(To be printed on local hospital headed paper)

PERSEUS1

PERSEUS1: Phase II Trial of the Immune Checkpoint Inhibitor Pembrolizumab For Patients Suffering from Metastatic Prostate Cancer

PARTICIPANT INFORMATION SHEET

PERSEUS1: Trial of Pembrolizumab in Patients with Metastatic Castration Resistant Prostate Cancer

We are inviting you to take part in a clinical study

- We are inviting you to take part in a clinical trial called PERSEUS1 for patients who have been diagnosed with Metastatic Castration Resistant Prostate Cancer (mCRPC) and are molecularly profiled. Part 1 of this information sheet tells you the purpose of the trial and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the trial.

- Before deciding to take part, please take time to read this information carefully and discuss it with friends and relatives if you wish. Please ask your study doctor or nurse if there is anything you do not understand or if you want more information.

- Thank you for taking the time to read this information.

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How to contact us

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

Part One: About the PERSEUS1 trial

1 Important information

What is the purpose of this study?

The main aims of this clinical trial are:

- To confirm whether a new drug called pembrolizumab is effective against mCRPC in a molecularly profiled population.
- To find out if a particular group of patients are more suitable for pembrolizumab treatment than others.

Why am I being invited to take part?

You have been invited to participate in this research study because you have been diagnosed with a specific type of prostate cancer called metastatic castration resistant prostate cancer (mCRPC) that is no longer responding to standard treatments and have qualified for screening for the PERSEUS1 study following molecular profiling through a separate screening study, such as the MAESTRO study, for patients with prostate cancer that identifies faulty genes from blood and tissue samples. The PERSEUS1 study is trying to find out whether a treatment called Pembrolizumab, is effective in the treatment of mCRPC.

Do I have to take part?

Your participation in this study is entirely voluntary. It is up to you to decide whether or not you wish to take part. You may wish to discuss study treatment with pembrolizumab versus alternate treatments available with your study doctor. Even if you refuse to participate in this clinical study, your future medical treatment will not be affected. If you do decide to take part you will be given this patient information sheet and consent form to read carefully and to sign. A copy of the signed patient information sheet and consent form will be provided to you for your records. If you do decide to take part, you are still free to withdraw from study treatment or from the study at any time.

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

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

Your participation in the study will continue until your study doctor feels that you are no longer gaining any benefit from treatment, or if you or your study doctor feels that any side effects you may be experiencing are unacceptable up to a maximum of 24 months. You may however decide

to stop your participation in the trial at any time. This means that the length of time each patient is in the study will vary.

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

What is pembrolizumab?

Pembrolizumab is the drug being tested in this study and is also called KEYTRUDA. It is made by a pharmaceutical company called Merck Sharp and Dohme (MSD). 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 not switched off and can attack the cancer cells. This study will look at how active pembrolizumab is in a specific type of prostate cancer called metastatic castration-resistant prostate cancer.

Why is pembrolizumab being used in this trial?

Lymphocytes are the type of cells of the body that contain an inhibitory ligand of programmed cell death 1 receptor. This receptor is responsible for inhibiting the immune response to cancer cells which express Programmed Cell Death Ligand (PD-L1 and PD-L2). Normally, in healthy indivuduals this effect is necessary to avoid inappropriate overreaction, such as auto-immune response. In cancer patients, antibody blockade against this receptor such as with pembrolizumab allows the immune system to target and destroy cancer cells. In laboratory experiments and clinical studies pembrolizumab has shown antitumour activity against a wide range of cancers.

To date, pembrolizumab has been shown to be a useful anticancer treatment in advanced melanoma, metastatic non-small cell lung cancer and metastatic urothelial cancer. Scientists believe that there is a larger group of prostate cancer patients who may also benefit from this treatment.

3 What happens during the trial?

What will my taking part in the trial involve?

If you agree to participate in PERSEUS1, you will be asked to sign an informed consent form and you will be registered into the study. At this stage, you will be asked to attend a screening visit where the research team will perform a number of tests to ensure that you meet the inclusion criteria for the study. These criteria are aimed at excluding patients in whom it may be unsafe to administer pembrolizumab and to reduce the risk of side effects. These tests are performed within a 28-day period prior to your intended first dose of pembrolizumab; this is called the "screening period". This screening period may include one or more visits to the hospital to have all the necessary tests performed. Your visit to the hospital for all these tests may take several hours.

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

What screening assessments will be performed?

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

- General medical history, oncology history and physical examination including vital signs (heart rate, blood pressure, respiratory rate, temperature, weight and height).
- List of medications you are taking (including prescription and over-the-counter vitamins and alternative medications).
- You will be asked about any disease-related symptoms you are experiencing.
- An ECG (electrocardiogram) to assess your heart rhythm.
- Assessment of your cancer by a CT (or MRI) scan of your chest, abdomen and pelvis and if needed other areas.
- A bone scan to evaluate the spread of cancer to your bones.
- A blood test to detect the number of cancer cells that are circulating around the body; these cells are called circulating tumour cells (CTC count). This test will be performed at the screening visit only if your disease cannot be measured on the CT scan.
- You will be asked to provide a urine sample for routine safety urine tests.
- You will be asked to provide a blood sample (approximately 91mls or 6 tablespoons in total), for measuring your full blood count, kidney function, thyroid function, blood salts (biochemistry), Prostate Specific Antigen (PSA), cholesterol and other lipids, coagulation studies if you are receiving anticoagulant therapy, testosterone, random glucose and for research into your disease.
- A fresh tumour biopsy will be performed within 28 days of cycle 1 day 1. It is possible that a fresh biopsy from a separate screening study, such as the MAESTRO study can be used instead for PERSEUS1 trial if certain requirements are met
- You may be asked if you wish to have an additional imaging test, a whole body MRI examination (WB-MRI), to evaluate your tumour in more detail. Your study doctors will go through with you what is involved, and potential side effects. This test is optional and

patients who wish to have WB-MRI will be required to indicate their wishes within a checkbox of the consent form. Not all the centres recruiting patients for this study have the facilities to perform these examinations. If you are interested, however, your study doctor will tell you if you can be invited to have this MRI examination done.

What happens if I am eligible for the study?

If your screening tests results show that you are eligible and you agree to continue in the study, we will ask you to attend the clinic for the first cycle of treatment. You will be given pembrolizumab 200mg as an intravenous (IV) infusion in the clinic every three weeks. You will be required to attend regular hospital appointments so that we can see how your cancer responds to the treatment as well as monitor any side effects you may experience. You will only sign one consent form prior to your screening assessments, if you are found to be eligible, this consent form will allow you to continue straight to treatment with pembrolizumab.

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

What happens next?

If you are found to be suitable for the trial based on the screening assessments and wish to continue with your participation in the study, you will be enrolled into the study and will be allocated a unique study number by a computer programme. You will be required to return to the clinic for a Cycle 1, Day 1 visit. During this visit your study doctor or nurse will:

- Conduct a physical examination including vital signs (heart rate, blood pressure, respiratory rate, temperature, weight and height)
- Obtain information about any disease-related symptoms you are experiencing
- Obtain information about any changes to any medications you are taking
- Obtain several blood samples (approximately 91mls or 6 tablespoons in total) and a swab of your cheek cells. These samples will be used for routine safety checks and for research into your disease.

If the safety assessments are met, you will receive an IV administration of pembrolizumab at the Cycle 1, Day 1 visit. After Cycle 1 Day 1 visit you will return to clinic at the start of each cycle (once every 21 days), for as long as you are on study treatment. Partway through your first 'cycle' of treatment at Cycle 1 Day 14, you will be asked to return to clinic for an additional tumour biopsy.

What happens after I have started pembrolizumab treatment?

After **3 weeks** of treatment you will have completed your first 'cycle' of treatment and this will mark the start of your next cycle and be your Cycle 2 Day 1 visit. At this visit your study doctor or nurse will:

- Perform a physical examination as clinically indicated.
- Measure your weight and vital signs.
- Take a blood sample: this sample will be used for assessment of safety and for research into your disease.
- Obtain a urine sample for routine safety tests.
- Discuss whether you have experienced any side effects, or had any changes to any

medications you are taking.
- A blood sample will be taken to test your PSA.

The above procedures will be repeated for Day 1 of every cycle.

From Cycle 5 Day 1 and every 12 weeks thereafter you will attend the clinic for the assessments you have at Day 1 of every cycle (every 3 weeks) as described above. The following additional assessments will be performed every 12 weeks timed from Cycle 5 Day 1:

- Assessment of your cancer by a CT (or MRI) scan of your chest, abdomen and pelvis and other areas if clinically indicated.
- A bone scan to evaluate the spread of cancer to your bones.
- An optional Whole Body MRI (WB-MRI), to evaluate your tumour in more detail.

Treatment discontinuation/off study visit

Your Pembrolizumab treatment will continue until your study doctor feels that you are no longer getting any benefit from the study drug, or if you or your study doctor conclude that any side effects you may be experiencing are unacceptable. You may also decide to stop your participation in the trial at any time. On the day you are taken off study treatment your study doctor or nurse will perform the assessments that you have at day 1 of every cycle. An optional fresh tumour biopsy will be performed at thetreatment discontinuation visit if your study treatment has been discontunued due to disease progression.A blood sample will also be taken for research purposes if your cancer progresses.

End-of-treatment (EOT) visit

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

- Physical examination including vital signs (heart rate, blood pressure, respirations, temperature, weight and height).
- List of medications you are taking (including prescription and over-the-counter vitamins and herbal remedies, vitamins, and supplements).
- You will be asked about any disease-related symptoms you are experiencing.
- You will be asked about any new or continuing side effects or illnesses you have had since your last visit.
- You will be asked to provide a urine sample for routine safety tests.
- A blood sample will be taken (approximately 91 mls or 6 tablespoon in total), for measurement of your full blood count, kidney function, blood salts (biochemistry), PSA, cholesterol and other lipids, testosterone and random glucose.
- A blood sample will also be taken for research purposes if your cancer progresses.
- If your study treatment has been discontinued due to disease progression, an optional fresh tumour biopsy will be performed at EOT visit if not previously performed at treatment discontinuation/off study visit.

Follow-up

Safety (short term) follow-up visits

If you stop your study treatment due to reasons other than progression of your cancer, your study team will continue to monitor you at clinic visits, every 12-weeks after your end of

treatment (EOT) visit. These visits will continue for two years after you last received the study drug. At these short-term visits your study doctor or nurse will:

- Measure your weight and vital signs.
- Take a blood sample for routine blood tests. A blood sample will also be taken for research purposes if your cancer progresses.
- Discuss whether you have started any new treatments for your cancer.
- Assessment of your cancer by a CT (or MRI) scan of your chest, abdomen and pelvis and other areas if clinically indicated.
- A bone scan.
- An optional whole body MRI (WB-MRI), to evaluate your cancer in more detail.
- A blood sample will be taken to test your PSA.
- One optional tumour biopsy (only if your cancer progresses).

If you start a different treatment or if your cancer progresses, you will move on to long-term follow-up visits.

Long term follow-up visits

You will move on to long-term follow-up for one of the following reasons:

- You have completed 2 years of safety (short-term) follow-up visits.
- If your disease progresses whilst on treatment or during your safety (short-term) follow-up visits.

Your study doctor or nurse will contact you to assess your health status and collect additional information such as any treatments that you are receiving or have received. Alternatively, your study doctor or nurse may access your medical records or publicly available records to find out this information.

Please refer to Appendix 2 – for schedule of collection of research tissue and blood samples

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

This study uses CT, MRI and bone scans to assess your prostate cancer. Arthritis and early bone disease flares from treatment can cause spots to appear on bone scans, therefore, the bone scan may need to be repeated several weeks later if the results are not conclusive. Cancer spots will remain the same, but arthritis spots and bone disease flares may disappear. PSA tests can be unreliable as an indicator of benefit to some new prostate cancer therapy such as immunotherapy. Additionally, early rises in PSA can occur because the death of prostate cancer cells may release PSA into the blood. Such early rises in PSA can be mistaken for progression of your cancer. Please ask your study doctor if you have any questions about this. Because scans and PSA tests can be very difficult to interpret, your study doctor may need to perform confirmatory scans at four or more weeks after your first scan to confirm your cancer is responding. This may require an unplanned visit to the clinic and unplanned PSA tests.

If you decide to participate, you will be asked to remain in the study until your cancer worsens (according to the CT, MRI, or bone scan results); or you are unable to tolerate the study

treatment; or your study doctors determine that you should begin another cancer treatment; or if you decide to withdraw your consent.

Description of specific research tests

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

Tumour tissue:

Prior to entry into the trial, we will ask you to consent to donate tissue from your primary archival sample or for analysis of a fresh biopsy. The archival sample is the one that was collected at the time of diagnostic biopsy or collected at a previous surgery for management of your prostate cancer, prior to entry into this study. The rationale of this is to study any abnormality in your prostate cancer that we think might predict your response to pembrolizumab. Further tests might be requested to ensure that you meet all the inclusion criteria for the trial.

In this study you will be asked to have up to 3 fresh tumour biopsies. The first mandatory fresh tumour biopsy may be performed during the screening period before you start treatment; if a fresh tumour biopsy was taken as part of the separate MAESTRO screening study, you may not need to have another fresh tumour biopsy to enter PERSEUS1, if it was obtained within 6 months from PERSEUS1 trial entry and certain requirements are met. Otherwise, a fresh biopsy within 28 days from trial entry will be required as part of screening procedures. The next mandatory biopsy will be taken at Cycle 1 day 14 and the third optional biopsy will be taken at the time of disease progression

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

These tumour biopsies are an important aspect of this study and will help us to further understand the effect of the study drug on your tumour, identify specific features in the cancer

that can predict responses to treatment and study reasons why prostate cancers stop responding to pembrolizumab treatment. The tumour tissue collected will help us in the future to predict which patients will benefit from pembrolizumab treatment.

Research blood tests:
Blood samples will be collected at mutiple time points during the study. A total of 27 blood samples will be taken for the purposes of research in the first year of study treatment. Tumour cells and other substances found in blood may be useful to identify which type of prostate cancer will benefit from pembrolizumab treatment.

Buccal swab:
A buccal or cheek swab will be collected to analyse germline DNA. To collect the sample the research nurse will use a sterile brush to gently swipe the inside of your cheek approximately ten times avoiding the gum line.

Genetic analysis performed in research samples

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

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

How is pembrolizumab given?

Pembrolizumab is given as an intravenous (IV) infusion and will be administered by your study doctor or nurse in the clinic. An infusion lasts approximately 30 mins. There is no prophylactic pre-medication given unless it is specifically required for an individual patient. Pembrolizumab is given once every 3 weeks, “a cycle”, on the first day of that cycle. Your study doctor will ensure before every cycle that it is safe for you to receive pembrolizumab. If you are unwell or experiencing side effects, the study doctor will modify or delay the study treatment until you are recovered. Your study doctor could also decide to stop study treatment permanently for safety reasons.

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 below (please note that this is a summary of side effects and is not an exhaustive list).

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 study doctor or nurse about it**. Your progress will be closely monitored and your study 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 occasions these can be serious.

Side effects of pembrolizumab	
Common side effects (occurring in at least 1 out of 100 patients (≥1%) treated with pembrolizumab)	• Anaemia • Diarrhoea (loose or watery stools) • Shortness of breath • Fever • Inflammation of the lungs (pneumonitis/pneumonia) so you may experience shortness of breath and coughing.
Uncommon side effects (occurring in at least 1 out of 1000 patients (≥0.1%) treated with pembrolizumab)	• Pain in limbs, joints or extremities. • Low level of sodium, calcium and potassium in the blood. • High levels of calcium in the blood. • Increase in bilirubin which may cause appearance of jaundice. • Low white blood cell counts (neutropenia, leukopenia, lymphopenia), which may increase your risk of infection. • Reduction in the function of the adrenal glands (adrenal insufficiency) which may result in lack of energy or motivation (fatigue), muscle weakness, low mood, loss of appetite and unintentional weight loss, increased thirst, dizziness, fainting, cramps and exhaustion. You may also develop small areas of darkened skin, or darkened lips or gums. • Underactive thyroid gland (hypothyroidism), which may cause tiredness, weight gain, depression, being sensitive to the cold, dry skin and hair, and muscle aches. • Inflammation of the liver (hepatitis), so you may feel tired. You may also experience loss of appetite, mild fever, muscle or joint aches, nausea, vomiting, and stomach pain among other symptoms. • Skin rash

Side effects of pembrolizumab	
	• Inflammation of the pituitary gland (hypophysitis) so you may have headaches, a change in eyesight, increased thirst and increased passing urine, among other symptoms. • Brain inflammation (encephalitis), so you may experience confusion or disorientation, seizures or fits, changes in personality and behaviour, difficulty speaking, weakness or loss of movement in some parts of the body and loss of consciousness. • Inflammation of the pancreas (pancreatitis) so you may have severe upper abdominal pain that may move to the back, nausea and vomiting that gets worse when you eat. • Inflammation of the pancreas which leads to diabetes mellitus, so you may feel very thirsty, urinate more than usual, feel very tired, lose weight without trying, heal more slowly, and get blurred vision and fruity-smelling breath. This condition may require insulin shots. • Overactive thyroid gland (hyperthyroidism), so you may feel nervousness, anxiety and irritability or mood swings; or have difficulty sleeping, persistent tiredness and weakness, sensitivity to heat, swelling in your neck from an enlarged thyroid gland (goitre), an irregular and/or unusually fast heart rate (palpitations), twitching or trembling, or weight loss • Difficulty sleeping (insomnia) • Nausea • Tiredness (fatigue) • Decreased appetite • Headache • Dizziness • Vomiting • Stomach pain • Constipation • Abnormal liver and kidney function tests, potentially including sudden onset of liver and/or kidney damage or failure. • Inflammation of the large intestine (colitis) so you may experience diarrhoea or an increased number of bowel movements, stools that are black, tarry, sticky or have blood or mucus; or severe abdominal pain/ tenderness.

Side effects of pembrolizumab	
	• Inflammation of the stomach lining (gastritis) so you may experience stomach pain, gas, indigestion, bloating, feeling sick (nausea), being sick (vomiting), or not feeling as hungry as usual. • Low platelet count (thrombocytopenia) which may cause an increased risk of bruising and/or bleeding • Build up of fluid under the skin causing swelling or puffiness • Inflammation of the kidney so you may pass less urine, have cloudy or bubbly urine, see blood in your urine, have high blood pressure, nausea, fatigue, swelling and low back pain. This can lead to kidney damage. (nephritis/glomerulonephritis) • Inflammation (swelling) of the muscles (immune-mediated or necrotising myositis) so you may feel weakness in the muscles closest to the centre of the body, such as the forearms, thighs, hips, shoulders, neck, and back (rarely, this may lead to polymyalgia rheumatica – pain and stiffness in the shoulders, neck and hips)
Rare side effects which can be serious (occurring in less than 1 out of 1000 patients (≤0.1%) treated with pembrolizumab)	• High blood pressure (hypertension). • Inflammation of the nerves (neuritis) so you may experience sensory alterations, weakness in the legs and/or arms, and sometimes difficulty breathing. • Guillain-Barre syndrome, which may cause numbness, pins and needles, muscle weakness, pain, problems with balance and co-ordination, or difficulty moving, breathing and/or swallowing. • Low red blood cell count, due to the body destroying and removing red blood cells from the bloodstream before their normal lifespan is over (Hemolytic anemia) • Myasthenic syndrome which may cause droopy eyelids affecting one or both eyes, double vision, slurred speech, difficulty swallowing, difficulty making facial expressions like smiling, problems with chewing, a change in your voice, choking or accidentally inhaling food which can cause chest infections, shortness of breath, weakness in your arms, legs, neck or other parts of your body, difficulty holding your head up, or aching muscles. • Small intestinal perforation, which can cause severe abdominal pain and tenderness. This can also result in sepsis, a condition caused by the

Side effects of pembrolizumab	
	body's abnormal response to an infection. Symptoms of sepsis include increased heart rate, increased breathing rate, fever, confusion, slurred speech, extreme shivering or muscle pain, passing no urine, severe breathlessness and skin that is mottled or discoloured. • Swollen fat beneath the skin causing bumps and patches that look red or darker than surrounding skin, which may also come with flu-like symptoms, such as a high temperature, tiredness, or joint and muscle pain (erythema nodosum) • Inflammation of the middle layer of the eye (uveitis) so you may have eye pain, eye redness, sensitivity to light (photophobia), blurred or cloudy vision, small shapes moving across your field of vision (floaters) and loss of the ability to see objects at the side of your field of vision (peripheral vision). This inflammation can lead to vision-threatening complications if it progresses to the posterior area of the eye, or the vascular layer of the eye (chorioretinitis). • Severe inflammation or blistering of the skin (Stevens-Johnson Syndrome or toxic epidermal necrolysis) • Sarcoidosis, an inflammatory disorder that can cause clusters of immune cells (granulomas) in the lymph nodes, eyes, skin or lungs. • Hair loss or colour change • Itching of the skin • Taste changes • Fever, flu-like illness or chills • Back or chest pain • Cough • Dry mouth • Dry skin • Dry eyes • Epilepsy • Skin redness, rash, widespread peeling of the skin • Pale white patches developing on the skin • Increase in a certain type of white blood cells (eosinophils), which may cause increased allergic reactions • Skin reactions (eczema, red flaky skin, areas of discolouration, acne, other changes to the skin)

Side effects of pembrolizumab	
	• Inflammation of fluid that surrounds tendons (tenosynovitis) which can cause joint swelling, pain and stiffness. • Physical weakness or lack of energy and enthusiasm (lethargy) • Peripheral neuropathy, so you may experience numbness and tingling in the feet or hands, burning, stabbing or shooting pain in the affected areas, loss of balance and co-ordination, and muscle weakness, especially in the feet • Inflammation of the muscle of the heart (myocarditis) that may cause chest pain or discomfort, a feeling of tightness in the chest, shortness of breath, unusual tiredness, palpitations, an irregular heartbeat, feeling light-headed or fainting, and swelling in hands, legs, ankles or feet. • Inflammation of the thyroid gland (thyroiditis) which may lead to either an underactive or overactive thyroid. • Inflammation of the spinal cord (myelitis), which can cause 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. • Vogt-Koyanagi-Harada syndrome, which may include changes in eyesight, eye pain, whitish patches on the skin and hearing loss • Inflammation of the blood vessels (vasculitis) that can lead to organ damage and/or blood clots. • Allergy reactions to pembrolizumab, which 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. You may also experience pain at the site of infusion. • Acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction (cytokine release syndrome). • White patches appearing in your mouth (oral lichen planus), that may cause burning pain or soreness in the mouth. • Inflammation and/or scarring in the bile ducts inside and outside the liver, which can eventually be narrowed or blocked. When this happens, bile can

Side effects of pembrolizumab	
	build up in the liver and cause further liver damage, including cirrhosis and liver failure. • Sjögren's syndrome, which may affect the different glands of the body that produce fluids, like spit or tears. This can cause dry mouth, eyes and skin among other symptoms. • Low parathyroid hormone (hypoparathyroidism), leading to lowered blood calcium levels and raised blood phosphorus levels, which can cause a wide range of symptoms, including muscle cramps, pain and twitching.

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
- Administration of 'killed' vaccines, such as the vaccine for COVID-19, is allowed. Please speak to your doctor about the timing of this vaccine whilst having pembrolizumab treatment.
- If you begin taking any new medications or supplements while taking part in the PERSEUS1 trial, please inform your doctor or nurse as soon as possible

What else will happen to me during the trial?

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

You will not be paid to take part in the study. You can however claim reasonable travel expenses for study-specific visits requiring you to attend your hospital, up until your short-term follow up visit.

You will be given a card, which will provide details about the PERSEUS1 trial and that you are taking pembrolizumab. Please carry it with you at all times while you are taking part in this trial, and show it to any medical professional you visit.

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

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

We don't know the effects pembrolizumab might have on the development of sperm and as such you must use adequate contraception during the study and for 4 months following your last dose of treatment. You should abstain from sperm donation for this time. If your partner becomes pregnant whilst you are taking part in the study you must contact your study doctor immediately.

Blood donation:

You are not allowed to donate blood while in the study or for 4 months following your last dose of study medication.

Other medicines:

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

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

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

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

What are the benefits of taking part?

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

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

What are the possible disadvantages of taking part?

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

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

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

As part of the study you will be required to have CT scans and bone scans at screening, cycle 5 and every 12 weeks thereafter to monitor your cancer (please refer to Appendix 1 – Description of Scans). As part of this study you will also have up to 3 tumour biopsies that may take place under CT guidance. You would not have as many of these CT and Bone scans if you did not take part in this study. Radiation can cause cell damage which may in the long term cause another cancer (after a delay that could be from 2-10 years for leukaemia and up to several decades for solid tumours). However in view of your existing clinical condition, the radiation exposure is not significant and the risk of long term harm is considered to be negligible. In rare cases, you may have an allergic reaction to the contrast material "dye" given for CT scans. If you have had allergic reactions to X-ray dyes in the past, you should let your study doctor know.

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

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

Occasionally during the course of a study you may be found to have a previously undiagnosed medical condition. In this situation your study doctor will take the necessary steps to ensure you receive appropriate treatment.

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

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

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

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. If your partner becomes pregnant during the trial, these risks could affect

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. 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 study:

Single method (one (1) of the following methods is acceptable for you or your partner):

- Vasectomy
- Intrauterine device (IUD)
- Contraceptive rod implanted into the skin

Combination method (two (2) of the following barrier methods in combination (you or your partner as appropriate):

- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- Condom
- Copper intrauterine device (IUD)
- Contraceptive sponge
- hormonal contraceptive:
  - registered and marketed as oestrogen and progestogen containing hormonal contraception:
    - oral
    - intravaginal
    - transdermal
  - registered and marketed as progestogen-only hormonal contraception:
    - oral
    - injectable
    - implantable

If your partner becomes pregnant, information on the outcome of your partner's pregnancy will be requested.

5 Further information about taking part

Will my GP be involved?

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

What happens when the research study stops?

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

What alternative treatments are there?

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

This completes Part 1 of the information sheet.

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

Part Two: General information

6 General information about how the PERSEUS1 trial is conducted

What will happen to any samples I give?

In the PERSEUS1 study we ask that all patients donate some of their initial tumour tissue, which was taken at the time of diagnosis or at another time point prior to starting the study. Additionally the patients will undergo fresh tumour tissue biopsies, for research into your tumour during the study. The samples will be collected for blood, and urine analysis. Details of the samples requested are described in Part 1 of this information sheet. Please tick the appropriate part of the consent form if you agree to the collection of these samples.

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

The group of medical professionals overseeing the PERSEUS1 trial will also oversee the sample collection. Your tumour tissue or blood samples may be labelled with your initials, date of birth and trial ID number when they are sent to the research lab. When they arrive at the laboratory they will be coded and personal details removed. The coding will maintain your confidentiality whilst allowing biological details to be compared to treatment findings.

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

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

How will confidentiality be maintained?

The Institute of Cancer Research is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we

are responsible for looking after your information and using it properly. The Institute of Cancer Research will keep identifiable information about you for at least 5 years after the study has finished.

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

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

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

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

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

All information which is collected about you during the study will be kept strictly confidential. When you join the trial, your full name, hospital number, date of birth, postcode and NHS/CHI number will be passed to The Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU) where the study 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 at your hospital will send to ICR-CTSU. All information about you will be stored securely. It will be treated as strictly confidential and nothing that might identify you will be revealed to any third party. Only members of the research teams at your hospital and the ICR-CTSU will have access to the information that could allow this 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.

Representatives from the ICR-CTSU, the NHS Trust relevant to your taking part in research, the Medicines and Healthcare products Regulatory Agency (MHRA) and ethics committee approving the trial, the pharmaceutical company (Merck Sharp and Dohme (MSD)) that manufacture the study drug Pembrolizumab and may have offices outside of the UK/EU, and third parties approved by ICR-CTSU may need to see your hospital or clinic records to the extent permitted by applicable laws and regulations to make sure the information received is correct. All information will be kept confidential.

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

Data sharing

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations 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.

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

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

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

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

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

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

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

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

What if there is a problem?

If you have any concern about any aspects of the study you should ask to speak with your study doctor or research nurse who will do their best to answer your questions (contact details in part 1). If you remain unhappy and wish to complain about any aspect of the way you have been approached or treated during the course of this trial, the normal National Health Service complaints mechanisms are available to you. We recommend that you obtain a copy of your hospitals complaints procedure or policy if you intend to make a complaint. Concerns should be raised by speaking to a member of staff at your hospital or by talking to the local Patient Advice and Liaison Service (PALS), which has been established in every NHS Trust and Primary Care Trust (PCT). The details for your hospital are: *[Insert appropriate name for hospital PALS]:* To find out more about this, ask a member of staff, look on the hospital or trust's website, or contact the complaints department for more information.

Your progress will be watched closely and you will be offered whatever help is available to cope with any side effects observed. Occasionally some patients need a short stay in hospital for side effects to be treated, and on rare occasions these can be serious. If this were to happen, full details of what has happened will be reviewed carefully by the consultant oncologist who has overall responsibility for the PERSEUS1 trial. These details may also be sent to the MHRA who oversee the safety of people who take part in any research involving drugs. We may also need to send this information to the ethics committee who approved the trial, all the doctors who are responsible for patients in this study, and to Merck Sharp and Dohme (MSD). We are required to provide this information to these parties by law, but you will not be identifiable in any of the information that is sent, and all information will be kept confidential.

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

disability, you may be able to claim compensation from The Institute of Cancer Research as Sponsor of the PERSEUS1 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 will happen to the results of the clinical trial?

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

What if relevant information becomes available?

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

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

Who is organising and funding the research?

The research trial is being carried out by a network of doctors across the UK. The trial is co-ordinated by The Institute of Cancer Research. The research is approved and funded by Merck Sharp and Dohme (MSD), the company who manufacture pembrolizumab and who are supplying the drug free of charge. Your doctor will not receive any payments for including you in this research trial.

Who has reviewed the trial?

The trial has been approved by the Health Research Authority (HRA), a Research Ethics Committee (London – Chelsea Research Ethics Committee), the UK Regulatory Agency (Medicines and Healthcare Regulatory Agency, MHRA) and the study sponsor's committee for clinical research. This patient information sheet and consent form have been reviewed by the patient review panel in Royal Marsden NHS Foundation Trust.

What do I have to do now?

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

7 Useful contact information

Who else can I contact for further information?

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

Your study doctor is: _____

Your study nurse is: _____

Contact phone numbers: _____

Out of Hour Numbers: _____

Macmillan Cancer Support is a registered charity providing information, emotional support and publications about all aspects of cancer for cancer patients and their families. They have published useful information about (1) prostate cancer (2) cancer treatments and (3) clinical trials in general. You can contact one of their specialist cancer nurses on their freephone number, 0808 808 00 00 or look on their internet website: (http://www.macmillan.org.uk/Home.aspx).

You can learn more about clinical trials and the results of this trial once available on the Prostate Cancer UK and Prostate Cancer Foundation websites:
http://prostatecanceruk.org
http://www.pcf.org

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

Appendix 1 - Description of scans

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

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

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

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

Optional Whole Body MRI (WB-MRI): WB-MRI provides additional information regarding the tumour, which cannot be evaluated with other imaging techniques. The WB-MRI studies will include a baseline scan and follow-up MRI scans during the treatment. Your study doctors will explain what is involved. This part of the study is optional and if you wish to have these additional imaging tests you will be required to indicate your wishes within a checkbox of the informed Consent Form. We are keen to evaluate if WB-MRI will provide a better way of studying prostate cancer in the bone.

Appendix 2 - Schedule of collection of biological research samples

Time points	Tissue samples			Blood samples
	Buccal swab	Archival	Fresh	
Screening		X	X	X
C1 D1 (up to -7 days prior to first dose of pembrolizumab)	X			X
C1 D14			X	
C3 D1				X
C4 D1				X
C5 D1				X
C6 D1				X
C9 D1				X
Treatment Discontinuation visit/End of treatment visit (EOT)			X†	X*
Safety (short term) Follow up Visit			X†	X*

* Required only once at treatment discontinuation visit /end of treatment visit or Safety (short term) Follow up Visit when disease progression is confirmed

†Fresh tumour biopsy optional at the time of disease progression and performed only once at treatment discontinuation/end of treatment or Safety (short term) follow up visit