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c-TRAK TN: A clinical trial utilising **c**tDNA mutation **t**racking to detect minimal **r**esidual disease **a**nd trigger intervention in patients with moderate and high ris**k** **t**riple **n**egative early breast cancer

PATIENT INFORMATION SHEET FOR REGISTRATION FOR ctDNA SURVEILLANCE

Version: 6.0
Date: 26 June 2020

c-TRAK TN: A clinical trial utilising **c**tDNA mutation **t**racking to detect minimal **r**esidual disease **a**nd trigger intervention in patients with moderate and high ris**k** **t**riple **n**egative early breast cancer

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How to contact us

If you have any questions about this trial, please talk to your doctor at:

Hospital Department
Hospital
Address
Address
Tel: XXXX XXX XXX

We are inviting you to take part in a clinical trial

- We would like to invite you to take part in our research trial called c-TRAK TN. Joining the trial is entirely up to you. Before you decide, we would like you to understand why the research is being done and what it would involve for you.

- Your doctor or a member of the research team will go through this information sheet with you, to help you decide whether or not you would like to take part and answer any questions you may have. Please ask if anything is unclear. Please feel free to talk to your family and friends about the trial if you wish.

Thank you for taking the time to read this information

Summary of the research

- This research trial is for patients with primary triple negative breast cancer (TNBC).
- We want to investigate whether blood tests can detect if low levels of cancer cells are left over after standard treatment for your type of cancer. If so, we want to determine if additional treatment with pembrolizumab might prevent or delay the cancer coming back.
- If you take part in the trial you will be asked to give blood samples every 3 months for 2 years.
- This research is important because it could change how we monitor and treat patients after their standard treatment.
- This research trial will take place in approximately 15 hospitals across the UK.

1 About the c-TRAK TN trial

Why am I being invited to take part?
You have been invited to participate in this research trial, called c-TRAK TN, because you have been diagnosed with triple negative breast cancer (TNBC) and are receiving or have finished, standard treatment (chemotherapy and surgery with or without radiotherapy).

Do I have to take part?
No, it is up to you to decide whether or not to take part in the c-TRAK TN trial. Your participation is entirely voluntary and you will be given sufficient time to decide whether or not you wish to participate. Your decision to participate or not in the trial will not affect the standard of care you receive. If you do decide to take part in the trial you are free to withdraw at any time and do not have to give a reason.

Why is this research trial being done in patients with TNBC and what is it trying to find out?
We know that in some patients, TNBC can have a high or moderate risk of coming back (relapse) after standard treatment and this usually happens within the first two years after finishing treatment. We have developed a blood test that may predict which patients have a risk of relapse despite having standard treatment. In this research trial we would like to determine whether having blood tests done regularly after surgery can predict with certainty if your cancer will come back. In addition, we would like to find out whether having additional treatment will benefit patients who have a positive blood result in the first year

How does the blood test work?
In all types of cells within the body, the genetic information is stored in the form of DNA. Cancer cells develop as a result of changes (mutations) in the DNA of normal cells which cause the cell to behave in an abnormal way. The abnormal cells (cancer cells) grow and multiply, eventually forming a tumour. In current routine practice, the usual way to identify the presence of a cancer tumour is using scans (e.g. CT, bone scan) and the most common way to identify the type of cancer mutations is to examine a sample of the tumour taken during surgery or from a biopsy.

Recent research has allowed development of a blood test that is able to detect very small amounts of cancer and may be able to do so before cancer becomes visible on a scan. Cancer cells release pieces of their DNA into the blood stream, we call this 'circulating tumour DNA' or 'ctDNA' for short. The blood test can detect very small amounts of ctDNA in the blood and works by looking for the cancer mutations found in the ctDNA. In an earlier research study, we showed that by regularly carrying out these blood tests to detect ctDNA after patients have completed treatment (which we call 'ctDNA surveillance'), we could identify which patients were at risk of relapse. However, the study was done in a small group of patients, and one purpose of the c-TRAK TN trial is to find out if we will get the same results in a larger group of patients.

Will the trial involve having any treatment?

A second purpose of the c-TRAK TN trial is to find out if patients who have ctDNA detected in their blood (i.e. have a positive ctDNA blood test) will benefit from having treatment with a drug called pembrolizumab. Pembrolizumab works differently to chemotherapy and radiotherapy. It is an immunotherapy treatment that causes the body's immune system to attack cancer cells and is already used in routine practice for treatment of other types of cancer. Recent evidence shows that treatment with immunotherapy can be beneficial in patients with TNBC.

In this research trial, we want to find out if pembrolizumab treatment will clear the ctDNA found in the blood (i.e. resulting in repeated negative ctDNA blood tests), and ultimately get rid of all the cancer cells left over in the body after standard treatment. It is uncertain if pembrolizumab treatment will work in this way, which is why we are running this trial. If you participate in this trial you will have your ctDNA measured regularly (surveillance), and if you have ctDNA detected in your blood (i.e. you have a positive ctDNA test) in the first year you may be eligible (depending on the results of the imaging assessments and other tests, including blood tests) to start pembrolizumab treatment.

When the trial started, patients with a positive ctDNA result were randomly allocated to either receive pembrolizumab treatment or continue ctDNA surveillance in an observation group without treatment. From now on, as a result of new information suggesting that the presence of ctDNA in the blood is an indicator that a patient's cancer will come back, all patients with ctDNA detected in their blood will be allocated to receive pembrolizumab. Please see the accompanying 'summary patient information sheet' for more information on this change. Further details about what will happen if you enter into ctDNA surveillance, and if you have a positive ctDNA test, are provided in the sections below.

How many patients will take part in c-TRAK TN?

For a patient to be able to take part in ctDNA surveillance, we first need to check we can identify the cancer mutations in the tumour sample taken from the patient during surgery or at diagnosis. If a cancer mutation is present we can look for these same mutations in the blood as ctDNA. Some cancers do not contain the kind of mutations that can be detected in ctDNA and therefore we might not be able to do this for all patients.

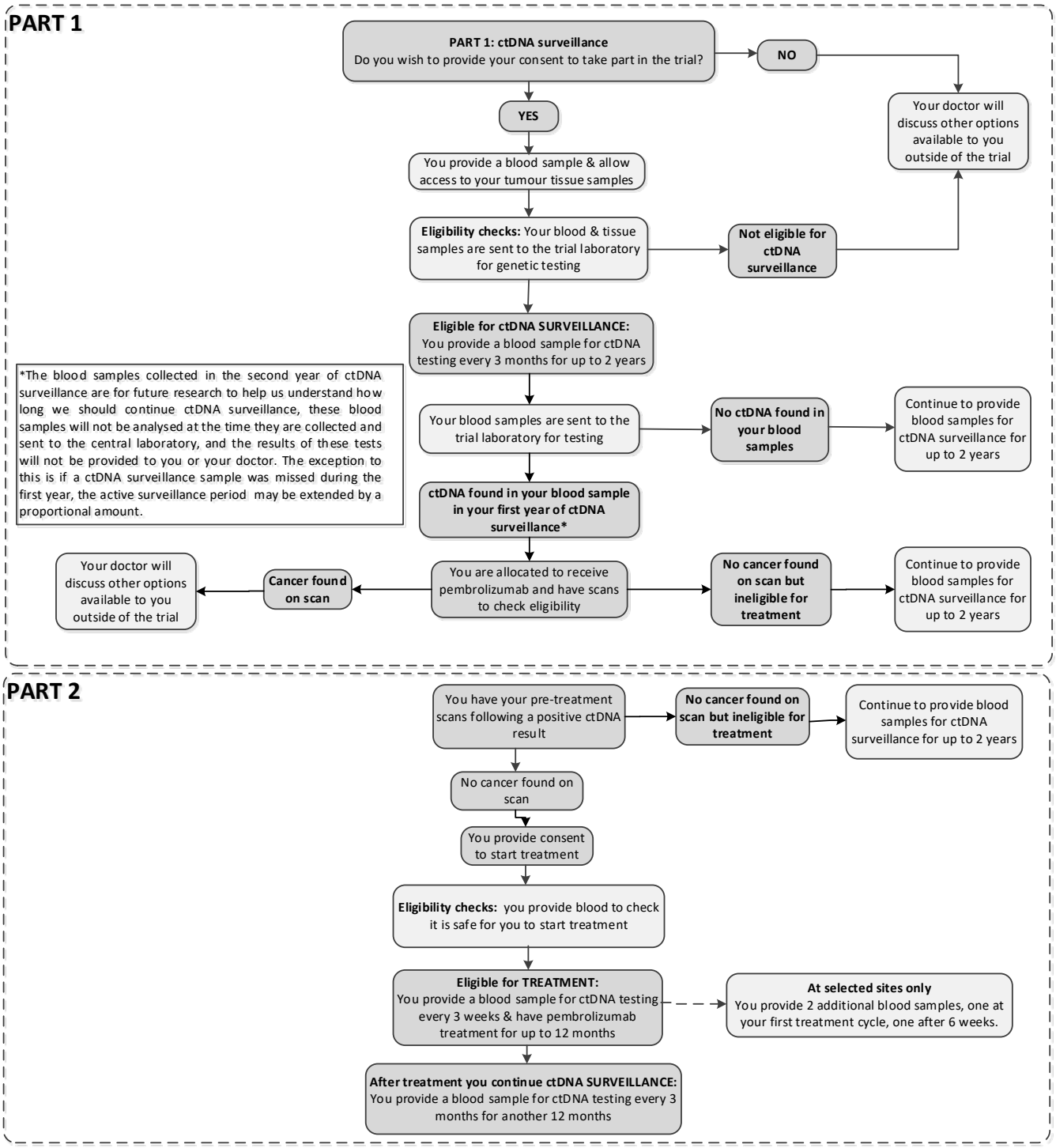
We estimate we will need to register about 200 patients in the trial in order to identify 150 patients who have a mutation we can test for and hence who are eligible to start ctDNA surveillance. We expect that about a third of patients who take part in ctDNA surveillance will have a positive ctDNA blood test and may be eligible to receive pembrolizumab treatment.

2 What taking part in the c-TRAK TN trial involves

What am I being asked to consent to?
This trial has two parts: **Part 1 ctDNA Surveillance** and **Part 2 Pembrolizumab Treatment**. Each part of the trial is explained in more detail in the sections below and in the following flow chart which sets out each step of the trial.

You are being asked to consent to participate in Part 1 of the trial for ctDNA surveillance. We do not know now whether you will be asked to take part in Part 2 and have pembrolizumab treatment as this depends on the results of your blood tests during ctDNA surveillance. It is important that you only agree to take part in Part 1 of the trial if you believe you would also be willing to take part in Part 2 of the trial and start pembrolizumab treatment should you have a positive ctDNA result. Taking part in Part 2 would also mean continued ctDNA surveillance for 1 year after finishing treatment.

You should continue to discuss the trial with your doctor or nurse until you are sure all your questions have been answered. You will be given time to ask all the questions you want.



Your doctor will be informed of the ctDNA positive result and will discuss Part 2 of the trial and pembrolizumab treatment with you

PART 1: ctDNA Surveillance

What happens in ctDNA surveillance?
During ctDNA surveillance, we would like to collect **a blood sample from you every 3 months for up to 2 years**. These blood samples will be tested to check if ctDNA is present in your blood. Normally, outside of this research trial, ctDNA surveillance is not done and after receiving standard treatment (chemotherapy and surgery with or without radiotherapy) no further treatment would be offered to you unless your cancer returned and could be seen on a scan.

If ctDNA is found in your blood during ctDNA surveillance, your doctor will be informed of this result. You may be eligible to start pembrolizumab treatment in Part 2 of the trial, depending on the results of tests which are described later on in this information sheet, in the section entitled 'What will happen if ctDNA is found in my blood sample during ctDNA surveillance?' . If the tests show that your cancer has come back you will not be able to start pembrolizumab treatment and instead your doctor will advise you on what options for treatment of disease recurrence are available to you outside of the trial.

If no ctDNA is found in your blood in the first year of surveillance you will continue with ctDNA surveillance for a second year, the blood samples collected in the second year are for future research to help us understand how long we should continue ctDNA surveillance for. The blood samples collected in the second year will not be analysed at the time they are collected and sent to the central laboratory, and the results of these tests will not be provided to you or your doctor.

Due to the coronavirus outbreak (COVID-19) blood sample collection was temporarily halted on 19 March 2020. This may have resulted in you missing blood samples for ctDNA surveillance. Where blood samples are missed, the first year of active ctDNA surveillance (where you may be allocated to treatment) may be extended by the number of missed surveillance samples so that you are not disadvantaged by the temporary halt. You will not be asked to provide extra blood samples at this time. Please discuss this with your treating team if you have any questions.

What will happen if I decide to take part?
If you decide to take part in the trial you will be asked to sign the c-TRAK TN registration consent form. You will be given a copy of the signed consent form and this information sheet to keep.

Following your consent, your doctor will check your medical records to ensure that you meet the eligibility criteria for the trial. These criteria are aimed at excluding patients who are not suitable for this treatment and in whom it may be unsafe to give pembrolizumab. At this time, your nurse or doctor may ask you questions which will help the researchers to understand the impact of your cancer diagnosis on your daily life. This may include questions about your employment status, whether you are a carer for a family member and about how far you travel to reach the hospital. You may be asked these same questions again later in the trial to check if anything has changed. You will also be asked about your medical history and any other medications you take.

If after these checks your doctor confirms that you meet the eligibility criteria, you will be asked to give a blood sample. Approximately 7 teaspoons (40 ml) of blood will be taken. In addition, the research team will arrange for two tissue samples, taken from your tumour tissue that was removed during your diagnostic biopsy and/or surgery, to be collected. Your blood and tissue samples will be sent to the trial central laboratory at the Royal Marsden NHS Foundation Trust and the Institute of Cancer Research for testing. The genetic material (DNA) will be extracted from these samples and will be analysed to see if we can find a mutation present only in your tumour that we can look for and track in your blood over time (ctDNA surveillance). Your doctor will contact you when the results of the genetic testing on your tumour tissue and blood become available and confirm whether or not you are eligible to undergo ctDNA surveillance. We estimate this will take up to 8 weeks.

If you have previously entered into another study that has looked for mutations in your tumour, for example the Genomics England (GEL) programme, you will be asked to give your consent for us to have access to this information. This may make it faster to check if you are eligible to enter ctDNA surveillance.

What will happen if I am <u>not</u> eligible for ctDNAsurveillance ?
If we cannot find a mutation in your tumour tissue that we can look for and track in your blood, then you will <u>not</u> be eligible to begin ctDNA surveillance and therefore will not continue in the trial. Your doctor will discuss your care outside of the trial with you.

What will happen if I am eligible for ctDNA surveillance?
If the mutation testing results confirm you are eligible for ctDNA surveillance you will be invited to attend the hospital to give a blood sample to start ctDNA surveillance.

Following this you will be asked to return to the hospital every 3 months for the next 2 years (approximately 8 hospital visits) to give a blood sample. Approximately 7 teaspoons (40ml) of blood will be taken each time. It is possible that you may be asked to give additional blood samples, for example, if there is a problem with the quality of a sample which means it cannot be analysed accurately. In such cases, you would need to make an extra visit to the hospital. Your blood samples will be sent to the trial central laboratory and tested to check if ctDNA is present.

What will happen if ctDNA is found in my blood sample during ctDNA surveillance?
If ctDNA is found in your blood during the first year of ctDNA surveillance (i.e. you have a positive blood test), the ICR-CTSU will inform your doctor who will then arrange an appointment with you to explain the results of your ctDNA test and arrange for imaging scans (e.g. CT scan, PET-CT, bone scan) to check your cancer has not come back.If your cancer has not come back your doctor will provide you with further information on receiving pembrolizumab treatment and will ask whether you would still like to receive this treatment. If so, you will undergo further pre-treatment assessments to ensure that it is safe for you to start pembrolizumab. If your cancer has come back you will not be able to start pembrolizumab and instead your doctor will advise you on what options for treatment for disease recurrence are available to you outside of the trial.

As part of your standard treatment you may receive a type of chemotherapy called capecitabine, which you may continue to take during ctDNA surveillance. If you have a positive ctDNA test result whilst still receiving capecitabine you will be asked whether you would like to switch your treatment to pembrolizumab. If you have a positive ctDNA test

result whilst still receiving adjuvant radiotherapy, you will be able to continue this radiotherapy alongside pembrolizumab treatment.

It will be up to you to decide whether you would like to receive pembrolizumab treatment. As with any treatment, pembrolizumab can have side-effects. These are explained below in Part 2: Pembrolizumab Treatment. The risks and potential benefits associated with pembrolizumab treatment will be explained fully to you again before you decide whether or not you want to have the treatment and you will be provided with further information at this time.

Due to the coronavirus outbreak (COVID-19) blood sample collection was temporarily halted on 19 March 2020. This may have resulted in you missing blood samples for ctDNA surveillance. Where blood samples are missed, the first year of ctDNA surveillance (where you may be allocated to treatment) may be extended by the number of missed surveillance samples so that you are not disadvantaged by the temporary halt. You will not be asked to provide extra blood samples at this time. Please discuss this with your treating team if you have any questions.

What if my cancer comes back during ctDNA surveillance?
If your cancer comes back whilst you are taking part in the trial, you will stop ctDNA surveillance and will not continue in the trial. Your doctor will advise you on which further options are available to you outside of the c-TRAK TN trial. As part of standard care at your hospital you may have a biopsy taken from the tumour that has come back. We would like to collect a sample of this tumour tissue to allow us to check if the mutations in this tissue are the same as those detected in your original tumour.

PART 2: Pembrolizumab Treatment

What will happen if I decide to have treatment?
If you decide you still want the pembrolizumab treatment you will need to have some pre-treatment assessments to check that it is safe for you to start the treatment.

The pre-treatment assessments will be fully explained to you at this time and will only be done after you have agreed to take part by signing the consent form for Part 2 (Pembrolizumab treatment). However, if you would like further information now, then please ask your doctor for a copy of the c-TRAK TN Patient Information Sheet for Pembrolizumab Treatment.

What will happen if it is deemed unsafe to give me pembrolizumab treatment?
If the results of the pre-treatment assessments confirm that it would be unsafe for you to be given pembrolizumab, then you will not be able to start the treatment. You will be asked to continue to give a blood sample for ctDNA surveillance every 3 months for up to 2 years from when you first started the ctDNA surveillance. The results of these further blood tests during ctDNA surveillance will not be analysed at the time that they are collected and sent to the central laboratory as they will be used for future research. The results therefore will not be shared with you or your doctor.

What will happen if cancer can be seen on the pre-treatment scan?
If your cancer has come back and can be seen on the pre-treatment scan (CT or bone scan) then you will not be able to start pembrolizumab treatment and will not continue in the

trial. Your doctor will advise you on which further options are available to you outside of the c-TRAK TN trial.

What will happen if it is deemed safe to give me pembrolizumab treatment?
If no cancer can be seen on your scan, and it is deemed safe by your doctor for you to commence treatment, you will be able to start pembrolizumab treatment. It is important for you to understand that treatment will last for up to 12 months and will not be available to you outside of the trial. During treatment you would need to attend the hospital every 3 weeks (approximately 17 hospital visits) to receive treatment and have a blood sample taken for ctDNA surveillance and to ensure it is safe for you to continue pembrolizumab.

Some hospitals will also be taking additional blood samples (30ml, or about 5 teaspoons) at the start of treatment and at 6 weeks after starting treatment. Using these blood samples we hope to identify whether your immune system can recognise the mutations present in your cancer, and whether this recognition increases following pembrolizumab treatment. This test is called peripheral blood mononuclear cell (PBMC) isolation.

After pembrolizumab treatment stops you will be asked to visit the hospital every three months for a further 12 months (additional 4 hospital visits) to give a blood sample for ctDNA surveillance follow-up. The results of these follow up ctDNA surveillance blood tests will not be analysed at the time of collection, these will be used for future research. The results therefore will not be shared with you or your doctor.

What are the side effects of treatment with pembrolizumab?
As with any treatment, pembrolizumab can have side-effects. No-one can predict before starting treatment who will have any of these, or how serious they might be. Not all patients will experience side-effects.

Side effects of pembrolizumab that have been previously reported are listed in the table below. There may also be risks involved in taking this medication that have not been identified in the studies done so far, **so if you receive pembrolizumab and anything is troubling you, please make sure you tell your trial doctor or nurse about it**. Your progress will be closely montiored and your doctor will offer whatever help is available to cope with any side effects you might have. In some case, medications can be given to make the side-effects less serious or less uncomfortable. Occasionally some patients need a short stay in hospital for side effects to be treated, and on rare occassions these can be serious.

Side effects of Pembrolizumab	
Very common side effects (occurring in at least 1 out of 10 patients (≥10%) treated with pembrolizumab)	• Diarrhoea (loose or watery stools) • Itching of the skin • Cough
Common side effects (occurring in at least 1 out of 100 patients (≥1%) treated with pembrolizumab)	• Joint pain • Anaemia • Shortness of breath • Stomach pain • Dry skin

Side effects of Pembrolizumab	
	• Underactive thyroid gland which may cause you fatigue, weight gain, constipation, being sensitive to cold (hypothyroidism) • Inflammation of the lungs so you may feel short of breath and cough (pneumonitis/pneumonia) • Fever • Rash • Back pain • Pale white patches develop on the skin • Low levels of salt in the blood that may cause you to feel tired, feel confused, have a headache, have muscle cramps, and/or feel sick to your stomach (hyponatraemia)
Uncommon side effects (occurring in at least 1 out of 1000 patients (≥0.1%) treated with pembrolizumab)	• Nausea • Tiredness (fatigue) • Decreased appetite • Headache • Dizziness • Vomiting • Constipation • Inflammation of the muscles so you may feel weak or have pain in your muscles (myositis) • Pain in limbs, joints or extremities • Physical weakness, lack of energy or enthusiasm • Build up of fluid under the skin causing swelling or puffiness in the legs or arms • Increase in results from liver and kidney function tests • Overactive thyroid gland which may cause you diarrhoea, anxiety, anger, sleeplessness, fatigue, excessive sweating , trembling (hyperthyroidism) • Dry eyes • Hair loss or colour change • Low level of, potassium in the blood • High levels of calcium in the blood • Difficulty sleeping (insomnia) • Inflammation of the liver so you may feel tired or not hungry, and may experience mild fever, muscle or joint aches, nausea and vomiting, and stomach pain (hepatitis) • Inflammation of the pituitary gland (a gland in the head) which may cause you headaches, change in eyesight, few to no menstrual cycles, weakness, vomiting and dizziness, or fainting (hypophysitis)

Side effects of Pembrolizumab	
	• Inflammation of the pancreas so you may have severe upper abdominal pain that may move to the back, nausea and vomiting that gets worse when you eat (pancreatitis) • Inflammation of the pancreas which can cause increased amylase in the blood and can lead to diabetes mellitus, so you may have too much sugar in your blood, thirst, and may need regular insulin shotsLow platelet count may cause bruising and an increased tendency to bleed (thrombocytopenia) • Low white blood cell counts may cause increased risk of infection (leukopenia) • Muscle and bone pain and stiffness • Reduction in function of the adrenal glands meaning they may not produce enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, having joint, muscle and stomach aches, nausea, vomiting, loose watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan (adrenal insufficiency) • Diminished hormone secretion by the pituitary gland, causing dwafism in children and premature ageing in adults • Increased liver enzymes in the blood, aspartate aminotransferase and alanine aminotransferase • Abnormal accumulation of fluid around the heart affecting heart function (pericardial effusion) • Scarring of the lungs causing stiffness and difficulty breathing • Reaction to pembrolizumab may cause dizziness, fainting (low blood pressure), flushing, rash, fever, shortness of breath or nausea at the time of receiving your intravenous (IV) infusion or just after, or pain at the site of infusion (infusion related reaction). Rarely, an extreme reaction can occur (cytokine release syndrome). • Inflammation of the bowels/gut/large intestine, which may cause severe pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus (colitis) • Inflammation of the skin so you may have itching, blistering, skin redness, rash, widespread peeling of the skin and possibly ulceration and pustule formation. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of

Side effects of Pembrolizumab	
	your skin to peel from all over your body which can cause severe infection
Rare side effects which can be serious (occurring in less than 1 out of 1000 patients (≤0.1%) treated with pembrolizumab)	• Taste changes (dysguesia) • Fever, flu-like illness or chills • Dry mouth • Skin conditions including but not limited to, eczema, red flaky skin, areas of discolouration, acne) • Inflammation of fluid that surrounds tendons which can cause joint swelling, pain and stiffness (tenosynovitis) • High blood pressure • Increase in bilirubin which may cause appearance of jaundice • Inflammation of the eye so you may have redness of the eye, blurred vision, be sensitive to light, see floaters, have eye pain or headaches (uveitis) • Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout the body, which can cause chest pain, shortness of breath, and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting (myocarditis) • Epilepsy • Numbness in fingers and toes • Increase in a certain type of white blood cells (eosinophils) may cause increased allergic reactions • Inflammation of the thyroid gland an organ that makes and stores thyroid hormones. This condition may lead to change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy (thyroiditis) • Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behaviour, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of conciousness (encephalitis). • Inflammation of the nerves that may cause pain, weakness, or tingling in your hands and feet, and may spread to your legs, arms, and upperbody, leading to severe muscle weakness and possible temporary paralysis (Guillain-Barré syndrome)Low red blood cells due to the body destroying and removing the cells before their normal lifespan is over (haemolytic anaemia or aplasia pure red cell)

Side effects of Pembrolizumab	
	• A condition that may make you feel weak and tired and may casue drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing (Myasthenic syndrome/Myaesthenia Gravis including exacerbation)Small patches of red and swollen tissue (formed from small clusters of immune cells), called granulomas, in the organs of the body – usually lymph nodes, eyes, lungs or skin – which can cause tender red lumps, shortness of breath and coughs (sarcoidosis) • Small intestinal perforation which can cause severe abdominal pain and tenderness, sepsis with an increased heart rate, increased breathing rate, fever and confusion • Inflammation of the fatty layer beneath the skin of the shins which may cause painful red lumps which look dark and feel hard (erythema nodosum) • Severe inflammation or blistering of the skin (Stevens-Johnson Syndrome or toxic epidermal necrolysis) • Inflammation of the nephrons within the kidney, leading to reduced kidney function • Changes in eyesight, eye pain, whitish patches on the skin and hearing loss (Vogt-Kayanagi-Harada disease) • Swelling around the eyes, mouth and face • Fluid retention (swelling) • Inflammation of the muscles or associated tissues such as blood vessels • Polymyalgia rheumatica – inflammation, pain and stiffness in the muscles around the shoulders, neck and hips • Excess protein excreted in urine due to damage to the blood vessels within the kidney • Depressed reflexes, weakness, sensory loss and slowed nerve conduction • Pressure ulcers • Low white blood cell counts may casue increased risk of infection (neutropenia & lymphopenia) • Low platelet count may cause bruising and an increased tendency to bleed (Immune thrombocytopenic purpura) • Inflammation of the two thin layers of a sac-like tissue that surround the heart (pericarditis) • Inflammation of the iris of the eye which can cause pain, light sensitivity and sight loss.

Side effects of Pembrolizumab	
	• Autoimmune responses which lead to inflammation of the pancreas or large intestine • Abnormal liver function as a result of drug induced liver injury • Anaphylactoid reaction: a serious allergic response that involves swelling, hives, lowered blood pressure and in severe cases, shock • Immune mediated response to the drug, symptoms can range from mild to severe and include rash, anaphylaxis and serum sickness. • A condition called haemophagocytic lymphohistiocytosis which is caused by overactive histiocyctes and lymphocytes and presents as persistent fever, rash, enlarged liver and spleen • Inflammation of the meninges, the membrane covering the brain and spinal cord, causing fever, neck pain, headaches and vomiting (asceptic meningitis) • Bruising • Type 1 diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination, and weight loss. You are likely to need regular insulin shots. • Inflammation of the kidney leading to reduced function so you may pass less urine, see blood in your urine or experience swelling and low back pain (nephritis) • Inflammation of the spinal cord with pain, numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating, and constipation (myelitis)

Other side effects may include solid organ transplant rejection.

What if my cancer comes back during treatment?

If your cancer comes back whilst you are receiving treatment, you will stop pembrolizumab treatment and will not continue in the trial. Your doctor will advise you on which further options are available to you outside of the c-TRAK TN trial. As part of standard care at your hospital you may have a biopsy taken from the tumour that has come back. We would like to collect a sample of this tumour tissue to allow us to check if the mutations in this tissue are the same as those detected in your original tumour.

3 What happens to the tissue and blood samples?

What will happen to my tissue and blood samples?
All of the tissue and blood samples that you donate will be sent to the trial central laboratory at the Royal Marsden NHS Foundation Trust and the Institute of Cancer Research where they will be stored and the genetic material (DNA) will be removed for mutation analysis. All your samples will be labelled with your date of birth, date of sample collection, initials and unique trial number when they are sent to the central laboratory so we can identify each sample. When they arrive at the trial central laboratory, a unique laboratory code will be allocated to each sample. The coding will maintain your confidentiality whilst allowing biological details to be compared to clinical findings.

In addition, we would like to use your tissue and/or blood samples for further research within the c-TRAK TN trial. For such research it may be necessary to use commercial companies to carry out tests on the the samples. For example, in situations where the researcher organisations do not have access to specialist equipment and/or where using a commercial company may be more cost-effective because they can carry out a greater volume of tests within a short time frame. In such cases, after testing is complete the commercial company would return all result data and any surplus samples to the research organisation and would not be permitted to use the data or samples for their own research.

In order to gather more information, we may share your samples and/or information we gain from your samples, including genetic details, with other cancer researchers at other specialist research laboratories in the UK, the EU or outside the EU. Your samples and information about your cancer will be anonymised before they are shared meaning you cannot be identified from the sample/information. This will not affect your care or influence whether or not you receive pembrolizumab treatment.

Can I access the results of my blood tests done during ctDNA surveillance?
If ctDNA is found in your blood during surveillance, you and your doctor will be informed of the positive result and you will be given the opportunity to receive pembrolizumab treatment.

What will happen to the results of the tissue and ctDNA surveillance?
If it is a useful way of advancing our knowledge of the treatment of cancer, in the future, the organisers of this trial would like to share the information we collect from your tissue and blood samples, including genetic information, with other cancer researchers, or combine this with information collected from other studies. Provided you give permission, information about you may be passed to other researchers but they would not be able to identify you from the information provided.

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

What are the possible benefits of taking part?

The ctDNA surveillance blood tests performed within the c-TRAK TN trial may identify that your cancer is at risk of coming back and therefore you may be potentially eligible for pembrolizumab treatment. It is possible that pembrolizumab treatment could clear the ctDNA in the blood which may delay or prevent the cancer coming back but we do not know this for certain.

It is important to note that you may not get any direct benefit from participating in the c-TRAK TN trial. However, your participation is likely to help us find answers to questions that could help to improve the treatment and/or quality of life for future breast cancer patients.

What are the possible disadvantages of taking part?
The disadvantages and risks of taking part are detailed below:

i. Blood tests and additional hospital visits:

As explained in section 2 of this patient information sheet, taking part in the c-TRAK TN trial requires you to give frequent blood samples which will involve regular visits to the hospital.

The number of blood samples required in this trial is more than if you were receiving standard care outside of this research trial. Risks linked with collecting blood samples from your arm include pain from the needle being inserted, bruising, light-headedness, possible fainting and (rarely) infection.

ii. Radiation exposure (scans):

If during ctDNA surveillance you have a positve ctDNA test result and become potentially eligible to receive pembrolizumab treatment, you would need to have a scan prior to starting treatment to check that your cancer has not come back. Your doctor will organise for you to have the same type of scan(s) as you had when you were first diagnosed with breast cancer. This might be a CT and /or bone scan, or a PET-CT. These scans involve some exposure to ionising radiation which can have an adverse effect on the body, including a small increased risk of causing a cancer several years after the exposure. However, in this case the benefits outweigh any such risk as the additional scan(s) will allow your doctor to detect if your cancer has come back.

CT scans (Computerised Tomography scan) use radiation (X-rays) to form detailed pictures of the structures inside the body The amount of radiation you will be exposed to during the scan is equivalent to seven years of exposure to natural radiation from the environment. CT scans are painless and generally safe and take about 10-20 minutes. You may have an injection of a type of dye (called contrast medium) just before the scan which helps to make the scan clearer. There is a small risk that you could have an allergic reaction to the dye used and the dye can cause kidney damage, especially if you are diabetic, dehydrated (lost body water) or elderly.

Bone scans look for changes or abnormal areas in the bones and require a tiny dose of radioactive material to be injected into your vein. You then lie on a bed so a camera can take special pictures of your bones. The tiny dose of radioactive material is safe, and virtually disappears from your body in your urine within 24 hours. The radiation

dose associated with a bone scan is equivalent to what you would receive from natural background radiation in around two years. The injection of the radiotracer may feel like a small sting and there may be possible bruising at the injection site. Other side effects are uncommon, and when encountered are usually mild, such as nausea and vomiting, or you may become uncomfortable lying still for the duration of the examination.

PET-CT uses X-rays to take pictures of the structures of your body. At the same time, a small amount of radioactive drug will be injected into your vein. This shows up areas of your body where the cells are more active than normal. The scanner combines both of these types of information. During a PET-CT scan you are exposed to radiation from the X-rays and the radioactive drug. The radiation in the radioactive drug is very small, and goes away (decays) very quickly. It does not make you feel unwell. Drinking plenty after the scan helps flush the drug out of your system. The radiation from the CT part of the scan is also kept to the minimum necessary. The risk of the radiation causing any problems in the future is very small. Doctors only do these scans if they are necessary. They make sure the benefit of having the scan outweighs any possible risks. The scan is generally painless and can take about 30-60 minutes. The radiation dose associated with a PET-CT scan is equivalent to what you would receive from natural background radiation in around 6 years.

iii. Risks to an unborn child:

Pembrolizumab can cause harm to an unborn or nursing baby or have an adverse event on sperm. Therefore, if you are pregnant, trying to become pregnant or breast-feeding, you cannot enter the trial. If you become pregnant during the trial, there is a risk that pembrolizumab treatment could affect you or your unborn child. If applicable, you must avoid having sex (abstinence) or use reliable birth control methods during the trial (including during ctDNA surveillance), which you can discuss with your trial doctor. Before receiving pembrolizumab treatment, a pregnancy test will be carried out for all women who are able to get pregnant. You must continue using birth control for at least 4 months after your last dose of pembrolizumab.

The following birth control methods are allowed during the trial:

- **Two** of the following barrier methods in combination:
    - Diaphragm
    - Condom
    - Copper intrauterine device (IUD)
    - Contraceptive sponge
    - Spermicide

OR

- **One** of the above barrier methods in combination with:
    - Hormonal contraceptives (including oral, subcutaneous, intrauterine, or intramuscular) that are registered and marketed containing oestrogen and/or a progestational agent

If you think you may be pregnant, you must tell your doctor immediately. Pregnancy will be a reason to stop participation in the trial. If you become pregnant, information on the outcome of your pregnancy will be requested.

iv. Side effects of pembrolizumab treatment:

Pembrolizumab is a licensed drug for the treatment of advanced melanoma (a type of skin cancer), non-small cell lung cancer, classical Hodgkin lymphoma (a type of cancer that affects certain blood cells) and bladder cancer. However, we are using it to treat patients who would not usually receive this drug i.e. in those with triple negative breast cancer. This means that the drug is regarded as experimental and not all of its side effects are yet known. If you receive pembrolizumab treatment you may therefore experience some side effects that are not anticipated and are not listed in section 2 of this information sheet. There is no way of predicting if you will experience any side effects, or how severe they will be. You should contact your trial doctor or nurse if you experience any side effects, even if you are not sure that any problems you may have are related to taking the trial treatment. Occasionally some patients need a short stay in hospital for side effects to be treated, and on rare occasions these can be serious.

5 Further information about taking part

How long will I remain on the trial?
You will be required to attend hospital visits for up to two years during ctDNA surveillance, or up to three years if you receive pembrolizumab treatment. Following completion of ctDNA surveillance and/or pembrolizumab treatment your doctor or a member of the research team would like to contact you by phone every 6 months to check how you are doing.

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

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

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

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

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

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

Will my taking part in this study be kept confidential?
All information which is collected about you during the research trial will be kept strictly confidential. When you register for the trial, your full name, date of birth, postcode, hospital number and NHS number (or Community Health Index (CHI) and/or hospital number in Scotland) will be passed to The Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU) where the trial is being coordinated. You will be given a unique Trial ID number, which will be used together with your initials and date of birth on forms that the research staff will send to ICR-CTSU. All information about you will be stored securely. It will be treated as strictly confidential and nothing that might identify you will

be revealed to any third party. Only members of the research teams at your hospital and the ICR-CTSU will have access to the information that could allow this Trial ID number to be linked to you. From time to time we would like to know how you are getting on. Ideally we would like to do this for life, and we would like to use national records, which are kept on everyone's health status to find this out. 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.
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 cancer doctor who has overall responsibility for the trial. These details may also be sent to the UK Regulatory Agency (Medicines and Healthcare Regulatory Agency, 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 Research Ethics Committee who approved the trial, all the doctors who are responsible for patients in this trial, and to the pharmaceutical company (Merck, Sharp & Dohme) which makes the trial treatment. However, your confidentiality will be protected at all times.

In addition, the pharmaceutical company which makes the trial treatment may need to use the results of the trial, which includes data collected about your treatment in the trial, to support an application to the regulatory authorities to obtain a license (also known as a marketing authorisation) for the drug being used in this trial. However, your confidentiality will be protected at all times.

Representatives from the ICR-CTSU, NHS Trust relevant to your taking part in research, the sponsor (The Institute of Cancer Research), the Medicines and Healthcare products Regulatory Agency (MHRA) and ethics committee approving the trial, pharmaceutical company that manufactures and supplies the trial treatment (Merck, Sharp & Dohme) and may have offices outside of the UK/EU, and third parties approved by the ICR-CTSU may need to examine your medical records to the extent permitted by applicable laws and regulations to make sure that the information received is correct. All information will be kept confidential.

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

Will my GP be involved?
Yes, your GP will be notified about your participation in this trial. By signing the consent form you are agreeing to this. This will ensure that your GP knows about any trial treatment you may be given in the event of any side effects.

Will information about me be shared with other researchers?
The organisers of this research would like to use your tissue and/or blood samples for further research within the c-TRAK trial. In order to gather more information, we may share your samples and/or information we gain from your samples, including genetic details, with other cancer researchers at other specialist research laboratories in the UK, the EU or outside the EU. Your samples and information about your cancer will be de-identified using a unique laboratory code before they are shared meaning you cannot be identified directly

from the sample and information. This will not affect your care or influence whether or not you receive pembrolizumab treatment.

When you agree to take part in a research trial, the information about your health and care (including genetic information obtained from analysis of blood and tissue samples) may be provided to researchers running other research studies in the sponsor organisation (The Institute of Cancer Research) and in other organisations now or in the future. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research: https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/.

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

Where there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee. Please initial the consent form to show that ICR-CTSU have your permission to do this. If any future research undertaken leads to a new treatment or test that becomes commercially viable, you will not financially benefit from this.

6 Information about how the c-TRAK TN trial is conducted

Who is funding and organising the research?
The research trial is funded by the NIHR Biomedical Research Centre (BRC) at The Royal Marsden NHS Foundation Trust and by Merck, Sharp and Dohme (MSD), the pharmaceutical company who manufacture pembrolizumab. MSD are supplying the drug free of charge and providing additional funding to support the management of the trial. The research is organised by the Institute of Cancer Research (led by Professor Nicholas Turner). The trial is coordinated by The Institute of Cancer Research Clinical Trials & Statistics Unit (ICR-CTSU). The research trial is being carried out by a network of doctors across the UK. The trial funding helps to cover the cost of including information about you in the trial, the laboratory tests and helps support the research staff. None of the researchers are personally benefiting from this funding.

Who has reviewed the trial?
Cancer Research UK has reviewed c-TRAK TN and supports the aims of the trial. c-TRAK TN has also been approved by the UK Regulatory Agency (Medicines and Healthcare Regulatory Agency, MHRA), a Research Ethics Committee (South Central – Oxford C Research Ethics Committee) and the Health Research Authority (HRA). Their approval means they are satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits, and that you have been given the right information to decide whether to take part.

What happens if I want to stop participating in the trial?
Your participation in this research trial is voluntary. If you agree to take part and then change your mind later on, you can withdraw from the trial at any point without giving a reason. By consenting to Part 1 you are under no obligation to consent to Part 2 of this trial even if ctDNA is identified in one of your blood samples and you are potentially eligible to receive pembrolizumab treatment. You can change your mind and are free to withdraw from any part of this trial at any time if you want to. If you withdraw from the trial, it will not affect the standard of care you receive. Your trial doctor will discuss alternative treatment with you and offer you the most suitable treatment available.

If you should withdraw fully from the trial, trial data collected before your withdrawal may still be processed along with other data collected as part of the clinical trial. However, you may request that all retained identifiable samples are destroyed to prevent future analysis.

If you were to withdraw from the trial, we would like your permission for your hospital to continue to send basic clinical information on your progress that would routinely be collected and written in your medical records to ICR-CTSU. This is so that the overall quality of the trial is not impaired. Please initial the consent form to confirm your permission for this.

What if there is a problem?
If you have any concern about any aspects of the trial you should first ask to speak with your trial doctor or research nurse, who will try to resolve the problem. If you remain unhappy and wish to complain formally about any aspect of the way you have been approached or treated during the course of this trial, you may do so under the standard

National Health Service (NHS) complaints procedure, which is available to you at your doctor's hospital. We recommend that you obtain a copy of your hospitals complaints procedure or policy if you intend to make a complaint.

[**Sites in England**] Concerns can also be raised by talking to your local Patient Advice and Liaison Service (PALS). You can contact the PALS team at [*insert Trust name*] on [*insert relevant contact details*].

[**Sites in Scotland**] Concerns can also be raised by talking to the Patient Advice and Support Service (PASS). You can contact PASS via the National Citizens Advice Bureau on 0808800 9060 or through your local Citizens Advice Bureau (www.cas.org.uk/patientadvice).

[**Sites in Wales**] Concerns can also be raised by talking to the Patient Support and Advisory Service (PSAS). You can contact PSAS on 0300 0200 159 or emailing hdhb.patientsupportservices@wales.nhs.uk.

[*Delete above sections as appropriate for location of trial site.*]

You will be closely monitored both during and after treatment and any side effects will be treated as appropriate. If you suffer any side effects or injury, please notify the trial doctor immediately so you can obtain appropriate medical attention.

In the unlikely event that you are injured by taking part, compensation may be available. If you are harmed due to the negligence of someone treating you, then you may have grounds for legal action but you might have to pay for it. NHS Trusts are responsible for clinical negligence and other negligent harm to individuals that are under their care and covered under the NHS Indemnity Scheme.

If you suffer adverse side effects of the trial treatment or harm caused by procedures you have undergone specifically for the trial you may be able to claim compensation from The Institute of Cancer Research as Sponsor of the c-TRAK TN trial. In deciding the level of compensation to be awarded, consideration will be given to the likelihood of side effects and any warnings that were given.

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 if relevant new information becomes available?

Sometimes during the course of a trial, new information becomes available about the treatment being studied. If this happens, your trial doctor will tell you about it and discuss whether you want to, or should, continue in the trial. If you decide not to carry on, your doctor will make arrangements for your continued care. If you decide to continue in the trial you may be provided with an updated information sheet and asked to sign an updated consent form.

If the new information means it would be in your best interests to withdraw you from the trial, your doctor will explain the reasons for this and arrange for your continued care. If the trial is stopped for any other reason, you will be told why and your doctor will arrange for your continued care.

What will happen to the results of the 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. Once available, the results will also be available on the Cancer Research UK trials database (http://www.cancerresearchuk.org/cancer-help/trials/).

The results will help to decide how to treat early breast cancer patients at high risk of relapse 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 happens now?
Take some time to think about the trial and make your decision. You may wish to discuss it with your GP, family or friends. Your doctor or nurse will be happy to answer any questions you might have. Once you have reached your decision please let your doctor or nurse know. If you choose to join the c-TRAK TN trial you will be asked to sign a consent form and will be given a copy to keep together with this information sheet.

7 Useful contact information

Who else can I contact for further information?
Macmillan Cancer Support is a registered charity providing information, emotional support and publications about all aspects of cancer for cancer patients and their families. You can contact one of their Cancer Information Nurse Specialists on the Macmillan Support Line; Freephone 0808 808 00 00, Monday to Friday, 9.00am to 8.00pm. In addition to their nurses, the Macmillan Support Line also has other specialist teams that can provide advice and information relating to welfare benefits, financial issues and everyday practical concerns.

You can learn more about clinical trials and the results of this trial once available on the Cancer Research UK's patient website (**http://www.cancerresearchuk.org/cancer-help/trials/**).

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

Your specialist is: _____

Contact phone numbers: _____