(To be printed on local hospital headed paper)

TOPARP Part B

Trial of Olaparib in Patients with Advanced Castration Resistant Prostate Cancer.

PART B MAIN TRIAL PATIENT INFORMATION SHEET

TOPARP: Trial of Olaparib in Patients with Advanced Castration Resistant Prostate Cancer

We are inviting you to take part in a clinical study

- We are inviting you to take part in a clinical trial called TOPARP for patients who have been diagnosed with advanced prostate cancer. Part 1 of this information sheet tells you the purpose of the trial and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the trial.
- Before deciding to take part, please take time to read this information carefully and discuss it with friends and relatives if you wish. Please ask your doctor or nurse if there is anything you do not understand or if you want more information.
- Thank you for taking the time to read this information.

Part One: About the TOPARP trial

1 Important information

What is the purpose of this study?

The main aims of this clinical trial are:

- To confirm whether a new drug called olaparib is effective against advanced prostate cancer.
- To find out if a particular group of patients are more suitable for olaparib treatment than others.

Why am I being invited to take part?

You have been invited to participate in this research study because you have been diagnosed with advanced prostate cancer that is no longer responding to standard treatment and have qualified for screening for the main part of the TOPARP study following pre-screening analysis of your tumour. This part of the study is trying to find out whether a new oral treatment called olaparib, is effective in prostate cancer.

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How to contact us

If you have any questions about this study, please talk to your doctor at
Hospital Department
Hospital
Address
Address
Tel: 01234 XXX XXX

Do I have to take part?

Your participation in this study is entirely voluntary. It is up to you to decide whether or not you wish to take part. Even if you refuse to participate in this clinical study, 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 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. If you do decide to take part, you are still free to withdraw from study treatment or from the study at any time.

Likewise, the doctor conducting the study (the "Study Doctor") may decide that your participation in the study is no longer in your best interest and you will be withdrawn from study treatment or from the study. When you stop taking part in the study, you must go through the study withdrawal procedures that the Study Doctor considers necessary for your safety. Your participation in the study may also be stopped by the study sponsor, ethics committee, or the regulatory authorities. Provided you are agreeable, your GP will be informed about your participation in this study. You will receive a card, which indicates that you are participating in a clinical study.

How long will I receive treatment for and how long will I remain on the study?

Your participation in the study will continue until your doctor feels that you are no longer gaining any benefit from treatment, or if you or your doctor feels that any side effects you may be experiencing are unacceptable. You may however decide to stop your participation in the trial at any time. This means that the length of time each patient is in the study will vary.

2 What do I need to know about the medicine used in this study?

What is olaparib?

Olaparib belongs to a class of drugs called Poly (ADP-ribose) polymerase (also known as PARP) inhibitors, which are currently in clinical development for different types of cancer.

Olaparib is a new drug that has been extensively tested in the laboratory and the clinic and has fulfilled the necessary safety and quality testing that needs to be done before government regulatory agencies will allow the drug to be given to patients in a clinical trial. More than 2100 (October 2013) patients with ovarian, breast, and a variety of other cancers have been treated with olaparib, either on its own or in combination with other anti-cancer drugs. The regulatory agencies are continuing to assess the research and test results in detail from ongoing clinical trials in a range of different cancer types. Olaparib is approved in Europe by the European Medicines Agency (EMA), and North America by the Food and Drug Administration (FDA), for the treatment of ovarian cancers.

Why is olaparib being used in this trial?

The cells of the body contain DNA, which is the genetic material that contains the inherited information that makes us who we are. The DNA in cancer cells is damaged, this damage can be repaired by chemicals in the cell such as a protein called 'PARP-1'. Olaparib is known as a PARP-1 inhibitor because it stops PARP-1 from working. Blocking PAPR-1 means the DNA in cancer cells cannot be repaired, which causes these cancer cells to die. In laboratory experiments, olaparib has antitumour activity against a wide range of cancers.

Some cancer cells rely more heavily on PARP-1 to repair any damage to DNA, whereas in normal cells there are alternative ways whereby the damage can be repaired. Because of this it is thought that olaparib could specifically target cancer cells, helping to slow the progress of your disease with less effect on normal tissue. To date, olaparib has been shown to be a useful anticancer treatment in some ovarian, breast and prostate cancers with inherited defects in DNA repair. Scientists believe that there is a larger group of prostate cancer patients who may also benefit from this treatment.

Part A of the TOPARP study is now complete. During this first part, olaparib was given to patients with advanced prostate cancer. From this work and other research, scientists think that it is possible some patients are more suitable for olaparib treatment than others, and that this is

dependent on the specific type of cancer cells found in different patients. These preliminary results, overall, show that olaparib has important antitumour activity against many but not all advanced prostate cancers.

We are inviting you to participate in the main part of TOPARP Part B because your tumour has some characteristics that may make olaparib more likely to have antitumour activity against your prostate cancer. This may have been detected during the pre-screening stage of this study, if you participated in that pre-screening phase, or if your tumour was tested as part of your participation in any other research studies. Your study doctor will have discussed the results of these tests with you and their implications in selecting the best treatment for you.

Please keep in mind that these tests have been performed for research purposes, and they may not benefit you directly.

By inviting you to participate in this main study, we are asking you to carefully read this information sheet. If you finally agree to take part in the main study, you will be requested to sign the consent form before any study related procedures are performed.

3 What happens during the trial

What will my taking part in the trial involve?

You will be asked to attend a screening visit where the research team will perform a number of tests to ensure that you meet the inclusion criteria for the study. These criteria are aimed at excluding patients in whom it may be unsafe to administer olaparib and to reduce the risk of side effects. These tests are performed within a 28-day period prior to your first dose of study treatment; this is called the “screening period". This screening period may include one or more visits to the hospital to have all the necessary tests performed. Your visit to the hospital for all these tests may take several hours.

If you are eligible to take part in this study, you will be asked to return to the clinic to receive your study treatment. You will also be required to attend regular hospital appointments so that we can monitor how your cancer responds to treatment and any side effects you may experience.

What happens if I am eligible for the study?

If your screening tests results show that you are eligible and you agree to continue in the study we will ask you to attend the clinic for the first cycle of treatment. You will be required to take olaparib tablets in the morning and in the evening every day, and to attend regular hospital appointments so that we can see how your cancer responds to the treatment as well as monitor any side effects you may experience.

You will be allocated at random to one of 2 treatment groups to help us understand which is the best dose of olaparib against prostate cancer. It is important that the patients in the two treatment groups are as similar to each other as possible because we need to be sure that if one group fares better than the other group, it is because of the treatment, and not because the patients in the groups are different from each other in some way.

The 2 treatment groups are as follows:

1. Olaparib 300mg (3 tablets) twice a day
2. Olaparib 400mg (4 tablets) twice a day

You have a 50:50 chance of being in group 1 or 2. A computer programme is used to perform the random allocation (randomisation) to make sure this is done fairly, however, if you or your doctor conclude during your treatment at the dose you are receiving is causing you too many side effects, it can be reduced during the course of the study. Moreover, if you are allocated to the 300mg arm and tolerates this well but his prostate cancer does not respond after at least 12 weeks of treatment, your doctor will discuss with you the possibility of increasing your dose to 400mg (4 tablets) twice a day.

If you are not eligible for the study: If your screening tests results show you would not be suitable for this study your doctor will discuss alternative treatment options with you.

What screening assessments will be performed?

The following will be performed or organised at your screening visit:

- General medical history, oncology history and physical examination including vital signs (heart rate, blood pressure, respiratory rate, temperature, weight and height)
- List of medications you are taking (including prescription and over-the-counter vitamins and alternative medications)
- You will be asked about any disease-related symptoms you are experiencing.
- You will be asked to complete a questionnaire to assess pain and medication use
- An ECG (electrocardiogram) to assess your heart rhythm
- Assessment of your cancer by a CT (or MRI) scan of your chest, abdomen and pelvis and if needed other areas
- A bone scan to evaluate the spread of cancer to your bones.
- You will be asked to provide a urine sample for routine safety urine tests and for research (small urine sample and 24 hour collection)
- You will be asked to provide a blood sample approximately 91mls or 6 tablespoons in total), for measuring your full blood count, kidney function, blood salts (biochemistry), PSA, cholesterol and other lipids, testosterone, random glucose and for research into your disease.
- A fresh tumour biopsy may be performed (this is optional, you can still participate in the study without having a fresh tumour biopsy).
- You may be asked if you wish to have an additional imaging test, a special MRI examination called diffusion weighted MRI (DW-MRI), to evaluate your tumour in more detail. Your doctors will go through with you what is involved, and potential side effects. This test is optional and patients who wish to have DW-MRI will be required to sign a separate consent form. Not all the centres recruiting patients for this study have the facilities to perform these examinations. If you are interested, however, your study doctor will tell you if you can be invited to have this MRI examination done.

What happens next?

If you are found to be suitable for the trial based on the screening assessments and wish to participate in the study, you will be allocated at random to one of the two treatment groups by a computer programme and you will be required to return to the clinic for a Cycle 1, Day 1 visit. During this visit your doctor or nurse will:

- Conduct a physical examination including vital signs (heart rate, blood pressure, respirations, temperature, weight and height)
- Obtain information about any disease-related symptoms you are experiencing
- Obtain information about any changes to any medications you are taking
- You will be asked to complete a questionnaire to assess pain and medication use
- Obtain several blood samples (approximately 91mls or 18 teaspoons in total). This sample will be used for routine safety checks and for research into your disease
- Urine collection for research (small urine sample and 24 hour urine collection)

If the safety assessments are met, you will receive a one-cycle (28 days) supply of study treatment at the Cycle 1, Day 1 visit. Your nurse or doctor will explain how to take the olaparib tablets each day and encourage you to keep a note of the tablets you take in the treatment diary provided. In Cycle 1 you will return to clinic on Day 8 for additional assessments. Thereafter the scheduled clinic visits will be at the start of each cycle (about once every 28 days), for as long as you are on study treatment.

What happens after I have started olaparib treatment?

Once you have started taking your tablets you will have an assessment

after **1 Week** of treatment (Cycle 1 Day 8), your doctor or nurse will:

- Perform a physical examination as

clinically indicated
- Measure your vital signs
- Discuss whether you have experienced any side effects
- Discuss whether you had any changes to any medications you are taking
- Check your treatment diary and ensure that there are no issues with compliance
- Collect a blood sample (approximately 74mls or 5 tablespoons in total), this sample will be used for routine safety checks and for research into your disease
- Optionally, to repeat your tumour biopsy (at any point in cycle 1, on or after day 8)
- Urine collection for research into your disease (24 hour urine collection)

After **4 Weeks** of treatment you will have completed your first 'cycle' of treatment. At this visit your doctor or nurse will:

- Perform a physical examination as clinically indicated
- Measure your weight and vital signs
- Take a blood samples: this sample will be used for assessment of safety and for biomarker research into your disease
- Obtain a urine sample for research into you disease (24 hour urine collection)
- Discuss whether you have experienced any side effects, or had any changes to any medications you are taking
- Check the number of tablets you have taken so you should bring all your medication bottles to this visit
- Complete a questionnaire to assess pain and medication use

Every 4 weeks thereafter you will attend the clinic to repeat the assessments you had at the 4-week visit. A twenty-four hour urine collection, and a further small urine sample for research into your disease, will be obtained at cycles 2, 3 and 6 and at the end of treatment. All participants' ongoing will have approximately 74-77mls of blood (5 tablespoons) collected at cycle 2 and cycle 3, 42-71mls of blood (3-5 tablespoons) will be taken at cycles 4 and beyond. Approximately 91mls of blood (6 tablespoons) will be obtained at the End of Treatment Visit . The blood samples obtained will be utilised for both routine safety checks and research into your disease.

At each of your 4 weekly study visits you will be assessed for any side effects and will be asked whether you have taken any new medications. If you suffer from a side effect caused by the study drug, it may have to be stopped for a period of time. If the side effect improves you may be asked to restart the study drug possibly at a lower dose.

Are there additional hospital visits?

In addition to the above clinic visits, you will have a CT (or MRI) scan and bone scan after every 3rd cycle of treatment. These will be organised approximately one week before your next clinic appointment. The scan results will be used to assess your disease status and response to olaparib treatment.

Treatment Discontinuation

Your olaparib treatment will continue until your doctor feels that you are no longer getting any benefit from the tablets, or if you or your doctor conclude that any side effects you may be experiencing are unacceptable. You may also decide to stop your participation in the trial at any time. On the day you are taken off study treatment you may have some extra research tests performed. These can either be done on the day you come off the study treatment or when you come back for your end of treatment (EOT) visit.

If you were receiving 300mg twice a day of olaparib and the disease has progressed, your doctor will discuss with you the possibility of receiving a higher dose (400mg twice a day). If your doctor considers this a good option for you, and you agree, you will start taking the higher dose and continue being reviewed every 4 weeks by the study team.

End-of-Treatment (EOT) Visit

The following will be performed and organised at your end of treatment visit (EOT) which will be thirty days after your last olaparib tablet:

- General medical history, oncology history and physical examination including vital signs (heart rate, blood pressure, respirations, temperature, weight and height)

- List of medications you are taking (including prescription and over-the-counter vitamins and herbal remedies, vitamins, and supplements)
- You will be asked about any disease-related symptoms you are experiencing
- You will be asked about any new or continuing side effects or illnesses you have had since your last visit
- You will be asked to complete a questionnaire to assess pain and medication use
- You will be asked to provide a urine sample for research into your disease (this should be done at either when you stop taking olaparib or when you come back for you final safety check during the EOT visit)
- Blood (approximately 18 mls or 1 tablespoon in total), for measurement of your full blood count, kidney function, blood salts (biochemistry), PSA, cholesterol and other lipids, testosterone and random glucose. The research bloods (73mls or 5 tablespoons in total) could either be done when the patients stop olaparib or when they present for the EOT visit.
- A fresh tumour biopsy (optional) will be performed (the biopsy can be performed at any point from stopping treatment to the EOT visit)
- You will be asked to return any unused medication or the empty bottle, if you have not done so already.

How will the scan results and PSA be used to interpret my disease response and duration of treatment?

This study uses bone scans to assess your prostate cancer in the bones. Because arthritis and early bone disease flares from treatment can cause spots to appear on bone scans, the scan may be repeated several weeks later if the results are not conclusive. Cancer spots will remain the same, but arthritis spots and bone flares may disappear. Prostate Specific Antigen (PSA) tests can be unreliable as an indicator of benefit to some new prostate cancer therapy such as PARP inhibitors. Additionally, early rises in PSA can occur because the death of prostate cancer cells may release PSA into the blood. Such early rises in PSA can be mistaken for progression of your cancer. Please ask your study doctor if you have any question about this. Because both bone scans and PSA tests can be very difficult to interpret, your doctor may need to perform a confirmatory bone scan at least 6 weeks after your last bone scan to confirm whether or not your cancer is truly progressing. This may require an unplanned visit to the clinic and unplanned PSA tests.

If you decide to participate, you will be asked to remain in the study until your cancer worsens (according to the CT, MRI, or bone scan results); or you are unable to tolerate the study treatment; or your doctors determine that you should begin another cancer treatment; or if you decide to withdraw your consent.

Description of specific Research Tests

Within this research study, specific research tests are being conducted to improve our understanding of the action of olaparib on cancer cells and to identify the type of prostate cancer that will respond best to this treatment. The samples that will be collected from you during the study will allow us to look at many different substances produced in the body and by your cancer to help us understand which patients to treat with olaparib in the future. A brief description of the different research samples to be collected is provided below:

Tumour Tissue: During the pre-screening part of this study you will have been asked to donate some of the tumour tissue that was obtained during a biopsy or at surgery, when you were first diagnosed with prostate cancer or at another time point prior to this study. If following the screening period, you are suitable for the study and decide to participate, you will be asked to have between 2 or 3 tumour biopsies. All these biopsies are optional and you can participate in the study without the need of new fresh biopsies. The first biopsy will be performed during the screening period before you start treatment. The second biopsy will be taken at any point from day 8 to day 28 of the first cycle to study the effect of the olaparib on your cancer. You will be requested to

have the final biopsy when you come off study treatment.

The biopsy procedure would involve taking a small sample of your tumour tissue using a special needle. The sample may be taken from the prostate itself or from another site such as lymph nodes, bone or liver where there is evidence of cancer. The location of the biopsy will vary between patients and will be decided based on what is suitable and feasible for the patient. In most cases the biopsy will be performed as a day case under radiological guidance (e.g. ultrasound or CT). You will receive local anaesthetic for this procedure to numb the area where the biopsy is being taken. You may experience some mild pain, bruising or soreness as a result of the biopsy. There is a very small risk of infection or of bleeding at the site of biopsy and an even smaller risk of damage to structures that lie close to the entry path of the biopsy needle. Painkillers will be prescribed for you to take home with you if required. In most cases these side effects can be easily managed with simple measures and will resolve. Your doctor will explain in detail the procedure and the potential side effects to you, depending on where the tumour is located.

These tumour biopsies are an important aspect of this study and will help us to further understand the effect of the study drug on your tumour, identify specific features in the cancer that can predict responses to treatment and study reasons why prostate cancers stop responding to olaparib treatment. The tumour tissue collected will help us in the future to predict which patients will benefit from olaparib treatment.

Research Blood Tests: Blood samples will be collected at mutiple time points during the study. Tumour cells and other substances found in blood may be useful to identify which type of prostate cancer will benefit from olaparib treatment. You may be asked not to eat anything from the night before your clinic appointment until after some of the blood tests.

Research Urine Test: Urine samples will be colleced at several time points during the study to examine the effect of olaparib on you cancer and on your bones. Two types of urine samples will be collected; 1) all urine produced in the 24 hour period preceeding your clinic visit and 2) the urine sample after you have completely emptied your bladder on the morning of your clinic visit

Research Saliva Collection: You will be asked to spit into a container several times to collect saliva as DNA from normal cells in saliva can be useful to help identify abnormalities in prostate cancer that associate with olaparib sensitivity in prostate cancer.

Genetic analysis performed in research samples

This study involves looking in great detail at the DNA of your tumour from biopsies and blood samples for your normal cells as a comparison. These tests are being performed to determine which subtypes of prostate cancer are sensitive to olaparib treatment.

We cannot guarantee giving you the results of these genomic tests due to unpredictable variability in sample quality. The results of these genomic analyses may sometimes provide us with information that could potentially be relevant for your treatment, or indicate that your family members may have a higher risk of getting cancer or another disease. If this arises, your doctors will refer you (and your family if indicated) to an appropriate doctor with genetic expertise. You have a choice about how much information you wish to receive about the results of these tests since they could potentially impact you and your family. You can indicate that you choose not to be made aware of these results in the consent form that you sign for this trial. Since you are participating in a cancer trial, however, we will always tell you about any results that may have a "direct impact" on the clinical management of your cancer. Please feel free to ask any questions and discuss your preferences with the study team members.

How and when should the tablets be taken?

Olaparib tablets should be taken with a glass of water and can be taken with a light meal. The tablets should be taken twice daily, three or four tablets in the morning and three or four in the evening with a gap of approximately 12 hours

(your study doctor will tell you if you have been allocated to the group receiving 3 or 4 tablets twice a day). Tablets must be swallowed whole with a glass of water.

On the days of your clinic visits the doctor may ask you to wait to take your morning tablets until after you have had your blood tests. This is because some samples need to be taken before you take your tablets and some after you take your tablets. It is extremely important that you take the trial medicine exactly as your doctor tells you.

What happens if I miss a dose?

If you forget to take your tablets, and it is within 2 hours of the time you normally take them, then you should take them as soon as possible. If it is more than 2 hours after the time you normally take them, you should wait until the next time you would have taken the tablets. You should never take more than a single day's dose of tablets within a day.

You are encouraged to keep a record of taking the medication each day in the diary that will be provided. You should make a note if you miss a dose and tell your doctor or nurse at your next visit. Take any unused tablets or empty bottles with you each time you visit the clinic, so that your nurse can record how many tablets you have taken. You will also need to tell your doctor about any changes to any other medications you are taking, and any side effects you experience while in the study. You should also not drink grapefruit juice as this can affect the way the study medication works.

What happens if I vomit after taking the tablets?

If you vomit within 30 minutes of taking your tablets, and the tablets can actually be seen in your vomit, you may take another dose. Otherwise the dose should be missed and you should then take the next prescribed dose.

What are the side effects of olaparib treatment?

Olaparib has been given to more than 2103 (October 2013) patients so far in clinical trials. We know that the following side effects have been seen in previous studies. No one can predict which of these you may experience and you may also experience side effects, which are not listed here.

Most side effects are mild to moderate and will disappear soon after starting treatment. It is, however, important to report them to your hospital team at each visit so that treatment for any unwanted side effects can be discussed. Some of the side effects that have been observed in clinical trials are highlighted below:

- **Anaemia:** the number of red cells in your blood may decrease, which can lead to shortness of breath, fatigue, and in some instances you may require blood transfusions (when you are given new blood or blood-based products from a donor).
- **Leukopenia & Neutropenia:** the number of a certain type of white blood cell may decrease, which can lead to a reduced ability to fight certain infections. Although this does not mean you will get an infection, it is important that you contact your Study Doctor immediately if you become unwell or have a fever, even if this is after-hours or at the weekend. If you have a fever or infection, you may be admitted to hospital for treatment with intravenous (i.e., given directly into a vein) antibiotics.
- **Thrombocytopenia:** the number of platelets (another type of cell) in your blood may decrease which could lead to easy bruising, prolonged bleeding, or rarely, spontaneous bleeding. This will be monitored by the laboratory safety tests that will be done in this study. However, if you do experience any symptoms, you should contact your Study Doctor as soon as you can. Rarely, if the platelet numbers are too low, a platelet transfusion may be required.
- **Nausea or vomiting** (feeling sick or actually being sick). If required you will be offered medication to control these symptoms.
- **Fatigue** (feeling tired, weary, exhausted).
- **Diarrhoea:** if required you will be offered medication to control these symptoms
- **Lung inflammation (pneumonitis).** Although this is rare you should inform

your Study Doctor if you experience any symptoms of shortness of breath.

- **Myelodysplastic syndrome and acute myeloid leukaemia:**
  These side effects have been reported in a small number of patients treated with olaparib in previous studies and the majority of cases have been fatal. It is not known if olaparib caused myelodysplastic syndrome and/or acute myeloid leukaemia in these patients as they had other possible causes, in particular they had received extensive previous chemotherapy. Your Study Doctor will monitor your blood cell levels during the study and may decide you need to have further tests, which may include a bone marrow sample or a blood sample.

  Myelodysplastic syndrome is a pre-cancerous condition where the bone marrow isn't as good at producing blood cells as it was before (red blood cells and/or white blood cells and/or platelets). This condition has the potential to transform into acute myeloid leukaemia.

  Acute myeloid leukaemia is a cancer of the bone marrow where many abnormal and immature white blood cells (blast cells) are made while normal functioning blood cells are not made.

  Other side effects, for example mouth ulcers, mild skin rash or skin inflammation, decrease in kidney function, abdominal pain or discomfort, decreased appetite, indigestion/ heartburn, change in taste of foods, headache, dizziness, seizure, decrease of electrolytes (salts) in your body, injury of blood vessels supplying the brain and causing a stroke have been infrequently observed in previous clinical trials. Assessing the full range of side effects of olaparib is an important part of this clinical trial.

- **Driving and using machines.** The study drug may affect your ability to drive or use machines. If you feel dizzy, weak or tired while taking your study treatment, take special care when driving or using tools or machines.
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What else will happen to me during the trial?

You will be able to continue day-to-day activities as normal during the trial. You will need to attend the clinic visits and have other tests such as the CT and bone scans as described. Some people may not feel like driving after having tests such as a CT scan; we recommend that someone comes with you when you attend for your hospital appointments.

You will need to store the tablets at room temperature and take the medication as instructed by your study team.

You will be given a card, which will provide details about the TOPARP trial and that you are taking olaparib. Please carry it with you at all times while you are taking part in this trial.

What precautions should I take if I choose to participate in this trial?

You are encouraged to report anything that is troubling you to your doctor.

We don't know the effects olaparib might have on the development of sperm and as such you must use adequate contraception during the study and for 3 months following your last dose of treatment. You should abstain from sperm donation for this time. If your partner becomes pregnant whilst you are taking part in the study you must contact your study doctor immediately.

Blood donation:

You are not allowed to donate blood while in the study or for 3 months following your last dose of study medication.

Other medicines:

Your doctor will closely monitor all the medications you are taking; you should tell your doctor of any changes to your medications while you are participating in the study including any over the counter or herbal medications you are taking.

How many other patients will be taking part in the TOPARP trial?

50 patients have taken part in part 1 of this study. Approximately another 100 patients with advanced prostate cancer will take part in this part of the study from hospitals across the UK.

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

What are the benefits of taking part?

There is no promise that the treatment you receive in this study will help you. It is hoped that potential benefits may include improving disease related symptoms and decreasing the size of your tumour. Participation in this trial is based on the expectation that the benefit associated with participation, even considering the risk of harmful reactions to the study medications, may be better than the alternative treatments. The information gained from this study may help in the treatment of future patients with cancer similar to yours.

Please discuss with your study doctor which alternative treatments are available for you.

What are the possible disadvantages of taking part?

You may experience some side effects that are not listed above. There is no way of predicting if you will experience any, or how severe they will be. You must contact your study doctor if you experience any side effects even or if you are not sure that any problems you may have are related to the taking the tablets.

Taking part in this research study will involve several additional visits to the clinic. Being involved in any research study requires a degree of commitment, such as regular clinic visits and additional tests.

During this study, blood samples will be drawn to perform a variety of tests. The number of blood tests required in this study is more than if you were receiving treatment outside of a research study. Risks linked with blood sampling include pain from the needle being inserted, light headedness, possible fainting and (rarely) infection.

As part of the study you will be required to have CT scans and bone scans at screening and prior to the start of cycles 4, 7, 10 and every third cycle of treatment thereafter to monitor your cancer. By taking part in this study you will have twice as many CT and bone scans as you would if you did not take part. Having a CT scan will expose you to an amount of radiation comparable to 8 years' worth of normal background radiation in the UK. Having a bone scan will expose you to an amount of radiation which is roughly the same as 1 years' worth of normal background radiation. As part of this study you may also have 2 or 3 tumour biopsies that may take place under CT guidance. You would not have this type of CT scan if you did not take part in this study. Having a CT-guided biopsy will expose you to an amount of radiation comparable to 3 years' worth of normal background radiation comparable in the UK. Radiation can cause cell damage which may in the long term be harmful. However in view of your clinical condition, the radiation exposure is not significant and the risk of long term harm is considered to be negligible. In rare cases, you may have an allergic reaction to the contrast material "dye" given for CT scans. If you have had allergic reactions to X-ray dyes in the past, you should let your study doctor know.

MRI scans involve the use of strong magnets to image the body. When having an MRI scan you will be made as comfortable as possible before you start. You will be asked to remain still during the entire procedure. People who are afraid of being in enclosed spaces may feel anxious or nervous while in the scanner. Also, some people find it hard or painful to hold one position for more than a few minutes.

The electrocardiogram for the electrical tracing of your heartbeat involves placing small electrodes on the surface of your skin. Rarely, a slight redness or inflammation may appear due to the adhesives used to attach the electrodes to the skin.

Occasionally during the course of a study you may be found to have a previously undiagnosed medical condition. In this situation your study

doctor will take the necessary steps to ensure you receive appropriate treatment.

Possible risks, discomforts or inconveniences associated with the collection of biopsies will depend upon the type of biopsy performed.

The local anaesthetic you receive before the biopsy procedures will be injected using a syringe and a small needle and may cause a brief stinging sensation. If you have any known allergies relating to anaesthetics these should be discussed with your study doctor. The taking of a biopsy may cause some pain, redness, swelling, slight bruising at the biopsy site and rarely fainting. There is a small risk of bleeding, infection, wound healing problems following your biopsy. You will have the opportunity to discuss all the possible side effects and the type of biopsy your tumour will require with your study doctor.

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 in the study will not affect the insurance.

5 Further information about taking part

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.

What happens when the research study stops?

You will be asked to take the study drug until your doctor thinks you are no longer gaining any benefit from treatment or you are going to start on a new treatment for your cancer. The study sponsor, the ethics committee or the regulatory authorities can stop the study if it is believed that the treatment is not providing benefit, or is not safe in some way. If your study treatment is stopped, by either the sponsor, your study doctor or at your own request, your study doctor will arrange your continuing care.

What alternative treatments are there?

If you do not want to take part in the study there may be other treatment options available. These may include other experimental anti-cancer drugs, chemotherapy and radiation therapy. There is also supportive care without anti-cancer treatment. Study staff will discuss these alternative treatments and the risks and benefits associated with these treatments with you before you decide to take part in this study.

This completes Part 1 of the Information Sheet.

Please read the additional information in Part 2 before making your decision.

Part Two: General information about how TOPARP is conducted

What will happen to any samples I give?

In the TOPARP study we ask that all patients donate some of their initial tumour tissue, which was taken at the time of diagnosis or at another time point prior to starting the study. Additional samples will be collected for research into your tumour during the study including blood, saliva and urine samples and, optionally, fresh tumour biopsies since your tumour may have changed since you were diagnosed. Details of the samples requested are described in Part 1 of this information sheet. Please tick the appropriate part of the consent form if you agree to the collection of these samples.

Any samples you donate will be used to help us understand why people develop prostate cancer and how they react to treatment with olaparib. If we can show why some patients react to their treatment differently, this knowledge could help many patients in the future.

The group of medical professionals overseeing the TOPARP trial will also oversee the sample collection. Your tumour tissue or blood samples may be labelled with your initials 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 biological details to be compared to treatment findings.

The tumour samples will be stored securely at The Institute of Cancer Research Laboratory. Any excess blood samples will be destroyed when the tests are completed. Much of the blood and tumour sample analyses previously described will be conducted in The Institute of Cancer Research Laboratory, but some of the samples may also be sent to other research institutes or companies approved by The Institute of Cancer Research for the respective analyses. In all cases, your confidentially will be maintained.

Surplus archival tumour and biopsy material will be stored at The Institute of Cancer Research Laboratory indefinitely and in some cases returned to the local laboratories after the study is complete, depending on local practice. You are asked to give permission for possible future research using these samples. The confidential nature of these samples and associated data will be fully protected, and any other research using your tissue will first be reviewed and approved by an ethics committee.

How will confidentiality be maintained?

Your medical notes will need to be seen by authorised members of the research team at your hospital, so that they can collect information needed for the TOPARP trial, and also to check that it is correct. Your name, date of birth, post code and NHS number (CHI number in Scotland) will be passed to the Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU) where the study is being coordinated when you join the trial so that they can find you again if you lose touch with your hospital in the future.

Information from your medical records about your treatment and disease will be sent to the Trials Office on specially designed forms. You will be given a unique trial registration number when you join the trial which will be used together with your initials and date of birth, on all the forms / information that are sent to the Trials Office. All information about you will be treated as strictly confidential and nothing that might identify you will be revealed to any third party.

We will be contacting your hospital from time to time to find out how you are getting on. Ideally we would like to do this for life, but patients sometimes change address and/or GP or lose touch with their hospital. If this happens we would like to use national records, which are kept on everyone's health status to find out how you are. One of these is held at the General Register Office (GRO). We will need to give them enough information to identify you. This is usually your name, date of birth postcode and NHS number (or Community Health Index (CHI) and/or hospital number in Scotland). Any details we receive from any source are confidential and will only be used for the purposes of the trial. Please initial the consent form to show that we have your permission to do this.

Representatives from the ICR-CTSU, the NHS Trust relevant to your taking part in research, the MHRA and ethics committee approving the trial, AstraZeneca (the pharmaceutical company that manufacture and supply olaparib) and 3rd parties approved by ICR-CTSU may need to see your hospital or clinic records to the extent permitted by applicable laws and regulations to make sure the information received is correct. All information will be kept confidential.

By signing the consent form you agree to access to your original medical records as outlined above.

Data Sharing

We would like to be able to combine the medical information we collect about patients in this trial with information collected as part of other studies, if in the future it is a useful way of advancing our knowledge about prostate cancer and its treatment. If this happens, the completely anonymised information about you may be passed to other researchers, but they would not be able to identify you from the information provided.

What happens if I don't want to carry on with the trial?

Your participation is voluntary. If you agree to take part and then change your mind later on, you can withdraw from the study at any point without giving a reason. If you withdraw from the trial, it will not affect the standard of care you receive. Your doctor will discuss alternative treatment with you and offer you the most suitable treatment available.

If you should withdraw fully from the study, study data collected before your withdrawal may still be processed along with other data collected as part of the clinical study. However no new data will be added to the study database and you may request that all retained identifiable samples are destroyed to prevent future analysis.

You will be asked to return to the clinic to undergo the tests and evaluations scheduled for the safety follow-up visit. You retain the right to decide whether data from the visit can be used.

If you were to withdraw from treatment, we would like your permission for your hospital to send information on your progress to the Trials Office. This is so that the overall quality of the trial is not impaired.

What if there is a problem?

If you have any concern 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 (contact details in part 1). 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).

Your progress will be watched closely and you will be offered whatever help is available to cope with any side effects observed. Occasionally some patients need a short stay in hospital for side effects to be treated, and on rare occasions these can be serious. If this were to happen, full details of what has happened will be reviewed carefully by the consultant oncologist who has overall responsibility for the TOPARP trial. These details may also be sent to the MHRA who oversee the safety of people who take part in any research involving drugs. We may also need to send this information to the ethics committee who approved the trial, all the doctors who are responsible for patients in this study, and to AstraZeneca. We are required to provide this information to these parties by law, but you will not be identifiable in any of the information that is sent, and all information will be kept confidential.

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.

What if I have private medical insurance?

If you have private medical insurance please check with the company that your medical insurance policy will not be affected before agreeing to take part in this trial.

What will happen to the results of the clinical trial?

Independent experts will review the progress of the research, and the results will be published in a scientific journal as soon as there is enough information to be sure the results are reliable. The results will help to decide how to treat advanced prostate cancer in the future. The results from this trial may also contribute to reviews of worldwide evidence about this type of cancer and its treatment. You will not be identified in any report or publication relating to this research.

What if relevant information becomes available?

Sometimes we get new information about the treatment being studied, which may affect your willingness to continue in the study. If this happens, your study doctor will tell you in a timely manner and discuss whether you should continue in the study. If you decide to continue in the study, you may be asked to sign an updated informed consent form. If you decide to discontinue, your study doctor will make arrangements for your future care.

If the study is stopped for any other reason, we will tell you and arrange your continuing care.

Who is organising and funding the research?

The research trial is being carried out by a network of doctors across the UK. The trial is co-ordinated by The Institute of Cancer Research. The research is approved and funded by Cancer Research UK. AstraZeneca, the company who manufacture olaparib, are supplying the drug free of charge and providing additional funding to support the management of the trial.
Your doctor will not receive any payments for including you in this research trial.

Who has reviewed the trial?

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

What do I have to do now?

You will have some time to think about the trial and make your decision. You may wish to discuss it with your GP, family or friends. Please keep this information sheet and a copy of the signed consent form. If, at any time, you have any questions about the trial you should contact your consultant.

Useful contact information

Who else can I contact 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 feel that you are developing any unwanted side effect, or 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. They have published useful information about (1) prostate cancer (2) cancer treatments and (3) clinical trials in general. You can contact one of their specialist cancer nurses on their freephone number, 0808 808 00 00 or look on their internet website: (http://www.macmillan.org.uk/Home.aspx).

You can learn more about clinical trials and the results of this trial once available on the Cancer Research UK's patient website (**http://www.cancerresearchuk.org/cancer-help/trials/**). Other useful websites on prostate cancer treatment and trials are the Prostate Cancer UK and Prostate Cancer Foundation websites:
http://prostatecanceruk.org
http://www.pcf.org

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

Appendix 1 - Description of Scans:

Computed Tomography (CT): CT scan uses x-ray equipment to take pictures of the inside of your body to evaluate the extent of the cancer. It involves you lying down and keeping still on the scanner table for about 20 minutes. Usually, an intravenous agent is injected into your vein to obtain clearer pictures and you may also have to drink an oral contrast agent. You may experience discomfort related to lying still while the CT scan is being carried out.

Magnetic Resonance Imaging (MRI): MRI scans use magnetic and radio waves to take pictures of the inside of your body. Although there is no x-ray exposure, the procedure takes longer (40 minutes to an hour) and involves keeping still while lying down on the scanner table. It can be noisy and you will be in a narrower tunnel compared to CT. Some patients may feel claustrophobic and may experience discomfort related to lying still in an enclosed space for a prolonged period of time while the MRI scan is being taken. A MRI will only be performed if your disease is better visualised on an MRI scan rather than a CT scan.

Bone scan: A bone scan is used to identify abnormal processes involving the bone such as tumour, infection, or fracture. A bone scan uses bone-seeking radioactive material that is injected into a vein so it travels through the bloodstream. The radioactive material collects in the bones in particular in areas where there is cancer. You then lie on a bed so a camera can take special pictures of your bones. The dose of radioactive material is safe, and virtually disappears from your body within 24 hours.

These imaging techniques will help your doctor to understand the extent and state of your cancer, before you start treatment, and to monitor your response to olaparib.

Diffusion-weighted MRI (DW-MRI): DW-MRI is a special form of an MRI and provides additional information regarding the tumour, which cannot be evaluated with other imaging techniques. The MRI studies will include a baseline scan and follow-up MRI scans during the treatment. Your doctors will explain what is involved. This part of the study is optional and if you wish to have these additional imaging tests you will be required to sign a separate Patient Information Sheet and Consent Form. We are keen to evaluate if DW-MRI will provide a better way of studying prostate cancer in the bone.

Appendix 2 – Schedule of Procedures and Clinic Visits

Procedures & Assessments	Pre-screening	Screening		Cycle 1	Cycle 1	Cycle X (Every Cycle)	Cycle 4, 7,10, every 3rd cycle	Dose escalation (300 mg group only)	End of Treatment (EOT) Visit	Follow Up
Activity day	**Anytime**	**Day -28 to Day -1**	**Day -14 to Day -1**	**Day 1**	**Day 8**	**Day 1**	**Up to 8 days before**		**Day 30 after last dose of drug**	**3 monthly from EOT**
Informed consent for pre-screening	X									
Confirmation of presence of the biomarker	X									
Informed consent for the main study		X								
Medical History			X							
Obtain Archival Tissue	X	X								
Tumour Biopsy	X (optional)	X (optional)			X(8± 21 days, optional)			X (optional)	X (optional)	
Assessment of Symptoms/adverse events			X	X	X	X		X	X	
Dosing compliance					X	X		X	X	
Concomitant medication			X	X	X	X		X	X	
Physical Examination & Vitals			X	X	X	X		X	X	
Complete Pain Questionnaire			X	X		X		X	X	
12 Lead ECG			X					X (if clinically indicated)	X (if clinically indicated)	
Urinalysis			X							
Safety Bloods			X	X	X	X		X	X	
Testosterone Level			X							
PSA Levels			X	X			X	X	X	
Imaging Assessments										

Bone Scan		**X**					**X**		**X**	
DW-MRI (optional)		**X**					**X**		**X**	
CT/MRI Scan		**X**				**(X, if RECIST confirmation)**	**X**		**X**	
Disease Progression Assessment		**X**				**(X, if RECIST confirmation)**	**X**		**X**	
Survival & further treatment										**X**

Appnedix 3 - Schedule of collection of biological research samples

Procedures & Assessments	**Pre-screening**	**Screening**		**Cycle 1**	**Cycle 1**	**Cycle 2, 3, 4 and every Cycle onwards**	**Dose escalation (300mg group only)**	**End of Treatment (EOT) (Can also be obtained at the time of treatment discontinuation)**
Activity day	**Anytime**	**Day -28 to Day -1**	**Day -14 to Day -1**	**Day 1**	**Day 8**	**Day 1**		**Day 30 after last dose of drug**
Saliva Collection	**X**		**X**					
Research Blood Test		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Research Urine Test			**X**	**X**		**X(C2,3,6)**	**X**	**X**