<Trust/Site address 1>
<Trust/Site address 2>
<Trust/Site address 3>
<postcode>
Tel: <telephone number>

PATIENT INFORMATION SHEET

DETECTION Circulating tumour DNA guidEd Therapy for stage IIB/C mElanoma after surgiCal resecTION

You have been invited to take part in a research study. Before you decide, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

- **Part One** tells you the purpose of the study and what will happen to you if you take part.
- **Part Two** gives you more detailed information about the conduct of the study.

The clinical team in charge of your care will go through the details with you, but please ask if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Important things that you should know

- We are looking for new and better ways to treat melanoma.
- We have developed a blood test that tells us whether cancer cells are still present or cancer is becoming active, even if a scan looks normal.
- The test looks for pieces of DNA that are known to have come from the cancer, which we call 'circulating tumour DNA', or ctDNA.
- If we do not find ctDNA you will stay on the study having blood tests either until the study ends (and we have not found ctDNA in your blood) or until we do find ctDNA in your blood.
- If we find ctDNA, you will be allocated to either receive the standard of care, which is ongoing follow up or nivolumab, an immune boosting drug which we know is effective at treating melanoma.
- Your doctor will inform you of the possible benefits and risks when taking nivolumab.
- We do not know whether treating early with nivolumab, on the evidence of ctDNA alone, is of benefit to you, and this is what we need to find out.

Contents

Thank you for reading this.

CONTACT DETAILS

Please contact:

Appropriate job title:

[Trust to insert contact details]

Contact Number is:

[Trust to insert contact details]

Part One

Why are we doing the DETECTION trial?

We are looking for new and better ways to treat melanoma, an aggressive type of skin cancer. Having surgery to remove the melanoma will cure the majority of patients with early stage disease. However, a small percentage of these patients will go on to develop further disease, which may spread to other places in their body.

We have developed a blood test that tells us whether cancer cells are still present or is becoming active, even if a scan looks normal. The test looks for pieces of DNA (the code containing all the instructions which tell a cell what to do) in your blood that are known to have come from the cancer, which we call 'circulating tumour DNA', or ctDNA. Our data shows that patients who have ctDNA in their blood have an extremely high chance of the cancer returning. We believe the possibility of treating a patient with detectable ctDNA who does not have disease present (a "false positive") is very low and we have tested the assay extensively to minimise this risk.

Through using the blood test that we have developed, we think that we can identify earlier than normal patients who potentially have recurrence of cancer. We believe that some of the treatments that are used when melanoma has spread may benefit patients at this earlier stage.

We want to see if these patients with ctDNA in their blood, who have a higher risk of their cancer returning or spreading, and receive treatment early have a better response compared to those patients who receive treatment when their cancer has returned and it can be seen on a scan. This could mean we would be able to offer patients earlier treatment in the future using just a blood test rather than a scan, while also providing reassurance to those patients that do not have ctDNA in their blood that they do not need treatment and their cancer is not returning.

DETECTION will test patients regularly after their surgery (every three months for three years and then every six months for a further two years) using blood tests to check for ctDNA, which might indicate that the cancer is becoming active. If we do not find ctDNA you will stay on the study having blood tests either until the study ends (and we have not found ctDNA in your blood) or until we do find ctDNA in your blood. If we find ctDNA, you will be randomised into one of two groups. Randomised means putting people in a research study into different groups without taking any similarities or differences between them into account. It could involve using a random numbers table or a computer-generated random sequence. It means that each individual has the same chance of being put into either group. The groups are known as 'arms'.

The first group (known as Arm A) will continue to have the blood tests for ctDNA, and also the scans and appointments as part of your normal care. You will only get treatment if your scan shows that the cancer has returned as part of normal patient care. It is important to remember, that this is the normal treatment you would have if you did not take part in the study.. You and your doctor will not be told that the test has shown ctDNA in your blood. We need an equal number of patients to those receiving treatment to NOT receive treatment to compare our results against (controls). Arm A must be treated in the same way as a patient not on the trial and knowing that ctDNA is present may mean patients act differently, for example requesting extra check ups and may have additional worry.

If you are in the second group (known as Arm B) you will have checks to see if it is safe for you to start receiving treatment and will have a discussion with your doctor to see if you are still happy to take part in the trial. If it is safe to do so, you will receive a drug called nivolumab, an immune boosting drug which we know is effective at treating melanoma. You will receive this drug every 4 weeks for 2 years.

There are no clinically approved treatment options available for participants that test positive for ctDNA, because ctDNA testing is not part of usual NHS care. There is currently no evidence of any clinical benefits of early treatment with nivolumab in patients with stage II melanoma. We do not know whether treating early, on the evidence of ctDNA alone, is of benefit to the patient, and this is what we need to find out.

The possibility of treating a patient with detectable ctDNA who does not have disease present is very low and we have put extra precautions in place to reduce the risk of this happening.

The results from this study will give us more information about treatments for patients with early stage melanoma and may help us to improve their future treatment.

Why have I been approached to join the trial?

You have been invited to take part because you have been diagnosed with an early stage melanoma which has been removed by surgery and you may benefit from regular blood tests to monitor for early signs of it coming back.

Do I have to take part?

No, taking part is voluntary. It is up to you to decide whether or not you want to take part. The decision you make on whether to take part or not will not affect the standard of care you receive now or in the future.

If you decide not to take part then you will still receive the usual treatment your hospital offers. Your doctor can provide you with more information on this.

You will be asked to sign a consent form if you decide to take part to show that you understand the trial and you agree to all or some of the different parts. You can choose to stop participating **at any time** without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of the care you receive now or in the future.

Will I be suitable for the trial?

If you consent to take part in the trial, we will do further checks to make sure that it is safe for you to be involved and that you meet the requirements that mean the trial would be most effective for you if it works. This process is called 'screening'. The main checks required only for screening are listed below and also include checks to make sure you do not have any cancer present using a scan (see explanation of procedures section), a clinical examination, some information about you, other health problems you might have and some blood tests. In addition, we have specific checks that we need to perform on your melanoma:

Testing of your melanoma to check eligibility for the study

To take part in the study we ask permission for us to test your primary tumour (in the skin) for the presence of faulty genes/mutations (the instructions of a cell). For this, we would use the tissue that was removed during your recent melanoma surgery.

***Testing for* mutations**

- In the first instance, any tissue that you agree to donate will be sent to specialist laboratories to test for these mutations. The mutations we are planning to look for include BRAF and NRAS, which occur commonly in melanoma. We have developed the blood ctDNA test to look for them in your blood. The results of the tissue mutation tests will be sent to the doctor leading this study in your hospital, which you will be able to receive.

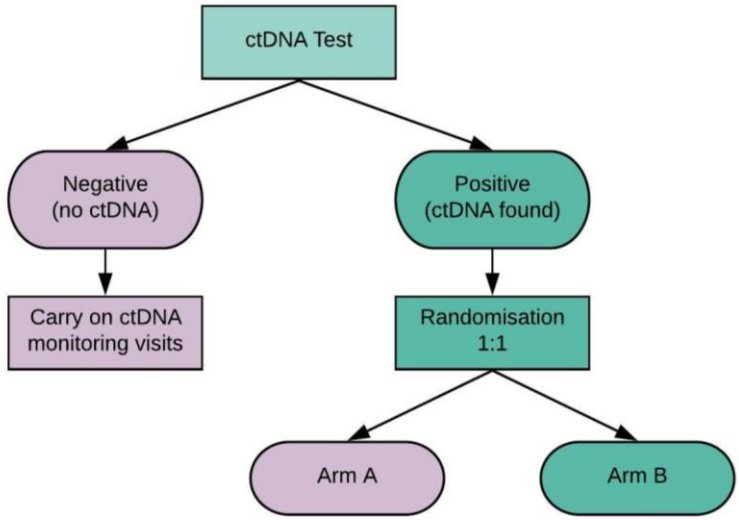
- **What happens if I do not have these mutations?**
  - If your tissue sample does not have these mutations, your doctor will discuss alternative options available to you, as you would not be eligible for the trial.

- **What happens if I do have these mutations?**
  - If your tissue does have the mutations, and you still want to take part in the study, we will ask you to undergo some further tests at the screening visit (see below).

If you have already had any of the "screening" tests in the last 4 weeks you may not need to have them repeated. Only checks that will help to identify you as suitable from your hospital notes will be done before you give your consent for the trial. If you do not give consent you will not have these checks.

What will happen to me if I take part?

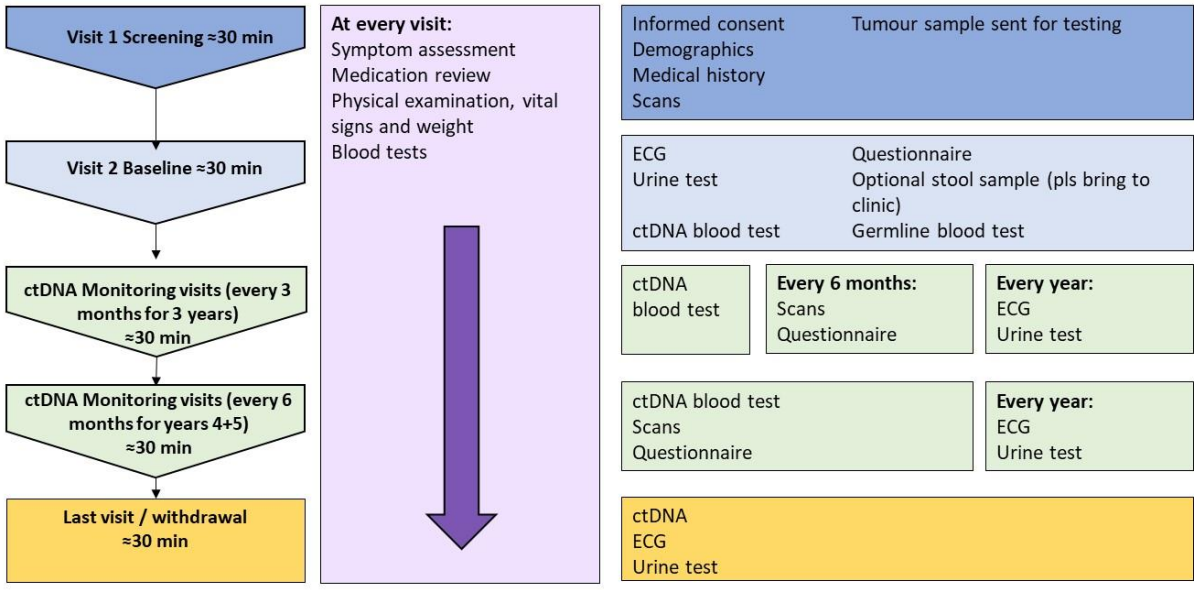
All patients will have test for ctDNA in their blood at specific time points.



Negative ctDNA test

If your ctDNA test comes back negative you will continue on the trial having visits and procedures according to the ctDNA Monitoring Schedule/Arm A patients diagram. All patients will have the visits as shown in the picture below. At every visit all patients will have the procedures listed in the purple box. You will have the procedures listed in the boxes on the right matching the visit on the left. *Explanations of the procedures* are included later in this section.

Monitoring Schedule/Arm A patients



Randomisation

If your ctDNA test comes back positive your eligibility will be checked and you will be randomised.

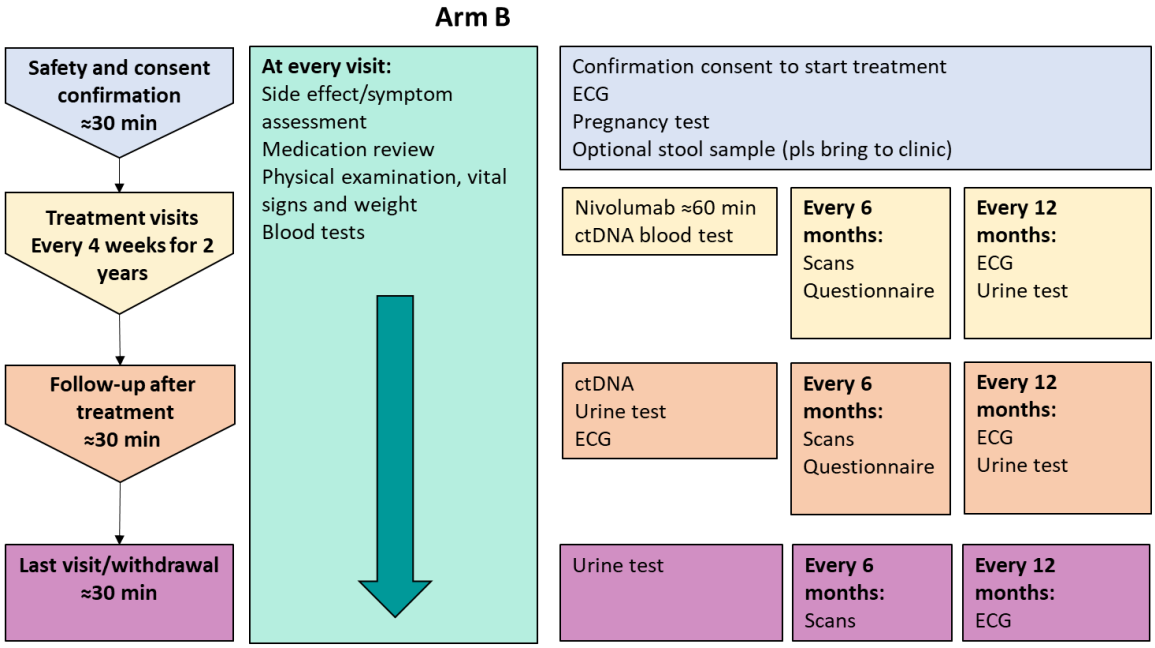
Arm A – Standard Care

If you are randomised into **Arm A**, neither you nor your doctor will be told that ctDNA has been detected. Arm A must be treated in the same way as a patient not on the trial and knowing that ctDNA is present may mean patients act differently. You will continue coming to hospital for visits according to the Monitoring Schedule/Arm A patients diagram. Your doctor will only offer you further treatment if the melanoma re-appears or if you experience symptoms of the disease.

Arm B – Early treatment based on the ctDNA result

If you are randomised into **Arm B**, you will be telephoned by the clinical team to return to the clinic, where you will be told the results of your ctDNA blood test. You will receive early treatment for melanoma with a drug called nivolumab, (which helps the immune system kill the cancer) for 2 years.

You will have visits and procedures as shown in the Arm B diagram below. You will be monitored for side effects on treatment and any signs of the cancer becoming active with regular blood tests, clinic visits and in addition, a CT scan every 6 months. If you experience any side effects please let your clinical team know.



End of Treatment / Withdrawal (Arm B only)

If you have any severe side effects from the drug or if you choose to withdraw from the study, you will stop having the treatment. We will ask you to carry on attending visits (post treatment follow-up) every 3 months for 3 years and then every 6 months for a further 2 years after that until the trial closes.

Follow-up after return of melanoma for all study patients

If your disease re-appears you will be offered treatment following discussion with your doctor as per standard NHS care. If your disease re-appears while you are receiving treatment (Arm B patients) you will stop having treatment. You will have care according to the standard NHS guidelines and will receive the best care possible.

If your melanoma comes back at any point during the study, we would like to continue to collect data about your health and the treatments you are receiving along with the response to these treatments. We may collect this data through your regular clinic appointment (in which case you do not need to attend for extra visits) or through telephone conversations with you and then reviewing your notes.

In addition, it is very important to try to understand why the melanoma came back in order to improve our management of melanoma. We therefore would like to take further blood tests at the time that you relapse and if you and your clinician feel that it would benefit you to have surgery for the relapse we ask to collect left-over tissue for our research.

Relapse	Symptom assessment Physical examination including weight ctDNA Bloods ECG Left over tissue collection (if you have surgery to remove the melanoma – to discuss with your doctor) Information regarding any future treatments you receive
	Optional Stool sample (pls bring to clinic) Biopsy of any melanoma that has come back to use for research purposes

Optional samples for future research

We would like to better understand why some melanomas return and how/why the immune treatment used in the DETECTION trial works or does not work. In order to do this we would like to obtain samples such as tumour biopsies, additional blood, and stool. We will also use them to understand how we can better treat the cancer in the future. We may also use the

samples for future research projects. The quality of any future research project will be assessed by the trial management committee.

You can choose whether or not to take part in this translational research and what type of samples you would be happy to donate. We would like to collect the following samples from you:

Stool samples

We would like to take samples to look at the bacteria in your gut and how these change with the treatment. You will be supplied with a sample collection container and a sealable bag. Instructions as to how to obtain the sample will be provided at the time and are also available at http://www.nhs.uk/chq/Pages/how-should-i-collect-and-store-a-stool-faeces-sample.aspx?CategoryID=69 .

You should collect the sample at home less than 24 hours before your appointment when you can drop it off.

Additional research biopsies (if the cancer returns)

We would like to take extra samples of cancer tissue from you to try to understand why the cancer has returned. We would only take tissue from areas that it is safe to do so. The procedure may cause you some discomfort but we would aim to minimise this. We would discuss this with you in more detail at the time of melanoma returning as the type of procedure will depend on where in the body the melanoma has come back.

After the study finishes

You will continue to be provided with the best standard of care the NHS can offer.

Explanation of the procedures

Informed consent	This is the process by which the trial is explained to you ensuring that you understand the full implications and procedures. This Patient Information Sheet contains all the information you require but you should also speak to your doctor or nurse and your family and friends. If you do decide you would like to participate in the trial then you will be given a consent form to complete, your doctor will go through this with you.
Medical history & demographics	Your doctor/nurse will go through your notes and talk to you to find out what medical conditions you have currently and any relevant conditions you have had in the past, and to check your age, sex, race etc.
Physical examination, vital signs and weight Lymph nodes	A physical examination is used to check your overall health and make sure you do not have any medical problems that you are unaware of. This is a routine test and usually performed by a doctor or nurse. Part of the physical examination may include: measuring height and weight; examining the skin, heart, abdomen and lungs; and taking blood pressure, pulse, oxygen levels and temperature. Your doctor will also check the area(s) where you had your melanoma and the lymph nodes around it.

Medication review	You will be asked what medications, if any, you are currently taking including herbal supplements and over-the-counter medications. This is so that the trial team can ensure that the drugs you are currently on and the drugs being investigated don't react together.
Blood tests including ctDNA and germline	Blood tests involve taking samples of your blood for testing in a laboratory. The purpose of the blood test is to assess your general state of health, and see how well certain organs such as bone marrow, liver and kidneys are working. At the same time we will take a test to check if ctDNA is present in your blood. At the baseline visit you will also have a blood test for germline DNA, which looks at the DNA that is present in every cell in your body. We need this to check our ctDNA results. The blood test will take a few minutes to complete and is usually carried out by a phlebotomist (someone trained to take blood) or a nurse. We will only take up to 60ml of blood, which is no more than 4 tablespoons.
Urine test	For a urine test you will be asked to provide a urine sample (urinate into a plastic pot) at your visit. This sample will be analysed either by putting a special stick into the urine and getting a result immediately or the urine will be sent to the labs in the hospital. Once the test has been completed your sample will be disposed of. This test is to make sure that your kidneys are working properly and that there is no sign of abnormality in your urine.
Urinalysis	A urine test (or urinalysis) involves taking a sample of your urine for testing. The purpose of the urine test is to check for any kidney problems or infections. Your urine may need to be sent to the lab for analysis. Urine samples will be analysed and disposed of as per normal NHS procedures and will not be kept for any other use in the trial.
Pregnancy test	This is relevant for females of child-bearing potential only. You will be required to undergo a test to confirm that you are not pregnant prior to being able to take part in the study. In addition, if you have ctDNA detected and are randomised to Arm B, you will have a repeat pregnancy test prior to starting nivolumab in order to ensure we are giving it to you safely. Patients who are pregnant are not able to commence nivolumab and therefore you will be withdrawn from the trial. The test requires a urine sample but if there is a problem with the urine sample a blood sample may be required. In addition, a urine pregnancy test will be required for all female participants of child bearing age before each PET scan.
ECG (electrocardiogram)	An ECG records the electrical activity of the heart. The heart produces tiny electrical impulses which spread through the heart muscle to make the heart contract. These impulses can be detected by the ECG machine. This is a routine test and involves placing sticky pads on your skin.
Scans: CT Scan PET -CT Scan MRI Scan	During the study, you will undergo regular scans to see if your melanoma has returned. These scans would be part of your normal care if you were not on the trial (every 6 months). As part of the trial, 2 extra scans will be performed in year 4 and 5 (6 monthly instead of annually). For most patients these scans will be Computed Tomography (CT) scans. A CT scan is a test that uses x-rays and a computer to create detailed pictures of the inside of your body. It takes pictures from different angles. The computer puts them together to make a 3 dimensional (3D) image. You usually have a CT scan in the x-ray (radiology) department. To minimise the risk of radiation, patients under 30 years age will have CT scans with a reduced radiation exposure combined with an MRI scan (see below). Some patients will have a PET-CT scan or an MRI scan instead of a CT scan. This will be decided by your doctor. A PET-CT scan combines a CT scan and a PET scan. The CT scan takes a series of x-rays from all around your body and puts them together to create a 3 dimensional (3D) image. The PET scan uses a mildly radioactive drug to show up areas of your body where cells are more active than normal. You usually have a PET-CT scan in the radiology department. An MRI (magnetic resonance imaging) is a type of scan that creates pictures using magnetism and radio waves. MRI scans produce pictures from angles all around the body and shows up soft tissues very clearly.
Post study anticancer therapy status	After you have stopped the study treatments, your doctor or nurse will check what additional therapies you have received to treat your cancer and how your health is in general. This follow up may be completed by a nurse looking at your notes or by phoning you to check your health. This will continue until the end of the trial or until you withdraw your consent.
Tissue Collection	If your melanoma comes back you may have surgery to remove it following discussion with your doctor. If you do have surgery, we would like to take a piece of the left-over tissue. This tissue will be used for future research in melanoma.We will only collect this tissue if you are having surgery as part of your

	routine care. You will not need to have an additional procedure for this unless you consent for optional biopsies (see later).
Optional samples for translational research	The trial will collect an optional stool sample and a biopsy, if the cancer returns, following the procedures described in the text above this table.

What do I have to do?

During your time on the study

- **Read this information sheet and give your consent to take part.**
- **Attend all study visits for at least 5 years**. If you cannot keep an appointment, please contact us to reschedule as soon as possible. Visits will be every 3 months for the first 3 years and then every 6 months for another 2 years. In total, depending on when you enter on study and if ctDNA is detected, you could be followed up for up to 8 ½ years.
- **Receive intravenous medication (Nivolumab) in hospital (outpatients) (ARM B ONLY)**.
- **Let us know about any other medication you are taking before and during the study.** Any treatment we give you may interact with other medications (including herbal medicines and alternative therapies), which might increase the chance or severity of side effects. Knowing what other medications you are taking helps us to monitor you more effectively.
- **Tell us about any side effects, doctor visits or admissions to hospital.** You may or may not experience any side effects. Please tell us about them – whether or not you think they are related to your treatment.
- **Use a suitable form of contraception during and after treatment (Arm B only).** You must not become pregnant or father a child while you are receiving treatment with nivolumab. If you are a woman of childbearing potential you **must** use a reliable form of contraception whilst receiving treatments and for at least 5 months after the treatment has finished. If you are a man receiving nivolumab and is sexually active with a woman of childbearing potential you **must** use a reliable form of contraception whilst receiving treatment and for at least 7 months after the treatment has finished
- If you or your partner become pregnant during treatment with nivolumab and for 5 months after treatment, you must tell your study doctor immediately. Your study doctor will seek permission from you and/or your partner if a woman to follow-up the pregnancy and the condition of the foetus or new-born baby. Pregnant patients will be immediately discontinued from trial treatment.

What is nivolumab?

The drug being tested is nivolumab. Only patients who are put into **Arm B** will be given this drug. Nivolumab is a type of immunotherapy. Immunotherapy uses our immune system to fight cancer. Our immune system works to protect the body against infection, illness and

disease. Nivolumab works by blocking a protein called PD-1 on the surface of certain immune cells, boosting these cells to find and kill cancer cells.

Nivolumab is a drug that has been approved for other types of cancer and later stage melanoma (confirmed to have spread to lymph nodes or throughout the body) and has been widely used. However, it is not usually given to patients that have early stage melanoma.

Nivolumab is given to patients very slowly through a tube and needle into a vein (intravenous infusion or 'IV'), usually in the arm. This takes about 60 minutes and will be given every 4 weeks for 2 years.

What are the alternatives for treatment with Nivolumab?
Normally, patients would just be followed up routinely to check for their melanoma returning. Patients would not usually receive treatment until melanoma is detected, so in your current condition there are no alternatives for treatment.

While patients randomised to Arm B will receive treatment, we don't know whether early treatment is better.

If you are not randomised to Arm B and your melanoma returns your doctor will discuss the treatment options available to you. These will be based on current UK guidelines for the treatment of melanoma.

What are the side effects of the treatment I will receive when taking part?
Like all medicines, Nivolumab can cause side effects, although not everybody gets them. Your doctor will discuss these with you and will explain the risks and benefits of your treatment.

You will need to make a note of any side effects you may have. You will be given contact numbers for your hospital if you need to speak to a nurse for advice in between appointments.

COMMON SIDE EFFECTS:
More than 10 in every 100 (>10%) people have one or more of the side effects listed: Skin reactions (rash and itchiness), feeling sick (nausea) and being sick (vomiting), diarrhoea, tiredness and feeling weak (fatigue), loss of appetite, and changes in the way the kidneys and liver work.

OCCASIONAL SIDE EFFECTS:
Between 1 and 10 in every 100 (1-10%) people have one or more of these effects

- Inflammation in the stomach or intestines (causing stomach pain, diarrhoea, and mucus or blood in the stools).

- Inflammation of the liver, severe skin rash, inflammation of the nervous system (causing muscle weakness, and numbness and tingling in the hands and feet), inflammation of the lungs (causing breathlessness and cough), and inflammation of other organs: pancreas, kidneys, eyes (causing blurred vision and eye pain), and hormone producing glands.
- High blood pressure, headache, sore/dry mouth and ulcers, weight loss, chest infections, hair loss, and pain in the joints.
- Infusion-related reactions include allergic reactions (causing a high temperature, chills, shivering (rigors), a headache, and feeling sick (nausea)), and pain at the site of the infusion.

OTHER RISKS: Nivolumab acts on your immune system and may cause inflammation in parts of the body. This can sometimes cause severe side effects, which (rarely) may be life-threatening. It is important that any side effects are treated when they occur to stop them from getting worse. Some side effects begin during treatment but they can sometimes happen months after the last treatment.

Please inform your study doctor or nurse <u>AT ONCE or phone 999</u> if you experience any of the following:

- Any new or increased shortness of breath;
- Any new or increased chest pain;
- Any new or increased pain/difficulty while breathing;
- Any new or increased cough or any significant change in your type of cough; for example any new or increased mucous or blood in your cough;
- Any change in the amount of oxygen you require;
- Any fever, fatigue, or other symptoms that occur at the same time as any changes to your breathing or other lung symptoms.

If you start to develop symptoms, your study doctor will ask you to return to the clinic for additional tests, which could include a physical exam, measurement of oxygen levels, blood tests, chest X-rays, and/or CT scans. You will be monitored very closely for changes in your overall lung symptoms, monitoring may require hospitalization. You may require specific treatment in order to control lung inflammation.

Prolonged treatment with medicines that suppress inflammation, sometimes needed to manage the side effects of nivolumab treatment, may lower your body's ability to fight off certain infections. These infections may require treatment with antibiotic or antifungal medications and may be fatal.

The risks are different for every individual. It is important that you are aware of any signs of inflammation and that you tell your doctor or a nurse involved with the study about them. You can talk to your doctor or nurse about what this means for you.

What are the possible disadvantages and risks of taking part?

There is a small possibility that ctDNA could be detected with no disease and therefore nivolumab (if randomised to Arm B) could be administered unnecessarily. We have tried to

reduce this risk as much as possible. Further disadvantages may include a small number of extra visits and tests that will need to be made. The extra visits would mainly affect patients on Arm B as the other visits are the same as standard care. You may be able to claim reasonable travel expenses and this will be discussed with you when necessary.

Apart from the side effects that may occur from taking nivolumab, we have summarised the risks and side effects that may occur with each of the procedures in this trial below. This may not cover all risks and side effects so if you have any concerns you should discuss these with your doctor.

Risks and side effects of the trial procedures

Blood tests	Putting the needle into the arm involves a pin-prick sensation but after that the rest of the procedure should be quite painless. Some people continue to feel some discomfort or pain and we are not sure why. It is probably because of nerves under the surface of the skin but this should settle quite quickly. If not you should go to see your GP or a member of hospital staff. You may get a bruise or a small lump after having blood taken. This will usually settle by itself and fade away in time. Pressing firmly on the site until the bleeding has stopped should help to reduce any bruising. If possible keep the arm slightly raised and avoid too much movement of the arm, such as lifting or carrying heavy parcels, for an hour or so after the blood test. Another disadvantage is that regular blood tests can lead to anxiety and this could affect your quality of life. Please let the research team know if you experience this.
Exposure to Radiation during CT Scanning	You will be exposed to radiation during CT scanning. Whilst all exposure to radiation carries a very low risk that it may itself cause cancer in the future, the majority of scans on this study would also be performed if you were on standard treatment. The only additional scans will be 3 extra scans in years 4 and 5, which is the equivalent of receiving 3.7 years of additional background radiation with a risk for causing potential cancers of 1 in 700. To minimise the risk of radiation, patients under 30 years age will have CT scans with a reduced radiation exposure combined with an MRI scan (see below).
Risks associated with PET-CT scanning	If your doctor thinks you should have a PET-CT instead of a CT, you will be exposed to radiation during PET-CT scanning. Whilst all exposure to radiation carries a very low risk that it may itself cause cancer in the future, the majority of scans on this study would also be performed if you were on standard treatment. You might get a small bruise or swelling around the area where they inject the radioactive tracer. There is a risk that the radioactive tracer will leak outside the vein. This can cause swelling and pain in your arm but it's rare. Rarely, people have an allergic reaction to the radioactive tracer. This most often starts with weakness, sweating and difficulty breathing. Tell your radiographer immediately if you feel unwell.
MRI scans	For those patients undergoing MRI scans, some people feel a bit claustrophobic when they are having an MRI scan. **If you think you will experience this please let your doctor and radiographer know before the scan.**
Treatment with nivolumab	If you are given nivolumab you are at risk of having side effects (see the section above about **What are the side effects of the treatment I will receive when taking part** on page **12)**. You should discuss these with the doctors and nurses involved in this trial. Medicines will be given to make side effects less serious and uncomfortable. Many side effects go away rapidly after completion of therapy, but in some cases side effects could be serious, permanent or life threatening. If you have any unexpected or severe side effects or other illnesses, we may ask you to stop treatment. Once you have started treatment you should report any side effects to us. If you have urgent concerns you can contact us by phone on the numbers listed at the end of this information sheet. In the case of an emergency you should dial 999. Sometimes when people have an infusion of a drug intravenously, they might also have a reaction to the infusion. This can be reduced by changing the speed of the infusion, by temporarily stopping the

	infusion and/or by giving you other medicines. This will be taken into account for your next infusion and any adjustments made in advance.
Private Medical Insurance	If you have private medical insurance, you should check with your insurance company before agreeing to take part to ensure that your medical insurance is not affected.

What are the possible benefits of taking part?

We hope that the treatments will help you. However, this cannot be guaranteed. The information we get from this study may help us to improve the future treatment of patients with early stage melanoma.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want to or should continue in the study. If you decide to withdraw your doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

On receiving new information your doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason you will be told why and your continuing care will be arranged.

What happens to me when the research study stops?

The research study will end once all the participants needed for the study have been followed up for at least 3 years. You will continue to be contacted to collect follow-up data about your condition until the end of the study (when the last patient recruited has been followed up for 3 years).

Once you have completed the trial you will return to standard NHS care. If your melanoma has not returned you will continue to be monitored as per NHS standard practice. If your melanoma returned during the trial you will continue to receive treatment as per NHS standard practice. You will only receive nivolumab after the trial has finished if it is part of NHS standard practice.

What will happen if I don't want to carry on with the study?

If you change your mind you can withdraw from the study *at any time*. This will not affect your relationship with the doctors and nurses or your subsequent care, in any way. You will receive treatment according to NHS standard practice as offered by your hospital.

If you decide to withdraw from the trial we will ask you:

- whether you only want to stop receiving treatment as part of the trial and are happy to continue coming in for trial visits to check on your health (we would recommend this so we can continue to make sure you are safe and healthy after receiving treatment)
- whether you are happy to continue providing samples if you have stopped receiving treatment and are still attending hospital
- whether you want to stop attending the hospital for visits but are happy for us to continue collecting information about your health through your hospital and GP
- whether you want to stop attending hospital and for us to stop collecting information about your health
- whether you are happy for us to keep all samples collected so far that have not already been used

Information on how we will handle your information in the event of you withdrawing is detailed in Part 2 of this Information Sheet.

This completes Part One of the Information Sheet. If the information in Part One has interested you and you are considering participation, please continue to read the additional information in Part Two before making any decision.

Part Two

Who is running the study?

This trial has been designed by a group of doctors and scientists specialising in melanoma cancer. The research is being organised by The Christie NHS Foundation Trust and the University of Manchester.

The Christie Hospital NHS Foundation Trust is the sponsor for this study and has overall responsibility for running the trial. They are based in Manchester in the United Kingdom. The day to day management of the trial is carried out by a team based at the Liverpool Clinical Trials Centre (LCTC, part of the University of Liverpool) on behalf of The Christie.

The study is funded by Cancer Research UK, with additional funding to be confirmed for future research examining how management of melanoma can be improved.

The drug used in this trial is being provided by Bristol-Myers Squibb (BMS) at no cost for treatment centres.

Your doctor will not receive any payment for including you in this study.

How will we use information about you?

The Christie NHS Foundation Trust is the Data Controller for this study, this means that they are responsible for looking after your information and using it properly. We will need to use information given by you, from your medical records and from your GP for this research project.

This information will include the following identifiable information:

- your initials
- your NHS number
- your name
- your month and year of birth
- your contact details such as telephone number and/or email address

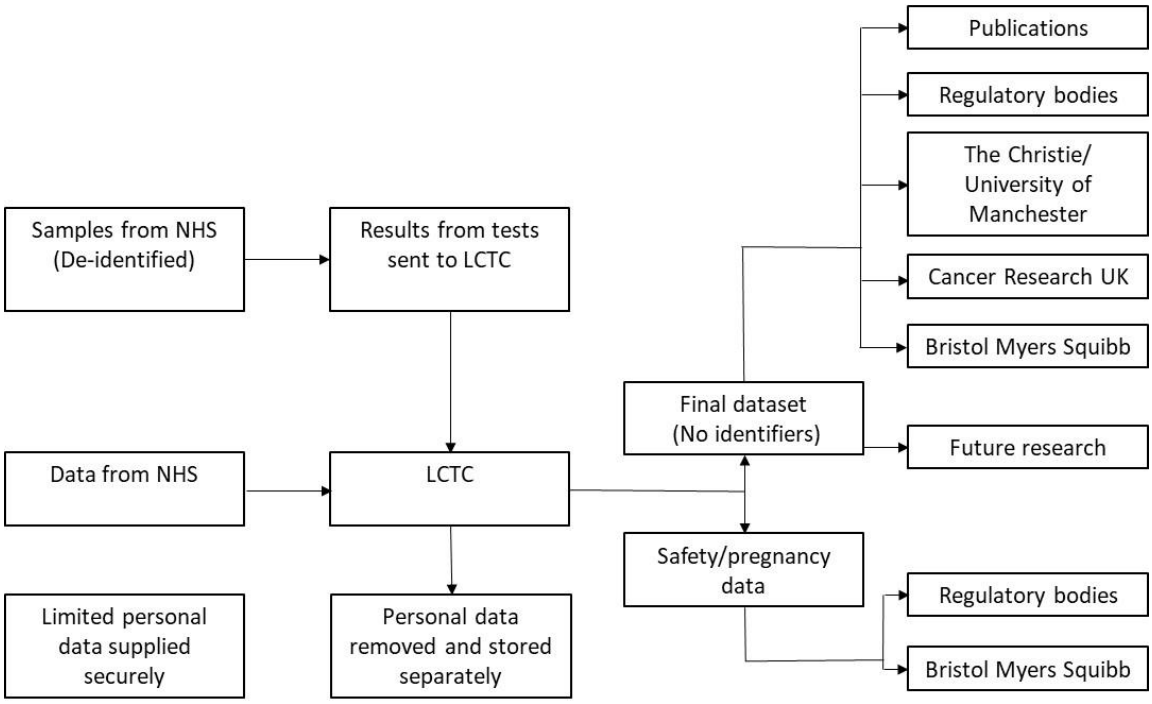
Individuals from The Christie, the LCTC and regulatory organisations may look at your medical and research records to check the accuracy of the research study data and to ensure the research is being done correctly. All will have a duty of confidentiality to you as a research participant.

Apart from what is described above, your identifiable data will not be accessible to anyone else and will not form part of the final results data (it will be stored separately). People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

We will inform your GP that you are taking part in this study.

How will my data be collected and handled?



Data will be sent from your hospital (which may include information collected from your GP) to the LCTC. Your hospital will send a tumour block to the Biomarker Centre and Manchester Centre for Genomic medicine laboratories with patient identifiable information on it as it is an NHS testing centre and the results of the tumour testing may be used as part of standard of care in future for the patient. Results from the tumour testing will be sent back to the treating clinician as per NHS standard procedures. In addition, a pseudo-anonymised result will be sent to LCTU and CBC.

All ctDNA samples sent to CBC will be pseudo-anonymised.

Your data may be reviewed at the LCTC by regulatory bodies in the UK (the Research Ethics Committee and the Medicines and Healthcare products Regulatory Authority - MHRA), the Sponsor and/or Cancer Research UK to ensure that the trial is being performed correctly and in compliance with the law.

Researchers at the LCTC will look at all of your data and determine whether the trial has been successful (statistical analysis). This will be done without transferring your data outside the LCTC.

Safety and pregnancy information will be provided confidentially and securely to the company who supply nivolumab (BMS) and to the regulatory bodies in the UK. This will include information on patients who are lactating. This is required by law. Even if you withdraw from data being collected about you for the trial, if you were on Arm B and received treatment we

may need to continue to collect this data. Your safety data may be reviewed outside the EU but no one will be able to identify you.

Data for the final results of the trial will only leave the LCTC in a format that the individual patients will not be identifiable. This will be sent to The Christie NHS Foundation Trust, to any publications where the results are being published and Cancer Research UK. This final anonymised dataset may be given to other researchers in the future including academic and commercial collaborators to answer clinically relevant research questions.

We are asking you to give consent to share your data as the results of our research with researchers in the UK and other countries after the study has ended. Some countries outside Europe may not have laws which protect privacy to the same extent as the Data Protection Act in the UK or European law. We will take all reasonable steps to protect your privacy with any confidential information (such as your name, address and GP details) removed before being shared. They must follow our rules about keeping your information safe.

Once we have finished the study, we will keep the data for 25 years, so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are my choices about how my information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
- If you choose to stop taking part in the study, we would like to continue collecting information about your health from central NHS records, your hospital and your GP. If you do not want this to happen, tell us and we will stop.
- In some cases however we may need to continue to collect limited information after you have stopped taking part in the trial about any side-effects of the study treatment you may experience or pregnancies.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.
- To safeguard your rights, we will use the minimum personally-identifiable information possible.
- If you agree to take part in this study, you will have the option to take part in future research using your data and samples saved from this study (consent options 17-21)*
- You can access results regarding the mutations present in your tissue, however we will not be able to provide the results of your ctDNA blood tests to you unless you are randomised to Arm B, in which case we will inform your doctor.

*Please note you will not be approached again to take part in these trials and the consent taken for this study will be used. You will still have the right to withdraw from any future research.

Information sharing for other research

When you agree to take part in a research study, the information about your health and care may be beneficial 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. Information that is identifiable to you will not be passed on with your data.

If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study. 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, or the regulatory standards of their country**.**

Where can I find out more about how my information is used?

You can find out more about how we use your information:

- at the DETECTION LCTC website: www.lctc.org.uk
- at www.hra.nhs.uk/information-about-patients
- in the Health Research Authority leaflet available from www.hra.nhs.uk/patientdataandresearch
- by contacting the The Christie NHS Foundation Trust Data Protection Officer:

  Data Protection Officer
  The Christie NHS Foundation Trust Wilmslow Road
  Manchester
  M20 4BX
  Telephone number: 0161 446 3043
  Email: the-christie.dpo@nhs.net
  https://www.christie.nhs.uk/about-us/data-protection
- by asking one of the research team
- by sending an email to detection@liverpool.ac.uk

What will happen to any samples I give (including optional)?

Some of your samples will be analysed at your hospital to ensure the safety of your treatment. The rest of the samples will be processed and stored by the DETECTION team, which includes your local hospital laboratories, laboratories at the Cancer Research UK Manchester Institute Cancer Biomarker Centre, and the Manchester Centre for Genomic Medicine and the Manchester Cancer Research Centre (MCRC) BioBank. The DETECTION researchers work closely with other scientists in the UK and around the world and, with your permission, your

samples may be transferred to these research collaborators for use in future scientific studies. This would need prior ethics approval and approval by the people managing the trial.

The samples will be kept in a secure place until we need them or for a maximum of 15 years after the end of trial; nobody outside of the study will have access to **any** confidential information that you give to us. Confidential details (such as your name, address and GP details) will be kept locally and not made available to collaborators.

Your sample will be coded and the researchers carrying out tests on the samples will not be given information they do not need to carry out the tests and analyse the results. The codes will be used to link the results from your samples to the data collected from your treating hospital. Coded is not the same as anonymous. It will be possible to use the codes to identify that a result is from your sample, though this will only be possible at the Liverpool Clinical Trials Centre and no other researchers will have access to this information. We will maintain this information so that we can properly manage the samples donated.

You can withdraw your consent for samples to be stored at any time. If you wish to withdraw then please contact your research nurse or the LCTU. The samples will be destroyed and a letter of confirmation will be sent to you. Depending on when you decide to withdraw some research may already have taken place on your samples but we will ensure that no further research work is done.

Will any genetic tests be done?

We will use your blood sample to obtain DNA (genetic material). We are asking you to allow us to extract DNA so that we can try to identify mutations and detect the cancer becoming active at an early stage. Furthermore, we would like to test both the blood DNA and tumour tissue to better understand why some melanomas return and others do not as well as why some melanomas become resistant to treatment. We may also use this genetic data for future research questions, which will be evaluated by the people managing the trial prior to any samples being used. The results of the mutation test from the tumour tissue will be sent back to your treating doctor, who will be able to provide them to you. The results from the ctDNA test will only be sent back to your doctor (who will inform you) if ctDNA is detected and you are randomised to Arm B (treatment with nivolumab).

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with one of your research team who will do their best to answer your questions (contact details are provided in the end of the Contents section above).

If you remain unhappy and wish to complain formally, you can do this by contacting local NHS Patient Advice and Liaison Service (PALS) or equivalent. Members of your local hospital team should be able to provide this information to you.

Every care will be taken in the course of this clinical study. However, in the unlikely event that you are harmed by taking part in this research project, and this is due to someone's negligence, then you may have grounds for a legal action for compensation against the NHS Trust where you are being treated but you may have to pay for your legal costs. The normal National Health Service complaints procedures should be available to you. If you are harmed and this is due to the design of the research, then you may have grounds for legal action for compensation against the University of Manchester.

In the event of a defective product then you may have grounds for a legal action for compensation against the manufacturer, but you may have to pay for your legal costs.

What will happen to the results of the research study?

It is intended that once the study is complete a report will be written and the results will be published in medical journals and presented at conferences. We do this to make the results available to the public and so that we can explain to the medical community what our research has found to improve healthcare around the world. They may also be used to apply to the regulatory authorities to make the drug widely available and/or for research related to the development of pharmaceutical products, diagnostics or medical aids. Confidentiality will be ensured at all times and you will not be named or identified in any publication.

What rights do I have to the results of the research?

Any information derived directly or indirectly from this research, as well as any patents, diagnostic tests, drugs, or biological products developed directly or indirectly as a result of this research may be used for commercial purposes. You have no right to this property or to any share of the profits that may be earned directly or indirectly as a result of this research. However, in signing this form and donating tissue, stool and/or blood samples for this research, you do not give up any rights that you would otherwise have as a participant in research.

We will update you, with your permission, as to the results of the research for the trial and any other studies using data/samples from DETECTION using a newsletter, through the DETECTION LCTC website www.lctc.org.uk, through Cancer Research UK, or through social media such as @DETECTION_Trial on Twitter. If you would like to receive a newsletter, please provide details of how you wish to be contacted to your research nurse/doctor.

Who has reviewed the study?

The study has been reviewed for scientific content by independent reviewers and members of the NCRI. The London-Harrow Research Ethics Committee has reviewed the study for ethical considerations. The trial has been reviewed by the Health Research Authority who oversee all research conducted in the NHS. The trial has been reviewed and approved by the

Medicines and Healthcare products Regulatory Agency, the government body responsible for clinical trials of drugs in the UK.

Thank you for taking the time to read and consider this information sheet. Should you decide to take part in the study, you will be given a copy of the information sheet and a signed consent form to keep.

<Trust/Site address 1>
<Trust/Site address 2>
<Trust/Site address 3>
<postcode>
Tel: <telephone number>

FOR SITE USE ONLY:

Site Name:			
Participant Study Number			
Participant Initials:		Participant Month and Year of Birth (MYOB):	/
Participant NHS Number			

DETECTION CONSENT FORM

	Please initial all boxes
1. I confirm that I have read and understood the **information sheet v5.0 dated 14/07/2021** for this study and have been given a copy to keep. I have had the opportunity to consider the information and ask questions and these have been answered satisfactorily.	
2. I understand that participation is voluntary and that I am free to withdraw from the study at any time, without giving a reason, and without my care or legal rights being affected. However, the study team may need to collect some limited information for safety reasons.	
3. I understand that my data will be collected, processed and stored in compliance with the law as part of participation in this trial, whilst in the UK. I understand that I can withdraw my consent for further data collection at any time, but that data already collected will be retained and that data legally required for the trial relating to safety will continue to be collected.	
4. I give permission to the LCTC to check that my consent is valid.	
5. I understand that relevant sections of my medical notes and any data collected during the study may be looked at by authorised individuals from the central study team and representatives of the Sponsor, LCTC (part of The University of Liverpool), regulatory authorities and the local NHS Trust. I give permission for these individuals to have access to my records and data. I understand that this information will be kept confidential. If applicable, de-identified safety and pregnancy/breastfeeding data will be provided confidentially and securely to the company who supply nivolumab (Bristol Myers Squibb, BMS).	
6. I agree to my GP being informed of my participation in the study and for my GP to provide	

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<Trust/Site address 3>
<postcode>
Tel: <telephone number>

FOR SITE USE ONLY:

Site Name:			
Participant Study Number			
Participant Initials:		Participant Month and Year of Birth (MYOB):	/
Participant NHS Number			

DETECTION CONSENT FORM

information about my medical history.	
7. I agree to take nivolumab if I am randomised to Arm B and I pass the eligibility and safety check for nivolumab treatment.	
8. I understand that if I am randomised to Arm B, I will need to use appropriate contraception whilst on nivolumab and for 5 months after (women of childbearing potential) or for 7 months after (men if sexually active with women of childbearing potential). I agree to follow instructions on the use of contraception.	
9. I understand that I will not benefit financially from this study or its results.	
10. I understand that my pseudo-anonymised study data will be kept by the Liverpool Clinical Trials Centre, The Christie NHS Foundation Trust and at the hospital where I receive treatment in a confidential manner for at least 25 years from the end of the study.	
11. I agree that if required, my de-identified data can be sent to researchers in the UK and internationally, for ethically approved research after appropriate review and approval by the people managing the study. These may be academic or commercial. I understand that I will not be identifiable from this data and that data protection laws within their respective countries will be complied with by the receiving researchers.	
12. I consent for my blood to be taken for the purposes of testing for ctDNA and for tests of organ function e.g. to ensure safety.	
13. I understand that genetic testing as described in this Patient Information Sheet will be performed on my samples.	
14. I agree for any samples of my tissue/blood that have already been taken, or will be taken as part of the DETECTION study and my routine care, to be stored and used by the DETECTION researchers for the DETECTION Trial and for future cancer research.	
15. I agree to take part in this study.	
16. I agree that if I become pregnant (female patients) during treatment with nivolumab and within 5 months of stopping it details regarding my pregnancy can be collected. I (male	

<Trust/Site address 1>
<Trust/Site address 2>
<Trust/Site address 3>
<postcode>
Tel: <telephone number>

FOR SITE USE ONLY:

Site Name:			
Participant Study Number			
Participant Initials:		Participant Month and Year of Birth (MYOB):	/
Participant NHS Number			

DETECTION CONSENT FORM

patients) agree that if my partner becomes pregnant during my treatment with nivolumab and within 5 months of stopping it they will be approached to provide information regarding the pregnancy (separate consent form).	

The following consent items are OPTIONAL and you do not need to agree to them to take part in the trial. Please indicate your preference by initialing EITHER Yes to give permission or No to decline permission.

17. I agree to additional blood being taken for research purposes.	***YES***	***NO***
18. I agree to further biopsies being taken if my cancer returns, which will be re-discussed with me at the time and will only occur if it is safe to perform them.	***YES***	***NO***
19. I agree that if required, my de-identified samples can be sent to researchers in the UK and internationally, for ethically approved research after appropriate review and approval by the people managing the study. These may be academic or commercial. I understand that data protection laws within their respective countries will be complied with by the receiving researchers.	***YES***	***NO***
20. I agree to my blood and tissue being used for future genetic research after the trial has ended.	***YES***	***NO***
21. I agree to be contacted with updates regarding the DETECTION trial and any studies that are using data/samples from the trial (if you agree to this statement provide your details below): Telephone number: Email address:	***YES***	***NO***

_____ _____ _____

<Trust/Site address 1>
<Trust/Site address 2>
<Trust/Site address 3>
<postcode>
Tel: <telephone number>

FOR SITE USE ONLY:																
Site Name:																
Participant Study Number																
Participant Initials:				Participant Month and Year of Birth (MYOB):			/									
Participant NHS Number																

DETECTION CONSENT FORM

Printed name of Patient (BLOCK CAPITALS)	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature

When completed file the original in the ISF, a copy in the patient's medical notes and give a copy to the patient.

Thank you for agreeing to participate in this research.