abnormality ('ARID1A loss') is known to be present more commonly in some specific types ('subtypes') of gynaecological cancers than others. Research has also shown that ATR inhibitors might still kill cancers which do not have an ARID1A mutation ('ARID1A no loss') when they are taken together with another type of drug called a PARP inhibitor.

To test this, the ATARI trial is designed to assess the response (tumour shrinkage) in different groups (cohorts) of patients selected based on their cancer cell subtype and the presence of an abnormality in ARID1A.

The purpose of the **tissue screening part** of the ATARI study is to profile patients to determine their cancer cell subtype and identify if they have an ARID1A mutation.

Depending on the results from this tissue screening, you may be offered the opportunity to take part in the **treatment part** of the trial and undergo treatment with a new drug called ceralasertib either on its own or in combination with another drug called olaparib.

What are mutations?

Cells within the body contain genetic information stored in the form of DNA, a molecule which holds instructions for building proteins necessary for all functions in the body. Permanent changes in the DNA sequence are known as **mutations**. Cancer cells contain mutations which change the way the cell functions, and makes them behave differently to normal cells. There are many different types of ovarian and endometrial (lining of uterus) cancers, which are defined by the mutations present within the cancer cells.

The most common way to identify these mutations is by the analysis of a tumour sample obtained either at surgery or during a biopsy, a procedure for collection of a small sample of tumour tissue. This could be assessed using a tumour sample previously collected during diagnosis of your disease (known as an archival sample) or a newly collected sample (known as a fresh sample).

Mutations and ovarian or endometrial cancer

The different types of ovarian and endometrial cancers are divided into various histological (tissue) subtypes, including (but not limited to) '**clear cell**'. Clear cell carcinomas (either ovarian, endometrial or endometriosis-related), as well as some other subtypes of gynaecological cancers (endometrioid, carcinosarcoma or cervical cancer), have been shown to share similar mutations in DNA, including a change in a specific gene, called 'ARID1A'. This gene is known as a **tumour suppressor gene**. The ARID1A gene provides instructions for building the ARID1A protein, a protein usually involved in DNA repair within normal cells. ARID1A helps to prevent cells with abnormal DNA from multiplying, helping to stop the development of tumours. A mutation within the ARID1A gene damages the protein building instructions, causing a "loss" of the protein. ARID1A is often found to have lost function in ovarian and endometrial clear cell cancers. The full significance of these gene mutations is still not fully known. However, loss of ARID1A function in tumour samples has been linked to the development of **resistance** to chemotherapy treatment. Resistance to treatment is when tumour cells no longer respond to the cancer treatment and the tumour grows ('progresses') or comes back again ('relapses').

Targeted Treatment

Due to the development of treatment resistance cancer research is now focussed on developing treatments tailored to the patient, that specifically act on (target) the particular mutations within their cancer cells. Treatments that target specific mutations within the cancer cells are known as '**targeted therapy**', and have led to significant improvements in the treatment of various cancers.

ARID1A loss occurs in quite a high number of ovarian,endometrial and endometriosis related clear cell cancers and some other subtypes of

gynaecological cancers (endometrioid, carcinosarcoma or cervical cancer), but these tumour types currently do not have any specific targeted therapy. **Ceralasertib** is a new, unlicensed drug which is being investigated in this trial for treatment of these specific types of cancer. ceralasertib belongs to a class of drugs called **Ataxia Telangiectasia and RAD3-related protein (ATR) inhibitors**. Ceralasertib is a drug which inhibits a protein called ATR kinase which helps cancer cells grow, multiply and spread. Recent work has shown an effect of ATR inhibitors on tumour cells that have lost the function of ARID1A protein. This suggests that there may be a role for these drugs in ARID1A-loss cancers.

As part of this trial, we are specifically looking at patients with relapsed ovarian,endometrial or endometriosis-related clear cell cancers who either have or have not lost function in ARID1A, and to establish the effectiveness of treatment with ceralasertib with or without olaparib. Patients with other relapsed gynaecological cancers (endometrioid, carcinsarcoma or cervical) are also being invited to participate.

In summary, the aims of the main clinical trial are:

i) To confirm whether a new drug called ceralasertib is effective, either on its own or in combination with another drug called olaparib, against relapsed ovarian and/or endometrial clear cell carcinoma.

ii) To confirm if a particular group of patients are more suitable for treatment with ceralasertib, or ceralasertib in combination with olaparib, than others.

The treatments being studied and what is involved in participating in the treatment part of the trial are described in more detail in separate information sheets.

2 Why am I being asked to take part?

Your doctor believes you may be suitable to take part in this trial because you have been diagnosed with relapsed ovarian, endometrial or endometriosis-related clear cell carcinoma or relapsed endometrioid, carcinosarcoma or cervical cancer, and your treatment options are being considered. If this tissue screening shows that you might be suitable for the treatment part of the trial, your doctor may offer you the option to participate. You will be given another Patient Information Sheet providing more detail on the treatment to be received and what taking part would mean for you. In that case, you will still need to have additional tests to check if you fulfil all the safety and eligibility requirements. We will be inviting patients with relapsed gynaecological cancers of specific sub-types from hospitals both across the UK and internationally to be screened for the trial.

3 What will I need to do if I take part?

Once you have read this information sheet, if you agree to take part in this study, you will be asked to sign a consent form before any study related procedures are performed. You will be asked to donate some of the tumour tissue that was taken as a biopsy or at surgery, when you were first diagnosed with ovarian,endometrial or endometriosis-related cancer or at any time prior to this study. This tissue will be checked to confirm the type of cancer and used to test for an ARID1A mutation.

If there is no tissue (or not enough) available, your doctor will discuss this with you. You may be asked to undergo a fresh tissue biopsy instead to assess your tumour, which will be necessary to enter the trial. If you have previously had your tumour sequenced as part of standard care or in another trial, please let your doctor know as you may be eligible for ATARI trial entry without repeating the tissue assessment, providing specific criteria have been met. If that is the case, you will be asked to give your consent for us to have access to this information.

Your donated samples will be sent to specialist laboratories at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research to test

for the type of ovarian or endometrial cancer you have and your ARID1A status. Once the samples arrive at the laboratories, the results of the tests will be available after approximately one week. In a few cases, when the samples are very old or do not contain enough tumour, the laboratory might not be able to test the tissue and will ask your doctor whether another sample is available. It might then take longer to obtain a test result for you, but your doctor will be able to inform you if this is the case.

The results will then be sent to your doctor who will tell you if you are eligible to be assessed for the treatment part of the trial. The results of this tissue screening will not benefit you in any way and are being done for research purposes only. If you are found to be eligible for the main study, your doctor will inform you in more detail about the required procedures, risks and potential benefits. You will then be able to make a final decision about whether you want to participate in the main study or not and signing a specific consent form if you wish to take part.

Checks and Tests

Accepting to take part in the tissue screening part of this study will not require any further hospital visits. If you agree to participate in the main part of the trial you will be informed of any additional visits and tests that will be required.

4 What are the possible benefits and disadvantages of taking part?

What are the possible benefits of taking part in this screening study?

There are no direct benefits from taking part in the tissue screening part of the trial. The main purpose is to see if you are eligible to take part in the treatment part of the trial.

What are the possible disadvantages and risks of taking part in this study?

If you hold private medical insurance, you should check with the company issuing the insurance before agreeing to take part in this clinical study, as you will need to ensure that your taking part will not affect the insurance.

You may be asked to undertake a fresh tissue biopsy if there is not enough archival tissue available to screen you for the trial. A biopsy is the removal of a small piece of tissue from the tumour. All biopsies in ATARI will be taken using a biopsy needle through the skin. The doctor will usually collect 2–4 samples and the whole procedure should take about 30 minutes to do.

Your doctor will discuss the best way to obtain a biopsy in your case. The biopsy site will be depend on the accessibility of the site to minimise any risk involved. The biopsy may be done by a surgeon or a radiologist, who may use an ultrasound or CT scan to see where the tumour is. You may have an anaesthetic first to numb the area. It may still be painful or a little uncomfortable afterwards, but mild painkillers such as paracetamol should help.

Irrespective of how the biopsy is performed, this will be done under sterile conditions using standard biopsy procedures in place at your hospital. The risks of biopsies include infection at the site of biopsy, although with proper sterilisation this complication is very rare. The biopsy may also be uncomfortable and bruising at the biopsy site or bleeding from the puncture wound may occur. The chance of minor bruising or bleeding is increased if you are taking aspirin, clopidogrel, anti-blood clotting medication (anti-coagulants) such as warfarin, and/or non-steroidal anti-inflammatory drugs such as ibuprofen. Depending on the site of the biopsy there may be a risk of damage by the biopsy needle to the surrounding area. Therefore tissue samples will be obtained only when it is safe for you and practical to do so. An allergic or other unwanted reaction to the numbing or sedative medicine used in the procedure may also occur.

Additional risks of a biopsy depend on the area of the body being biopsied. Biopsies will be done in different ways in different patients, therefore the specific risks and how likely they are to occur will vary according to the biopsy type, the type of anaesthetic and your general health. The doctor performing the biopsy will talk to you about the risks associated with the biopsy in your individual case.

Your doctor or nurse will give you information about how to care for the biopsy wound. Very few biopsies start to bleed again. If this does happen, press on the area with a clean cloth. This will help your blood to clot and the bleeding to stop. If it does not stop please contact your doctor. Some wounds may require some stitches, which will need to be removed after a few days; your doctor or nurse will give you information about how to arrange this.

5 Samples and ARID1A status

What samples will I be asked to donate?

We ask that all patients donate some of their tumour tissue from an existing sample taken at the time of diagnosis, during surgery or during any other biopsy. You may be asked to undergo a fresh biopsy if not enough tissue is available from these samples.

Will the results be used to determine my treatment?

You may be eligible to participate in the main part of the ATARI trial. If you are found to be eligible for the main part of this trial, your doctor will give you further information about the treatments being studied and what is involved. Entry into the main part of the trial is completely up to you, if you do decide you would like to take part you will be given a separate consent form to sign.

Can I access the screening results from my tumour sample?

You will not be sent a copy of the report, but your trial doctor will have access to your screening results. You can ask them to share the results with you.

It is important to note that the results are generated in a research environment within ATARI and that we are only screening for the ARID1A status of the tumour sample, **not** all possible mutations present.

What will happen to samples I give?

The group of medical professionals overseeing the ATARI trial will also oversee the sample collection.

Your tumour tissue may be labelled with your study registration ID number, date of birth and hospital pathology number when they are sent to the research lab. When they arrive at the laboratory they will be coded and personal details removed. The coding will maintain your confidentiality whilst allowing your tumour's biological details to be compared to the treatment findings.

The tumour samples will be stored securely at the Royal Marsden Translational Diagnostic Laboratory whilst they are being analysed and then transferred to the biobank at the Institute of Cancer Research Centre of Molecular Pathology (CMP) Laboratory.

Your ARID1A status will be determined using a non-CE marked immunohistochemical (IHC) assay. The test will be performed in a GCLP accredited diagnostic laboratory at The Royal Marsden (the ATARI central laboratory). The ATARI trial immunohistochemical assay will be performed at the ATARI central laboratory and used on the premises of manufacture, in accordance with the Guidance on the In Vitro Diagnostic Medical Devices Directive 98/79/EC (August 2013). All assays will be subject to strict validation prior to use.

Surplus archival tumour and biopsy material will be stored at The Institute of Cancer Research CMP biobank indefinitely and in some cases returned to the local laboratories after the study is complete, depending on local practice. You are being asked to give permission for possible future research using these samples. If you agree to allow your tissue to be stored and used for future research, samples may be shared with other organisiations including transferring samples outside UK. The confidential nature of the tissue and associated data will be fully protected with identifiable information removed. Any other research using your tissue will first need to be reviewed and approved by an ethics committee.

6 More information about taking part

Do I have to take part in the screening study?

No, your participation in screening is voluntary. It is up to you to decide whether or not you wish to

take part. If you choose not to participate, you will not be disadvantaged in any way and your future medical treatment will not be affected. If you do decide to take part you will be given this patient information sheet and a consent form to read carefully and to sign. A copy of the signed patient information sheet and consent form will be provided to you for your records.

Will my GP be involved?

Yes, your GP will be notified about your participation in this study. By signing the consent form you are agreeing to this.

Who is organising and funding the study?

The Chief Investigator of the trial is Dr Susana Banerjee, who is based at The Royal Marsden Hospital in Sutton (also the lead site for the trial). The research trial is being carried out by a network of doctors across the UK and internationally in France and Canada. The trial is co-ordinated by The Institute of Cancer Research. The research trial is approved and endorsed by Cancer Research UK. AstraZeneca, the company who manufacture ceralasertib and olaparib, are supplying the drugs free of charge and providing funding to support the trial. The Lady Garden Foundation charity has also provided funding to support the trial.

Your doctor will not personally receive any payments for including you in this research trial.

Will I be compensated?

No, there is no compensation for participating in this trial. We are also unable to reimburse any travel costs incurred as part of your participation.

Who has reviewed the ATARI trial?

The trial has been approved by Cancer Research UK's Clinical Research Committee, The National Institute for Health Research, one of the UK National Research Ethics Committees, the Health Research Authority (HRA) and the UK Regulatory Agency (Medicines and Healthcare Regulatory Agency, MHRA).

How will confidentiality be maintained?

The Institute of Cancer Research is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The Institute of Cancer Research will keep identifiable information about you for at least 5 years after the study has finished.

The Institute of Cancer Research's lawful basis for processing your information is for the performance of a task carried out in the public interest and it is necessary to process sensitive health and genetic information for the purposes of scientific research with appropriate safeguards in place to protect personal information, as required by the General Data Protection Regulation (GDPR).

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at:
www.icr.ac.uk/our-research/centres-and-collaborations/centres-at-the-icr/clinical-trials-and-statistics-unit/transparency.

[Insert appropriate name for NHS site] will collect information from you and your medical records for this research study in accordance with our instructions.

[Insert appropriate name for NHS site] will use your full name, hospital number, date of birth, postcode and NHS number (or Community Health Index (CHI) and/or hospital number in Scotland) to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study.

All information which is collected about you during the study will be kept strictly confidential. When you enter the tissue screening part of the study, your initials and full date of birth will be passed to The Institute of Cancer Research Clinical Trials and

Statistics Unit (ICR-CTSU) where the study is being coordinated. If you are eligble and enter the main part of the study your full name, post code, hospital number and NHS/CHI number will additionally be passed to ICR-CTSU. You will be given a unique study ID number, which will be used together with your initials and date of birth on forms that the research staff at your hospital will send to ICR-CTSU. All information about you will be stored securely. It will be treated as strictly confidential and nothing that might identify you will be revealed to any third party. Only members of the research teams at your hospital and the ICR-CTSU will have access to the information that could allow this study ID number to be linked to you.

Representatives from the ICR-CTSU, the NHS Trust relevant to your taking part in the research and the ethics committee reviewing the study may need to see your hospital and clinic records to the extent permitted by applicable laws and regulations to make sure the information is received as correct. All information will be kept confidential.

[Insert appropriate name for NHS site] will keep identifiable information about you from this study for at least 5 years after the study has finished.

Data Sharing

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

Your information could be used for research in any aspect of health or care, and could be combined with information about you from other sources held by researchers, the NHS or government. Where this information could identify you, the information will be held securely with strict arrangements about who can access the information. The information will only be used for the purpose of health and care research, or to contact you about future opportunities to participate in research. It will not be used to make decisions about future services available to you, such as insurance.

Where there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee

Our main privacy policy can be found at https://www.icr.ac.uk/legal/privacy. If you have any questions about your rights under the GDPR or how we use your information please contact our Data Protection Officer at dataprotectionofficer@icr.ac.uk

What if something goes wrong?

If you have any concerns about any aspects of the study you should ask to speak with your study doctor or research nurse who will do their best to answer your questions. If you remain unhappy and wish to complain about any aspect of the way you have been approached or treated during the course of this trial, the normal National Health Service complaints mechanisms are available to you. We recommend that you obtain a copy of your hospitals complaints procedure or policy if you intend to make a complaint. Concerns should be raised by speaking to a member of staff at your hospital or by talking to the local Patient Advice and Liaison Service (PALS), which has been established in every NHS Trust and Primary Care Trust (PCT).

Healthcare professionals working on clinical trials are covered by NHS Indemnity, and if you are harmed by taking part in this trial you may have grounds for a legal action, but you may have to pay for it.

7 Contacts for further information

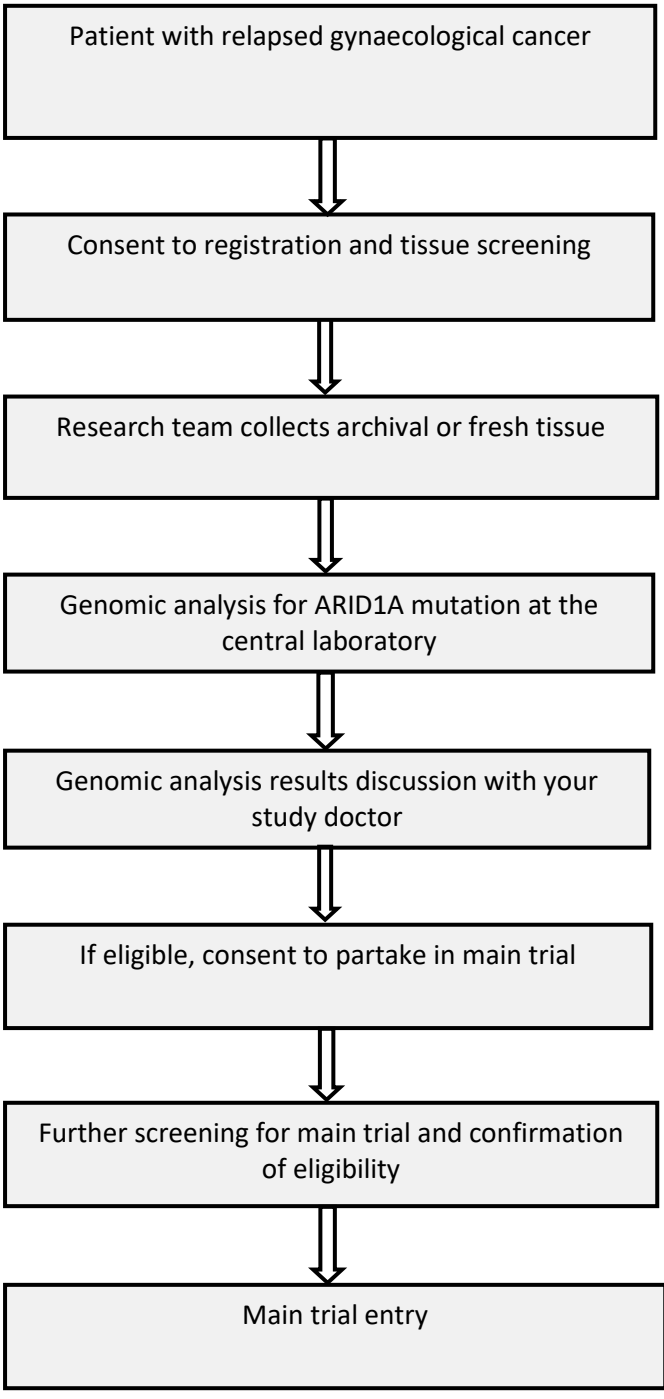
You have the right to ask questions about this study at any time and are encouraged to do so. You can call the study doctor or hospital if you believe you have been injured as a result of your receiving study treatment, or if you have any questions about this study or your participation in this study.

Macmillan Cancer Support is a registered charity providing information, emotional support and publications about all aspects of cancer for cancer

patients and their families. You can contact one of their Cancer Information Nurse Specialists on the Macmillan Support Line; Freephone 0808 808 00 00, Monday to Friday, 9.00am to 8.00pm. In addition to their nurses, the Macmillan Support Line also has other specialist teams that can provide advice and information relating to welfare benefits, financial issues and everyday practical concerns. You can learn more about clinical trials on the Cancer Research UK's patient website (www.cancerhelp.org.uk).

Thank you for taking the time to consider taking part in this study.

ATARI Screening Flow Chart



IRAS number : XXXXXX REC Ref: XX/XX/XXX

Patient's Hospital Number: Trial Entry number (ID):

Name of clinician: Centre:

ATARI: ATr inhibitor in combination with olaparib in gynaecological cancers with ARId1A loss or no loss

ATARI REGISTRATION CONSENT FORM

Please initial to confirm

1. I confirm that I have read and understand the ATARI Registration information sheet *version __ dated ___/___/___* for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐	
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐	
3. I agree to take part in the registration pre-screening for the ATARI trial. I understand that this will require further tests to confirm eligibility.	☐	
4. I give consent for my historical tumour tissue taken at the time of my disease diagnosis (or any time before joining this study) to be used within the ATARI trial. I consent for the investigators to request and collect samples from tumour biopsies or excisions relating to my gynaecological cancer performed in the past either in this or another hospital.	☐	
5. In the instance that no histological specimen is available I consent to a fresh tissue biopsy for confirmation of histological subtype and ARID1A status	☐	N/A ☐
6. I understand that my samples may be labelled with my study registration ID number and date of birth when they are sent to the Institute of Cancer Research and Royal Marsden Hospital. My tissue sample will also be labelled with my hospital pathology number.	☐	
7. I understand that my clinical samples may be sent to other institutions as explained in the Patient Information Sheet.	☐	
8. I understand that sections of any of my medical notes may be looked at by responsible individuals from the research team, from regulatory authorities, ethics committees, Astra Zeneca (the pharmaceutical company who manufacture ceralasertib) and third parties approved by ICR-CTSU or from the NHS Trust where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	☐	
9. I agree that data will be passed to The Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU) and that my name, date of birth, hospital number, post code and NHS number (CHI number in Scotland) will be given when I join the	☐	

trial. Thereafter I will be identified by a unique trial number, initials and date of birth.			
10. I consent to my samples being stored for possible future research, with the understanding that the confidential nature will be protected, and that ethics committee approval will be obtained before any future research is conducted (**optional**).	Yes ☐	No ☐	
11. I consent to the possible future sharing of information collected about me, including biological material, with other organisations which may be outside the European Economic Area (EEA), with the understanding that I will not be identifiable from this information (**optional**).	Yes ☐	No ☐	
12. If prior tumour sequencing has been conducted to determine my ARID1A status outside of the ATARI trial, I consent for my ARID1A results to be provided to ICR-CTSU and the ATARI central laboratory (**optiona**l). If Yes, name of study for which ARID1A testing was performed: _____	Yes ☐	No ☐	N/A ☐

_____ _____ _____
Name of patient Signature Date

I confirm that I have explained the nature, purposes and foreseeable effects of the trial to the subject whose name is printed above.

_____ _____ _____
Name of person taking consent Signature Date

_____ _____ _____
Name of researcher (if different from above) Signature Date

One copy for participant, one copy for medical records and original to be kept in site file