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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 PEMBROLIZUMAB TREATMENT

Version: 6.0
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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** triple negative 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: 01XXX XXX XXX

Invitation to have treatment within the c-TRAK TN trial

- You have been given this patient information sheet because you previously agreed to participate in ctDNA surveillance in the c-TRAK TN research trial.
- We are now inviting you to participate in Part 2 of this trial to receive pembrolizumab treatment because of the result from your recent ctDNA blood test.
- Participating in Part 2 of this trial is entirely up to you. Before you decide, we would like to remind you why the research is being done and for you to understand 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 have treatment and answer any questions you may have. Please ask if anything is unclear and 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

- We want to determine whether blood tests can detect if low levels of cancer cells are left over after standard treatment for your type of cancer, and if so, we want to study if additional treatment might prevent or delay the cancer coming back.
- We want to investigate if a treatment called pembrolizumab might help to get rid of cancer cells found in your blood.
- If you take part in Part 2 of the trial, you may be given pembrolizumab treatment for up to 12 months. During treatment you will be asked to give blood samples every 3 weeks and then every 3 months for another 12 months after completing treatment.

1 About the c-TRAK TN trial Part 2

Why am I being invited to take part in Part 2 of the c-TRAK TN trial?
You have been given this patient information sheet because you have been taking part in Part 1 (ctDNA surveillance) of the c-TRAK TN trial and we would now like to invite you to take part in Part 2. You have been giving blood samples every 3 months for ctDNA (circulating tumour DNA) surveillance and we have recently found ctDNA in your blood sample (i.e. a positive ctDNA blood test). Because of this, we would now like to offer you pembrolizumab treatment for up to 12 months. We want to find out if the pembrolizumab treatment might remove the ctDNA in your blood.

Do I have to take part?
No, it is up to you to decide whether or not to take part in Part 2 of the c-TRAK TN trial and have pembrolizumab treatment. Your participation is entirely voluntary and you will be given sufficient time to decide whether or not you wish to participate. Whether or not you decide to participate in the trial will not affect the standard of care you receive. If you do decide to take part in Part 2 of the trial you are free to stop participating at any time and do not have to give a reason.

What is the purpose of Part 2 of the c-TRAK TN trial?
The purpose of Part 2 of the c-TRAK TN trial is to find out if patients who have had ctDNA detected in their blood (i.e. have a positive ctDNA blood test) will benefit from having treatment with a drug called pembrolizumab. 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 the standard treatment.

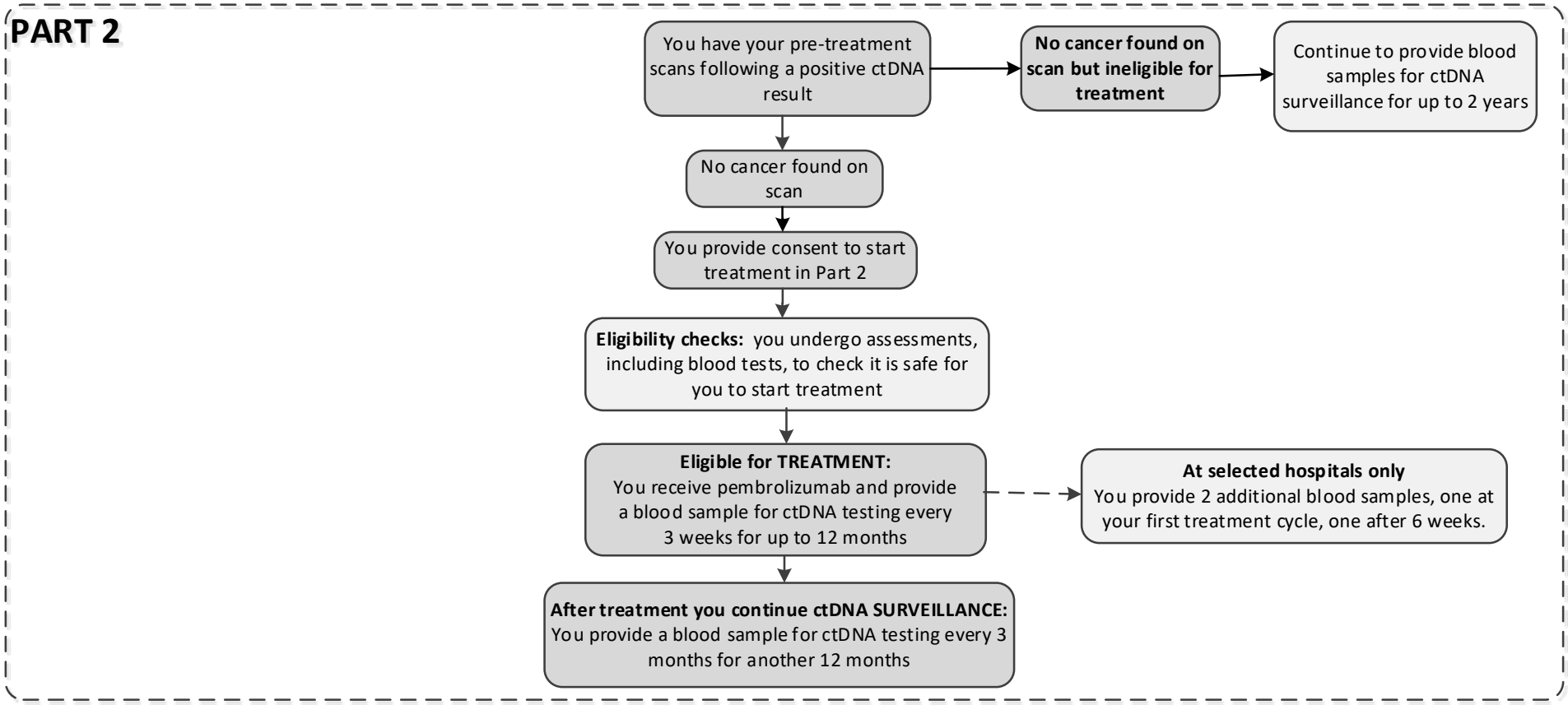
What is pembrolizumab?
Pembrolizumab is the drug being tested in this trial and is also called KEYTRUDA. Pembrolizumab works differently to chemotherapy and radiotherapy. It is an immunotherapy treatment that causes the body's immune system to attack cancer cells and is already used in routine practice for treatment of other types of cancer, such as malignant melanoma (a type of skin cancer). Pembrolizumab is currently being studied to see if it is effective in treating more than 30 types of cancer and to see what side effects it may cause.

How does pembrolizumab work?
Pembrolizumab works by blocking the actions of cancer cells which stop the body's immune system from working properly. Our immune system protects us from infection and diseases (including cancer) by detecting and destroying infected and faulty cells in the body. Cancer cells however, have a way of stopping the immune cells doing this. Immune cells have a protein present on their surface called Programmed Cell Death 1 (or PD1). Cancer cells have a partner protein on their surface called PD1 ligand (PDL1), which can stick to the PD1 protein on the immune cell. When the immune cells find cancer cells in the body, if the PD1 and PDL1 proteins stick together, much like a key in a lock, a reaction takes place, which switches the immune cells off. This makes the immune cells die or become exhausted and stops them attacking the cancer cells. Pembrolizumab works by stopping the PD1 protein on the immune cells from reacting with the PDL1 on the cancer cells. The result is that the immune cells are <u>not</u> switched off and can attack the cancer cells.

2 What taking part in Part 2 of the trial involves

What am I being asked to consent to?

You are now being asked to consent to Part 2 of the c-TRAK TN trial. This will involve you having pembrolizumab treatment every 3 weeks for up to 12 months and, in addition, to have ctDNA blood tests done every 3 weeks during treatment and then every three months for a further 12 months after stopping pembrolizumab treatment. Some hospitals will also be taking additional blood samples at the start of treatment and at 6 weeks after starting treatment.



What will happen if I decide to take part?
If you decide to take part in Part 2 of the trial you will be asked to sign the c-TRAK TN Pembrolizumab Treatment consent form. You will be given a copy of the signed consent form and this information sheet to keep.

If you are not currently receiving chemotherapy, you will need to have some pre-treatment assessments to check that it is safe for you to start the treatment. These assessments are described later on in this section of the patient information sheet.

If you are currently receiving a type of chemotherapy called capecitabine, your doctor will dicuss with you the option of stopping capecitabine treatment and switching to treatment with pembrolizumab. If you do decide to switch to pembrolizumab, you will need to have the same pre-treatment assessments desribed below to check that it is safe for you to start the treatment. You will also need to wait 4 weeks from stopping treatment with capecitabine before starting treatment with pembrolizumab.

If you are receiving adjuvant radiotherapy, you will be able to continue this radiotherapy alongside pembrolizumab treatment.

The pre-treatment assessments will only be done after you have agreed to take part by signing the consent form. They may all be done during one visit to the hospital or across a few different visits. Your doctor will talk to you about this. The pre-treatment assessments are shown in the following table:

Pre-treatment safety assessments	
Assessment	**Further details**
Review of your medical history, current medical conditions and any medications you are taking	To check that it is safe to give you pembrolizumab treatment.
Scan (eg CT, bone scan or PET-CT or MRI)	You doctor will have organised a scan for you to check that your cancer has not come back. You will have the same type of scan as you had when you were first diagnosed with breast cancer. This can be a CT and/or bone scan or a PET-CT.
Physical examination	Including blood pressure, heart rate, height and weight.
An electrocardiogram (ECG)	To assess your heart rhythm.
Collection of urine sample	For a pregnancy test (will only be carried out for women who are able to get pregnant).
	For routine safety checks.
Collection of blood samples	Approximately 3.5 teaspoons (20ml) of blood will be taken for routine safety checks.

What will happen if the tests show that I am <u>not</u> suitable to receive treatment or if I decide I do not want to have treatment?

If you decide that you do not want to have pembrolizumab treatment or if the results of these pre-treatment assessments confirm that it would be unsafe for you to be given pembrolizumab, then you will not 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 shared with you or your doctor, this is because we do not yet know if ctDNA can predict if the cancer will come back.

What will happen if cancer can be seen on the pre-treatment scan?

You will have provided consent for pre-treatment imaging scans to take place following a positive ctDNA result during consent for registration for ctDNA surveilance.

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 trial.

What will happen if the pre-treatment assessments show I am suitable to receive treatment?

If deemed safe and no cancer can be seen on your pre-treatment scan, you will be able to start pembrolizumab treatment. Your doctor or member of the research team will arrange an appointment for you to start pembrolizumab treatment. This should begin within 8 weeks of your doctor being informed that you have been randomly allocated to receive pembrolizumab treatment.

Pembrolizumab will be given in 3-week cycles over 12 months. Therefore you will need to attend the hospital every 3 weeks (approximately 17 hospital visits) to receive treatment and have blood samples 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 treatment stops you will need to attend the hospital every 3 months for another 12 months (additional 4 hospital visits) to have further blood samples taken for ctDNA surveillance.

You can change your mind and are free to stop participating in the trial at any time if you want to.

How will pembrolizumab treatment be given?

Pembrolizumab will be given through a drip put into your blood via a vein (intravenous infusion) at a dose of 200mg over 30 minutes. The first infusion will be given on the first day of trial treatment (Cycle 1 Day 1) then infusions will be given every 3 weeks. Treatment will continue for a maximum of 12 months. You may withdraw from pembrolizumab before this time if you experience unacceptable side effects or if your doctor believes further treatment is no longer appropriate or if your cancer comes back and can be seen on a scan. If your cancer comes back while you are receiving pembrolizumab treatment your doctor will stop the treatment and will advise you on which further options are available to you.

What assessments will take place during treatment?

You will be seen by a member of the research team at every hospital visit and you will have assessments done as outlined in the table below, to monitor your progress and any side effects you may have.

Assessments done at every hospital visit during treatment (every 3 weeks)	
Assessment	**Further details**
Medication review	Discussion with your doctor or research nurse to document changes in your health or medications since your last visit.
Physical examination	Including blood pressure, heart rate, height (at first cycle only) and weight (every 4 cycles).
Safety review	Discussion with your doctor or research nurse to document any side effects since your last visit
Collection of urine sample	For routine safety checks
Collection of blood samples	Approximately 3.5 teaspoons (20ml) of blood will be taken for routine safety checks.
	Approximately 3.5 teaspoons (20ml) of blood will be taken for ctDNA surveillance.
	Approximately 5 teaspoons (30ml) of blood will be taken at 2 visits, for assessment of your immune system's recognition of mutations present in your cancer (patients at selected sites only).

Before you are given each infusion of pembrolizumab your research nurse will review your medication, you will be asked if you have had any side effects and a doctor will perform a physical examination. You will have a blood test to ensure it is safe to continue with pembrolizumab treatment. You may need to visit the hospital on a different day prior to having your infusion to have the routine blood tests done so that the doctor can see the results and check it is safe for you to have the treatment. Your doctor may also perform an ECG to check your heart rhythm before you start your next treatment cycle.

Should you have any side effects that start before your next hospital visit, you should call your research nurse straight away.

What assessments will take place after stopping treatment?

You will need to visit the hospital when you stop receiving pembrolizumab treatment for assessments to be done. These might be done on the day you receive the last planned infusion or if your doctor decides that you should stop treatment early, then these might be done at the next planned visit soon after the decision to stop treatment. You will also need to visit the hopsital 30 days after the last infusion was given. At these visits your research nurse and doctor will check any medications you are taking, ask if you have any lasting side effects and conduct a physical examination and perform blood tests for routine safety checks.

You will then need to attend the hospital every 3 months for another 12 months after stopping pembrolizumab treatment to have a ctDNA blood test done. Once you have completed 12 months of ctDNA surveillance you will no longer need to come to the hospital. However, your doctor or a

member of the research team would like to contact you by phone every 6 months (from the date of your first ctDNA blood test) to check how you are doing and to document any changes in your health or medications since your last visit. We would also like to keep in touch with your doctor to continue to collect information about your health status. Ideally we would like to do this for life.

You need to consider carefully how these assessments and hospital visits will affect you and your family. Please ask your doctor or nurse if you have any questions about the assessments

Assessments done at hospital visit after stopping treatment		
Assessment	**Further details**	**Timing of assessment**
Medication review	Discussion with your doctor or research nurse to document changes in your medications since your last visit	▪ around the time of stopping treatment
Physical examination	Including blood pressure and heart rate	▪ around the time of stopping treatment
Collection of urine sample	For routine safety checks	▪ around the time of stopping treatment ▪
Safety Review	Discussion with your doctor or research nurse to document any side effects since your last visit	▪ around the time of stopping treatment ▪ at 30 days after stopping treatment
Collection of blood samples	Approximately 3.5 teaspoons (20ml) of blood will be taken for routine safety checks	▪ around the time of stopping treatment ▪ at 30 days after stopping treatment
	Approximately 3.5 teaspoons (20ml) of blood will be taken for ctDNA surveillance	▪ around the time of stopping treatment ▪ every 3 months from day of stopping treatment, for up to 12 months
Telephone call	To monitor your progress and find out about any side effects you may have	▪ every 6 months from day of your first ctDNA blood test

What are the side effects of treatment with pembrolizumab?

As with any treatment, pembrolizumab can have side effects. No-one can predict before you begin treatment whether you 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 monitored 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 • 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

Side effects of Pembrolizumab	
	• 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 to have headaches, change in eyesight, few to no menstrual cycles, weakness, vomiting and dizzines, or fainting (hypophysitis) • 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 shots • Low 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).

Side effects of Pembrolizumab	
	• 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 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)

Side effects of Pembrolizumab	
	• 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) • 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. • Autoimmune responses which lead to inflammation of the pancreas or large intestine

Side effects of Pembrolizumab	
	• 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.

Can I take other medication whilst having pembrolizumab treatment?
There are certain medications you cannot take whilst having pembrolizumab treatment. Examples include:

- Drugs that suppress the immune system
- Any other investigational medicine
- Herbal medication
- Live vaccinations including, but not limited to, measles, mumps, rubella, varicella herpes zoster, yellow fever, rabies BCG and typhoid (oral)
- If you require a flu vaccine you must ensure it is NOT a live vaccine. Seasonal flu vaccines are generally inactivated and are allowed; however nasal influenza vaccines (e.g. Flu-Mist) are live vaccines and are NOT permitted. Please check with your research nurse or doctor before having a flu vaccination
- If you begin taking any new medications or supplements while taking part in the c-TRAK TN trial, please inform your doctor or nurse as soon as possible

Will there be anything extra I need to do if I take part in Part 2 of the c-TRAK trial?
If you decide to take part, you will need to:

- Sign the consent form for entry into Part 2 to show you understand what participation involves
- Attend all scheduled appointments
- Talk to your trial doctor or nurse first if you want to stop receiving the pembrolizumab treatment for any reason
- Report all symptoms and side effects that you may experience to your trial doctor or research nurse as soon as they occur, whether or not you think they are caused by the trial treatment
- Tell your doctor about any other medicines that you take, even if you buy them without a prescription; this includes over the counter medications or herbal supplements
- Tell your doctor about any medical problems you have

Can I access the results of my ctDNA blood tests during treatment?

No, the results of the ctDNA blood tests will not be shared with you or your doctor. This is because we do not yet know for certain if finding ctDNA in the blood means that your cancer will come back in the future. In addition we do not know if pembrolizumab will have any effect in clearing the ctDNA in your blood and whether you will get any direct benefit from this. We hope that the results of this research trial will help us to understand this further and we need to make sure that there are no factors that might change the way patients are followed up as this could distort (or bias) the results of the trial.

What if my cancer comes back during the trial?

If your cancer comes back whilst you are taking part in the trial, you will stop ctDNA surveillance and 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 are the possible advantages and disadvantages of taking part?

What are the possible benefits of taking part?
It is important to note that whilst pembrolizumab treatment may clear the ctDNA in your blood we do not know for certain if you will get any direct benefit from this. 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?
It is possible that you will not have any therapeutic or other direct health benefits during or following completion of this trial. The risks of taking part are detailed below:

i. 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. 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.

ii. **Blood tests:**
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.

iii. Intravenous (IV) line:
The insertion of an IV line is required to administer the pembrolizumab treatment. This may cause discomfort, irritation, mild bruising, bleeding, leakage of drug solution, and rarely, infection, nausea, and light-headedness. Because pembrolizumab is an antibody, there is the possibility that you may experience an acute infusion reaction. These are side effects that develop during or immediately after the administration of pembrolizumab. The possible signs and symptoms are listed in the table below:

Signs and symptoms of an acute infusion reaction	• Blood pressure changes (increase or decrease) • Cough • Dizziness • Fast heart beat • Feeling cold

	• Feeling that the tongue is swelling or your airway is closing and you have trouble breathing • Fever • Headache • Joint pains • Muscle pains • Nausea • Rash, hives, or itching • Shortness of breath • Sweating • Tiredness • Vomiting

iv. Heart assessment (Electrocardiogram):

The electrocardiogram (ECG) for the electrical tracing of your heart involves placing small electrodes on the surface of your skin which may cause mild discomfort. Occasionally, a slight redness or inflammation may appear due to the adhesives used to attach the electrodes to the skin.

v. Radiation exposure (scans):

You will be required to have a scan prior to you receiving pembrolizumab treatment. This is to ensure there is no cancer visible on the scan and it is safe for you to have pembrolizumab treatment. 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.

vi. Risks to an unborn child:

It is not known if pembrolizumab may affect an unborn or nursing baby or have an adverse event on sperm. Therefore, if you are pregnant, trying to become pregnant or are 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, 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.

vii. Other medical condition identified:

If your trial doctor discovers during the trial that you have another medical condition e.g. high blood pressure, of which you were previously unaware you will be referred to the appropriate doctor for treatment of this condition. You may be able to continue or you may need to stop pembrolizumab treatment. Your doctor will discuss this with you if necessary.

viii. Additional hospital visits:

You will need to visit the hospital more frequently than you would if you were not taking part in the trial. Whilst having pembrolizumab treatment you will need to visit the hospital every 3 weeks for 12 months. After you stop having treatment you will need to visit the hospital every 3 months for another 12 months. This may cause some disruption to your normal activities and home life and this should be discussed with your family and friends if it will impact on them.

4 Further information about taking part

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 find out 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 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 trial 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 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 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.

5 General information about the c-TRAK TN trial

Who is funding and organising the research?
The research trial is funded by the NIHR Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and by Merck, Sharp and Dohme Limited (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. You are under no obligation to consent to part 2 of this trial even though ctDNA has been identified in one of your blood samples and you have been randomised 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.

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

If you were to withdraw from 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.

6 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: _____