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(To add on hospital headed paper)

Patient Information Sheet and Informed Consent Form

Study Doctor:
Contact details:

1. Invitation Paragraph

You are being invited to take part in this research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

2. Study Title

PELICAN: A phase II study of etoposide-carboplatin chemotherapy in combination with pembrolizumab and lenvatinib maintenance in advanced high-grade neuroendocrine tumours (HG-NETs).

3. What is the purpose of the study?

The purpose of this study is to assess the efficacy of carboplatin and etoposide when given alongside pembrolizumab followed by pembrolizumab and lenvatinib as maintenance therapy. Carboplatin and etoposide are types of chemotherapy that are already offered to patients with high-grade neuroendocrine tumours, as well as other cancers such as small cell lung cancer. Both of these drugs work by preventing cancer cells from replicating by forcing them to undergo cell death instead. Pembrolizumab, on the other hand, is a form of targeted therapy called monoclonal antibodies. They work by helping the body's natural defence system (the immune system) to fight cancer cells. Antibodies are proteins that form a vital part of the natural human immune system. Monoclonal antibodies are copies of human antibodies, but they have been engineered to bind to specific proteins involved in specific diseases, in this case cancer. Lenvatinib is another kind of targeted therapy like pembrolizumab, however it is not a monoclonal antibody but is what is known as a multiple kinase inhibitor. All the drugs that have been mentioned will be explained further in Section 9.

In this study, pembrolizumab will be given with carboplatin and etoposide for a total of 4 cycles, and then be given with lenvatinib as maintenance treatment afterwards. The study aims to evaluate how effective this two-part regime in is in halting disease progression and prolonging survival. Pembrolizumab and lenvatinib are already approved for use in the UK to treat other types of cancer, but not in combination with each other or with carboplatin and etoposide, and not as yet to treat high grade neuroendocrine tumours.

4. Why have I been chosen?

You have been invited because you have been newly diagnosed with a high-grade neuroendocrine tumour (HG-NET), and your physician has declared you fit to receive systemic treatment. Participation in this study is an option and not the only form of treatment you can have.

About 20 patients with HG-NETs in the UK are expected to participate in the study. The duration of your participation is expected to be up to 2 years. After completing all study treatment, or after you withdrawn from treatment, you will be asked to continue follow-up visits to monitor for possible side effects and potential benefits.

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5. Do I have to take part?

No, it is up to you to decide whether or not to join the study. Even if you do decide to take part, you are free to withdraw at any time, without giving a reason. This would not affect your future medical care in any way.

If you agree to take part, you will be given this information sheet to keep and be asked to sign a consent form.

6. What will happen to me if I take part?

You will be assigned to receive carboplatin, etoposide and pembrolizumab in combination on Day 1 and etoposide again on Days 2 and 3 of each 21-day cycle. After 4 cycles, you will move on to the maintenance phase of the study and will continue to receive pembrolizumab on day 1 of each cycle as well as a prescription for lenvatinib for you to take daily. This is an 'open label' study, which means you and your study doctor will know what drugs are being given.

Carboplatin, etoposide and pembrolizumab are all administered by intravenous (IV) infusion. This process involves inserting a needle attached to a cannula (like a small straw) into a vein in your arm. Each drug will have different infusion times; carboplatin is administered over 30-60 minutes; etoposide usually takes 60 minutes and pembrolizumab over 30 minutes. A pump will be used to ensure that they are given over the proper amount of time.

Lenvatinib is an oral drug and will come as hard capsules. Each capsule will have 10mg of drug and so you will be asked to take two capsules daily for the duration of the maintenance treatment phase. It is up to you to remember to take these capsules. We will provide you with a diary to help you keep note of when you have taken them.

There will be three periods to the study: screening, treatment and follow-up periods. All study visits will be at a hospital within the NHS trust where your study doctor works. A summary of the schedule of visits and procedures/assessments is provided on Section 8. Each visit will take a few hours to complete, so you should set aside a whole day for each one, just in case. The study team will do its best to minimise waiting times and make you comfortable during these visits, including providing food and drink during the longer visits.

Screening

Certain examination and tests, which we may refer to as screening tests, are required to help your study doctor determine whether you are eligible for this study. The Screening Period of the study can take between 1 and 28 days to complete. This period may include more than one study visit in order to complete between the various procedures.

Before any study-related procedures that are not standard care are performed, you will be asked to read this information and sign the attached consent form. It is your right as a patient to have the study fully explained to you and you can ask your study doctor to explain or go over any parts of this information, or the consent form, that you do not understand.

The following tests and procedures will be performed by the study staff to determine whether you are eligible to participate in this study:

- Review of your medical history; you must not have known HIV infection or have had active Bacillus Tuberculosis (TB - a bacterial infection that usually affects the lungs) in the past

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- Review of medications you are currently taking and have taken in the past, including herbal medications
- A physical examination including measurement of your height, weight and vital signs (temperature, blood pressure and heart rate)
- You will be asked about the symptoms you are having from your disease (performance status)
- Collection of your blood (approximately 6 teaspoons/30 mL) for laboratory tests to check your general health and pregnancy (for women only and this must be within 7 days of due start date of treatment), and for monitoring your disease
- Collection of urine for laboratory tests to check your general health and (optionally) for further study of your disease
- Optional collection of blood (approximately 11 teaspoons/55 mL), and stool (poo) samples for further study of your disease
- Biopsy of tumour tissue. Furthermore, if you have had a tumour biopsy or cancer surgery in the past, samples will be requested from the medical facility where it was done. In order to participate in this study, you must give us your consent to obtain these original samples and allow your study doctor to send them to an external laboratory for tests to study your disease.
- Computed tomography (CT) scan of your chest, abdomen and pelvis. The x-ray images from the CT scan will allow your doctor to monitor your disease before, during, and after you receive the study drugs.
- Electrocardiogram (ECG), which is an electrical tracing of the heartbeat
- And will also ask you to complete a quality-of-life questionnaire

If, based on the results of the screening visit tests and procedures, you are eligible to participate in the study, you will return to the hospital for treatment.

It is possible that after the results are reviewed you may not be eligible to take part in this study. Or even though you may meet all the criteria for participation, your study doctor may decide not to enrol you in this study. In either of these situations, your study doctor will discuss other treatment options with you.

Treatment

The Treatment Period is made up of four 21-day (3-week) cycles followed by further 21-day cycles of pembrolizumab and lenvatinib dual therapy up to 2 years of treatment. During the first four cycles of the treatment phase, you will attend the hospital for 12 visits, on days 1, 2 and 3 of each cycle. On Day 1 of each cycle, you will have the following assessments, as well as dosing with carboplatin, etoposide and pembrolizumab:

- Review of your symptoms and medications
- A physical examination as required by your symptoms, and measurement of your weight and vital signs
- Collection of your blood (approximately 5 teaspoons/25 mL) for laboratory tests to check your general health and to monitor your disease
- Collection of urine for laboratory tests to check your general health

On Day 1, the infusions of carboplatin, etoposide and pembrolizumab will be one at a time using the same needle, separated by a few minutes' break. If you experience any changes in your body or develop any new or worsening symptoms during or after any of the drug infusions, you should inform the study doctor or nurse immediately.

After four cycles of this treatment plan, you will then move on to the maintenance part of the treatment period and continue to receive pembrolizumab infusions on Day 1 of each 21-day cycle, but this time

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you will also be given a prescription of lenvatinib. This is an oral drug, which you will have to take every day. The same procedures and assessments listed above will be performed on these visits except for the first one when you will also have CT scan and you will be asked to complete some quality-of-life questionnaires

You may be discontinued from treatment based on your disease assessments, or because of possible side effects of the study therapy. Based on discussions between you and your study doctor, you may discontinue for other reasons.

Follow-up

The Follow-up Period is split into two parts – the safety and survival phases.

The first study follow-up visit will take place 30±7 days after you stop the study treatment, and this will be the safety visit. The survival follow-up visits will take place every 8 weeks after the initial follow-up/safety visit and may continue for up to 2 years.

At follow-up visit 1, or the safety visit, you will have the following assessments:

- Review of your symptoms and medications
- A physical examination as required by your symptoms, and measurement of your weight and vital signs
- Collection of your blood (approximately 5 teaspoons/25 mL) for laboratory tests to check your general health and to monitor your disease
- Collection of urine for laboratory tests to check your general health

7. Will my costs be covered?

You will be reimbursed for reasonable travel expenses related to your participation in the study.

8. What will I have to do?

You need to attend all scheduled study visits as described in Section 6 and summarised on the tables below.

Doctors will check if you are on any medication that might interfere with the study treatment

Apart from the study drugs we administer to you it is important that you take any other prescribed medicines as directed. You must inform your study doctor of any non-study medication or therapy that you have from screening until Follow-up 1/Safety Visit. If you plan to receive a vaccine, non-study anti-cancer therapy, or immunosuppressive therapy during the screening and treatment periods, you must inform the study team in advance because some of these are prohibited.

You must not enter any other research studies using investigational products whilst participating in this study.

You will be given a subject alert card (providing the contact details of your study doctor) to remind you and others that you are in a research study. Please carry this card with you at all times. If you seek emergency care, or if hospitalisation is required, please inform the treating doctor that you are participating in a research study.

The requirements for contraception, and reporting pregnancy, are described in detail in Section 13.

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	Screening	Induction Treatment Cycles								Maintenance Phase		End of Treatment	Follow-up
	Pre Induction -28 to -1	C1 D1	C1 D2-3	C2 D1	C2 D2-3	C3 D1	C3 D2-3	C4 D1	C4 D2-3	C1D1	C2D1		
Informed Consent	x												
Eligibility Assessment	x												
Demographics and Medical History	x												
Tumour Imaging (RECIST)[1] Chest Abdomen Pelvis CT scan with contrast	x									*x*		*x*	
Full Physical Examination	x									x		x	x
Directed Physical Examination		*x*		x		x		x			x		
Vital Signs, Weight & Height[2]	x	x		x		x		x		x	x	x	x
ECOG Performance Status	x	x		x		x		x		x	x	x	x
12 – Lead ECG	x											x	
QoL Assessment: DASS-21, SCNS-SF34, FACT-G	x					x				x		x	
Pregnancy Test – Urine or Serum beta-HCG	x												
PT/INR and aPTT	x	x		x		x		x		x	x	x	x
Tumour markers[2]	x	x		x		x		x		x	x	x	x
Haematology[3]	x	x		x		x		x		x	x	x	x
Biochemistry[4]	x	x		x		x		x		x	x	x	x
Urinalysis[5]	x	x		x		x		x		x	x	x	x
T3, T4 and TSH	x	x		x		x		x		x	x	x	x
Cortisol	x	x		x		x		x		x	x	x	
EP Administration (IV)		x		x		x		x					

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Carboplatin Administration (IV)		x		x		x		x				
Pembrolizumab Administration		x		x		x		x		x	x		
Etoposide Administration (D2-3, IV)			x		x		x		x				
Lenvatinib Administration (oral)										x	x		
Archival Tissue Collection[6]	x												
Biomarker Biopsy Sample[7]	x												
Record of Concomitant Medications	x	x		x		x		x		x	x	x	x
AE Assessment (NCI-CTCAE v4.03)	x	x		x		x		x		x	x	x	x
Survival and Post-study anticancer therapy status[8]													x
Optional Biomarker Blood Sample[9]	x					*x*				*x*		*x*	
Optional Research Blood Sample – Circulating Tumour Cells (CTCs)[9]	x									*x*		*x*	
Optional Biomarker Urine Sample [9]	x					*x*				*x*		*x*	
Optional Biomarker Stool Sample[9]	x									*x*		*x*	

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9. What is the drug or intervention that is being tested?

Pembrolizumab belongs to a group of cancer drugs known as monoclonal antibodies. It uses the body's own immune system to fight the cancer, by targeting and blocking specific proteins on the surface of the immune system cells called T-cells. Pembrolizumab works against a protein receptor named PD-1, by blocking this receptor from binding to its usual ligand programmed death-ligand 1 or PD-L1 for short, pembrolizumab keeps the T-cell switched on and therefore able to elicit a combative response against cancer cells.

Lenvatinib is also a form of targeted therapy, like pembrolizumab, but it is what we call an angiogenesis inhibitor. To put it simply an angiogenesis inhibitor is a drug that stops the formation of blood vessels in and around tumours thereby cutting the nutrient supply to cancer cells; effectively starving them. Lenvatinib works by blocking proteins known as kinases and inhibits the three main vascular endothelial growth factor receptors VEGFR 1, 2 and 3, which are responsible for stimulating blood vessel growth. Without blood vessels providing nutrients, cancer cells cannot grow and replicate.

10. What are the alternatives for diagnosis or treatment?

Other treatments available for your condition include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study of an investigational drug
- Getting no treatment

Talk to your doctor about your choices before you decide whether to take part in this study.

11. What are the side effects of any treatment received when taking part?

Treatments for cancer often have side effects, including some that are life-threatening. There is the possibility of death occurring as a result of this treatment and its side effects. There may be additional unknown risks.

If you experience severe side effects associated with the study drug, your doctor may prescribe medications to treat the side effect(s), future treatments may be delayed, or treatment may be stopped permanently. Any significant new findings that develop during the course of the research and may relate to your willingness to continue participation will be provided to you.

Pembrolizumab and lenvatinib may cause the side effects listed below. The severity or duration of these side effects may vary for each patient. This information is based on data from patients in other clinical trials with pembrolizumab and/or lenvatinib. In addition, there may be side effects that are not yet known. Carboplatin and etoposide are already routinely used in this clinical setting and is not being investigated in this study. The side effects of these two drugs are widely known and accepted, however they may cause other side effects when given in combination with pembrolizumab. **You should tell your study doctor or nurse about all symptoms you experience, whether or not you think they are caused by the study drugs.**

For pembrolizumab:

Very common

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Out of 100 people who receive pembrolizumab, 20 or more people may have the following:

- Itching of the skin
- Loose or watery stools
- Cough

Common

Out of 100 people who receive pembrolizumab, at least 5 but less than 20 people may have the following:

- Joint pain
- Rash
- Fever
- Back pain
- Pain in your stomach
- Loss of skin colour
- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, or have infrequent or hard stools (hypothyroidism)
- 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 nauseous (hyponatremia)

Uncommon

Out of 100 people who receive pembrolizumab, at least 1 but less than 5 people may have the following:

- Inflammation of the lungs, so you may feel short of breath and cough (pneumonitis)
- Too much thyroid hormone, so you may feel anxious, feel angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools (hyperthyroidism)
- Infusion reaction, where you may feel dizzy or faint, feel flushed, get a rash, have a fever, feel short of breath, experience a decrease in your blood pressure at the time of receiving your infusion (IV) or just after, or have pain at the site of infusion
- Inflammation of the bowels/gut, which may cause severe pain in your stomach 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 peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e., peeling, itching and redness) could also be widespread throughout your body. 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 (Severe skin reactions, including Stevens-Johnson syndrome/or toxic epidermal necrolysis)

Rare

Out of 100 people who receive pembrolizumab, less than 1 person may have the following:

- Inflammation of the nerves that may cause pain, weakness or tingling in your hands and feet, and may spread to your legs, arms and upper body, leading to severe muscle weakness and possible temporary paralysis (Guillain-Barré syndrome)

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- Inflammation of the muscles, so you may feel weak or have pain in your muscles (myositis)
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels), so you may have severe pain in the top part of your stomach that may move to your back, feel nausea, and have vomiting that gets worse when you eat (pancreatitis)
- Inflammation of the eye, so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters or have headaches (uveitis)
- Inflammation of the liver that may make you feel nauseous and vomit, feel like not eating, feel tired, have a mild fever, a pain in the right side of your stomach, yellow eyes and skin, and dark urine (hepatitis)
- Inflammation of the pituitary gland (a gland in the head), which may cause you to feel nauseous or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting (hypophysitis)
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, having joint, muscle and stomach aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan (adrenal insufficiency)
- 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, so you may pass less urine or have cloudy or bloody urine, swelling and low back pain (nephritis)
- Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your 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)
- 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)
- A condition that may make you feel weak and tired and may cause drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing (myasthenic syndrome/myasthenia gravis including exacerbation)
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs (sarcoidosis)
- Inflammation of the brain with confusion and fever. This may also include disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness (encephalitis)
- 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)
- Inflammation of blood vessels that may casus headache, fatigue and fever.

Additionally, since pembrolizumab was approved in September 2014, the following side effects have been reported by people receiving pembrolizumab. These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of these side effects:

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- Inflammation of the joints which may include joint pain, stiffness and/or swelling (arthritis)
- Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin and brain. This may include fever, rash, and inflammation of the liver, yellowing of the skin, an enlarged liver and spleen, low blood counts, and enlarged lymph nodes. The nervous system may also be affected and cause confusion, seizures, and even coma (hemophagocytic lymphohistiocytosis)
- Changes in eyesight, eye pain, whitish patches on the skin and hearing loss (Vogt-Koyanagi-Harada syndrome)
- Scarring, thickening and inflammation of the bile ducts (Sclerosing Chlangitis)

If you have had an allogeneic stem cell transplant (a procedure in which a person receives blood-forming stem cells from a donor), you may experience graft versus host disease (GVHD), which may include diarrhoea, skin rashes, and liver damage, after receiving pembrolizumab. Sometimes this condition can lead to death.

If you have had a solid organ transplant (for example, if you have received a kidney or heart transplant), you may experience rejection of the transplanted organ. Your doctor will monitor you and should tell you what signs and symptoms you should report depending on the type of organ transplant that you have had.

For lenvatinib:

Serious Side Effects - Common (may affect up to 1 in 10 people)

- Stroke, mini-stroke, or bleeding in the brain –may result in numbness or weakness on one
- Blood clot in the legs or lungs (pulmonary embolism) – may cause swelling of the calf associated with warmth or tenderness, sudden onset of shortness of breath, rapid breathing, tightening of chest or chest pain, cough or coughing up blood, rapid heart rate and a blue tinge to the lips
- Heart problems, heart palpitations or heart attack – may cause chest pain or pressure, pain in the arms, back, neck or jaw, shortness of breath, rapid or irregular heart rate, coughing, bluish colour to lips or fingers, feeling very tired
- Fistula formation or bowel perforation – abnormal connections between different organs in the body or between an organ and another part of the body such as the skin or windpipe, or formation of a hole in the wall of the gut which can cause severe abdominal pain.
- Bleeding inside the body particularly from the gut – may cause black, tarry, or bloody stools
- Dehydration and kidney failure – may result from diarrhoea, feeling and being sick which are very common side effects
- Heart failure – a decreased pumping ability of the heart which may cause severe shortness of breath
- Liver damage or failure – may cause yellowing of the skin or eyes (jaundice), tiredness or sickness, loss of appetite, abdominal pain or high temperature.
- Hepatic encephalopathy – may result in confusion, drowsiness, poor concentration or loss of consciousness. side of the body

Serious Side Effects - Uncommon (may affect up to 1 in 100 people)

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- Posterior reversible encephalopathy syndrome (PRES) is a potentially fatal condition that may have the following symptoms: headache, confusion, convulsions and vision disturbance. An MRI scan may be required to diagnose this condition
- Pneumothorax – a leak of air from the lung into the chest so the lung cannot inflate. This may cause sudden chest pain or sudden shortness of breath. There may be a higher chance of this occurring if cancer has spread to the lungs or if treatment is for solid tumour cancers such as osteosarcoma or soft tissue sarcoma or in patients under the age of 25.
- Aortic dissection – tearing in the wall of the aorta (a large artery) which may cause severe pain in the back, chest or abdomen and internal bleeding.

Other Side Effects – Some May be Serious

Very Common (affects more than 1 in 10 people and up to 8 in 10 people)

- High or low blood pressure
- Loss of appetite or weight loss
- Feeling sick and being sick, constipation, diarrhoea, abdominal pain, indigestion
- Feeling very tired or weak
- Dry, sore, or inflamed mouth or throat high levels of protein in the urine
- Hoarse voice
- Headache
- Hand-foot syndrome (redness, soreness and swelling of the skin on the hands and feet)
- Joint pains
- Cough
- Low level of platelets in the blood which may lead to bruising
- Musculoskeletal, muscle, limb or back pain
- Swelling of the legs
- Underactive thyroid and change in blood test result for thyroid stimulating hormone (high) - may result in fatigue, weakness, dry skin, hair loss, intolerance to cold
- Rash
- Feeling dizzy
- Bleeding (most commonly nose bleeds, but may include bleeding from other sites such as blood in the urine, bruising, bleeding from the gums, coughing up blood)
- Odd taste sensation
- Trouble sleeping
- Hair loss
- Urinary infections (increased frequency in urination and pain in passing urine)
- Changes in blood test results for potassium levels (low) and calcium levels (low) – may increase the chance of having an abnormal heart rhythm

Other Side Effects – some may be serious

Common (may affect up to 1 in 10 people)

- Loss of body fluids (dehydration)
- Dry skin, thickening and itching of the skin
- Feeling bloated or having gas in the bowel
- Feeling unwell

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- Inflammation of the gallbladder
- Changes in blood test results for liver
- Changes in blood test results for magnesium (low) – may increase the chance of having an abnormal heart rhythm
- Changes in blood test results for kidney function
- Changes in white blood cells (low) which may increase risk of infections
- Changes in blood test results (high) for lipase and amylase (enzymes involved in digestion)
- Changes in blood test results for cholesterol (high)

Other Side Effects – Some May be Serious

Uncommon (may affect up to 1 in 100 people)

- Painful infection or irritation near the anus
- Splenic infarction (severe pain in the upper left part of the stomach (abdomen) which may be associated with fever, chills, nausea and vomiting)
- Inflammation of the pancreas which may cause severe pain in the abdomen or back
- Impaired healing – wounds may take longer to heal

For pembrolizumab and lenvatinib together:

Researchers are studying the use of pembrolizumab together with lenvatinib to treat certain cancers. There is a limited amount of information about the risks of using these two drugs together. Previous research studied 283 patients who received pembrolizumab and lenvatinib together for an average of 6 months. Based on these patients if you are taking pembrolizumab together with lenvatinib:

- You are still at risk for all the side effects listed above for each of the drugs when taken alone.
- There were no NEW side effects when patients took these 2 drugs together. However, some of the side effects seen when patients took either drug alone were seen more often when patients took the two drugs together.

Below are the side effects that were seen more often when patients took the 2 drugs together (compared to taking either drug alone):

Very common: Out of 100 people who receive pembrolizumab and lenvatinib together, 20 or more people may have the following:

- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, have infrequent or hard stools

Uncommon: Out of one hundred people who receive pembrolizumab and lenvatinib together, at least 1 but less than 5 people may have the following:

- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe pain in the top part of your stomach that may move to your back, feel sick, and vomiting that gets worse when you eat
- Inflammation of the adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling

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faint, joint, muscle and stomach aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan
- Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, swelling and low back pain

For carboplatin:

Known important side effects:

- Abnormal bruising, bleeding
- Signs of infection such as a sore throat and high temperature
- Severe itching of the skin (with raised lumps) or swelling of the face, lips, tongue and/or throat, which may cause difficulty in swallowing or breathing (angioedema)
- Stomatitis/mucositis (e.g., sore lips or mouth ulcer
- Severe allergic reactions (anaphylaxis/ anaphylactoid reactions). Symptoms of a severe allergic reaction include sudden wheeziness or tightness of chest, swelling of the eyelids, face or lips, facial flushing, hypotension (low blood pressure), tachycardia (fast heartbeat), urticaria (hives), dyspnoea (shortness of breath), dizziness and anaphylactic shock

Very common - may affect more than 1 in 10 people

- Changes in your red and white blood cells and platelets (myelosuppression). Your doctor may want to monitor you
- Anaemia (a condition in which there is a decreased number of red blood cells which lead to tiredness)
- Increase in the level of the creatinine and urea in your blood. Your doctor may want to monitor you
- Slight loss of hearing
- Abnormal liver enzyme levels. Your doctor may want to monitor you
- Increased uric acid levels in the blood which may lead to gout
- Feeling or being sick
- Abdominal pain and cramp
- Unusual feelings of tiredness or weakness
- Decrease in the level of salts in your blood. Your doctor may want to monitor you
- Damage to the kidneys (renal toxicity)

Common – may affect up to 1 in 10 people

- Unusual bruising or bleeding (haemorrhagic complications)
- Reduced function of your kidneys
- Diarrhoea, constipation, sore lips or mouth ulcers (mucositis)
- Pins and needles (peripheral neuropathy)
- Hair loss
- Feeling unwell
- Decreased serum levels of calcium
- Allergic reaction including rash, urticaria, skin reddening, itching, high temperature
- Ringing in the ears (tinnitus), hearing impairment and hearing loss
- Flu-like syndrome

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- Loss or lack of bodily strength
- Fever

For etoposide:

Common – over 30% of patients

- Low white blood cell count. (This can increase your risk for infection).
- Low platelet count (This can increase your risk of bleeding).
- Hair loss
- Menopause (chemotherapy induced)
- Loss of fertility. Meaning, your ability to conceive a child may be affected by etoposide. Discuss this issue with your health care provider.
- Nausea and vomiting (especially at high doses)
- Low blood pressure (if the drug is infused too fast)

Less common – 10-29% of patients

- Mouth sores (especially at high doses)
- Diarrhea (especially at high doses)
- Poor appetite
- Skin reaction

Occasional side effects-

- Metallic taste during infusion of drug
- Inflammation at injection site
- Peripheral neuropathy (numbness in your fingers and toes) may occur with repeated doses. This is a rare side effect but can be irreversible. Report numbness or tingling of feet or hands to your health care provider.
- There is a slight risk of developing a blood cancer such as leukemia years after taking etoposide. Talk to your doctor about this risk.

Please inform your study doctor or nurse AT ONCE if you experience any of the following:

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

Prolonged treatment with medicines that suppress inflammation, sometimes needed to manage the side effects of study drug treatment, may lower your body's ability to fight off certain infections (i.e., opportunistic infections). These infections may require treatment with antibiotic or antifungal medications and may be fatal even after treatment.

If you start to develop symptoms, your study doctor will ask you to return to the clinic for additional tests, which could include a physical exam, measurement of oxygen levels, blood tests, chest X-rays,

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and/or CT scans. You will be monitored very closely for changes in your overall lung symptoms, monitoring may require hospitalisation. You may also be seen by a special doctor called a respiratory physician, who has special training to be an expert in how your lungs work.

Other side effects

Side effects associated with blood tests or use of an IV catheter may include infection, bruising, redness, discomfort, or bleeding at the needle puncture site.

There may be risks or side effects which are unknown at this time.

Your condition may not get better or may become worse while you are in this study.

Certain drugs may increase the severity of these side effects if taken during the study. Ask your study doctor for a full list of prohibited medications.

12. What are the other possible disadvantages and risks of taking part?

To enroll in this study, we ask all patients to have a tumour biopsy prior to treatment. Removal of tumour tissue would need to be done under local anaesthetic and can be painful and cause pressure or discomfort in the area where the tissue was taken. Pain and discomfort can last for several hours and up to several days after the biopsy procedure. You may experience redness, swelling, bruising, or infection in the area where the tissue was taken, and/or feel faint or dizzy.

As part of your involvement in this study you will receive a number of CT scans of your body. CT scans use X-rays to take a picture of what the inside of your body looks like. CT scans will expose you to ionising radiation and this carries a risk of causing cancer later in life after a delay called a latency period. This latency period can be from 2-10 years for leukaemia, and up to several decades for solid tumours. The risk to a healthy 40-year-old from the total radiation dose involved in this study is estimated to be about 1 in 105.For someone with your pre-existing clinical condition, the chances of you taking part in this study and developing another cancer later on may be considered very small.

You will also be attending extra visits to enable a thorough monitoring of your trial medication

Sometimes patients can have allergic reactions to the dyes used in CT scans. This is rare. It can involve itching or a rash. In severe cases, you may have difficulty breathing and a dangerous lowering of your blood pressure. If you know you have an allergy to the dye, or to iodine or shellfish, please let your study doctor and radiologist know.

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.

If you have private medical insurance, you may wish to check with the insurance company before agreeing to take part in the study, in case participation affects the validity of your insurance policy.

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13. Are there any risks for reproduction, unborn babies and breastfeeding infants?

13A. General statement for women of childbearing potential:

You must not be pregnant or breastfeeding and should not become pregnant or breastfeed while you are taking the study treatments. You must be using an adequate method to avoid pregnancy until 5 months after the last dose of study drug. Your study doctor will discuss with you the acceptable methods. You should immediately contact your study doctor if there is a change in your method to avoid pregnancy.

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (oestrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the participants preferred and usual lifestyle. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

There may be unknown risks to you, your unborn baby or breastfeeding infant if you become pregnant or are breastfeeding during this study.

You will have a pregnancy test within 24 hours of your first dose of study medication.

If you become pregnant, suspect pregnancy or if you missed your period or it is late, or if you have a change in your usual menstrual cycle (e.g., heavier bleeding during your period or bleeding between periods), you must inform your study doctor immediately.

Should you become pregnant during the study, you will immediately have the investigational product discontinued and be referred for obstetric care. You will continue to be followed for any side effects or potential benefits of the study treatment, provided it is safe for you and your unborn baby to do so. Your doctor will discuss this with you, as well as options for additional appropriate care for your cancer.

13B. General statement for men (with female partners of childbearing potential):

You must be using an adequate method to avoid impregnating a partner until 7 months after the last dose of study drug. Your study doctor will discuss with you the acceptable methods. You should immediately contact your study doctor if there is a change in your method to avoid pregnancy.

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If a female partner becomes pregnant while you are in the study, you must inform your study doctor immediately.

14. What are the possible benefits of taking part?

Carboplatin and etoposide are already a mainstay treatment for HG-NETs. As this disease is known to heavily rely on the PD-1 activated pathway which pembrolizumab acts on, the addition of pembrolizumab to carboplatin and etoposide is expected to have a harmonious effect. The addition of pembrolizumab **might** help by shrinking the cancer further and prolonging your time before progression. Maintenance treatment with lenvatinib and pembrolizumab then **might** also prolong this further.

However, pembrolizumab and lenvatinib **might not** lead to improvement of your high-grade neuroendocrine tumours compared to if you were to just receive routine standard of care and just receive carboplatin and etoposide alone.

The knowledge gained from this study may also be of help to other patients with cancer in the future.

15. What if relevant new information becomes available?

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

Also, on receiving new information your study doctor might consider it to be in your best interests to end your participation in this study. He/she will explain the reasons and arrange for your care to continue.

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

16. What happens when the research study stops?

At the end of the study, the study drug will no longer be provided to participants. Your study doctor will ensure that you receive the appropriate standard care for your condition.

17. What will happen if I do not want to carry on with the study?

Your participation in this study is entirely voluntary. It is up to you to decide whether to take part or not. Even if you do decide to take part, you are free to discontinue treatment or withdraw consent from the study at any time without giving a reason. This will not affect your future medical care in any way.

Please note that any information collected before you withdraw will be kept and used to complete the research.

If you decide to stop study treatments, your study doctor will not presume that you have withdrawn from the study but will assume that you will continue to participate in any follow-up activities described

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in Section 6. If you do not want to participate in any or all follow-up activities, you must inform your study doctor in writing and clearly identify the activities you do not want to do.

18. What if something goes wrong?

Complaints:

If you wish to raise a complaint about how we have handled your personal data, please contact the research team first by sending an email to pelican-trial@imperial.ac.uk or by ringing us on 02083831362.

Following our response, if you are not satisfied, please contact Imperial College London's Data Protection Officer via email at dpo@imperial.ac.uk, via telephone on 020 7594 3502 and/or via post at Imperial College London, Data Protection Officer, Faculty Building Level 4, London SW7 2AZ.

If you remain unsatisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO)- via www.ico.org.uk. Please note the ICO does recommend that you seek to resolve matters with the data controller (us) first before involving them.

Harm:

Imperial College London holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you will be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (Insert name and contact details). The normal National Health Service mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial College, Research Governance and Integrity Team

19. How will we use information about you?

Imperial College London is the sponsor for this study and will act as the Data Controller. This means that we are responsible for looking after your information and using it appropriately. Imperial College London will keep your personal data for:

10 years after the study has finished in relation to data subject consent forms.

10 years after the study has completed in relation to primary research data. The study is expected to finish in July 2026.

For more information / confirmation regarding the end date please contact the study team, see '**WHERE CAN YOU FIND OUT MORE ABOUT HOW YOUR INFORMATION IS USED'** for contact information.

We will need to use information from you and from your medical records for this research project.

This information will include your

- initials

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- NHS number
- name
- contact details

People within the College and study team (see section sharing your information with others) will use this information to do the research or to check your records to make sure that research is being done properly and information held (such as contact details) is accurate. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

As a university we use personally identifiable information to conduct research to improve health, care and services. As a publicly funded organisation, we have to ensure that it is in the public interest when we use personally identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study. Our legal basis for using your information under the General Data Protection Regulation (GDPR) and the Data Protection Act 2018, is as follows:

- Imperial College London - “performance of a task carried out in the public interest”); Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research

Where special category personal information is involved (most commonly health data, biometric data and genetic data, racial and ethnic data etc.) Imperial College London relies on “scientific or historical research purposes or statistical purposes”.

INTERNATIONAL TRANSFERS

There may be a requirement to transfer information to countries outside the European Economic Area (for example, to a research partner). Where this information contains your personal data, Imperial College London will ensure that it is transferred in accordance with data protection legislation. If the data is transferred to a country which is not subject to a European Commission (**EC**) adequacy decision in respect of its data protection standards, Imperial College London will enter into a data sharing agreement with the recipient organisation that incorporates EC approved standard contractual clauses that safeguard how your personal data is processed.

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SHARING YOUR INFORMATION WITH OTHERS

We will only share your personal data with certain third parties for the purposes referred to in this participant information sheet and by relying on the legal basis for processing your data as set out above.

- Other Imperial College London employees (including staff involved directly with the research study or as part of certain secondary activities which may include support functions, internal audits, ensuring accuracy of contact details etc.), Imperial College London agents, contractors and service providers (for example, suppliers of printing and mailing services, email communication services or web services, or suppliers who help us carry out any of the activities described above).

COMMERCIALISATION

Samples and data from the study may also be provided to organisations not named in this participant information sheet, e.g., commercial organisations or non-commercial organisations for the purposes of undertaking the current study, future research studies or commercial purposes such as development by a company of a new test, product, or treatment. We will ensure your name and any identifying details will NOT be given to these third parties, instead you will be identified by a unique study number with any sample / data analysis having the potential to generate 'personal data'.

Aggregated (combined) or anonymised data sets (all identifying information is removed) may also be created using your data (in a way which does not identify you individually) and be used for such research or commercial purposes where the purposes align to relevant legislation (including the GDPR) and wider aims of the study. Your data will not be shared with a commercial organisation for marketing purposes.

POTENTIAL USE OF STUDY DATA FOR FUTURE RESEARCH

When you agree to take part in a research study, the information collected either as part of the study or in preparation for the study (such as contact details) may, if you consent, be provided to researchers running other research studies at Imperial College London and in other organisations which may be universities or organisations involved in research in this country or abroad. Your information will only be used to conduct research in accordance with legislation including the GDPR and the UK Policy Framework for Health and Social Care Research.

This information will not identify you and will not be combined with other information in a way that could identify you, used against you or used to make decisions about you.

WHAT ARE YOUR CHOICES ABOUT HOW YOUR INFORMATION IS USED?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have because some research using your data may have already taken place and this cannot be undone.

- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you if this could affect the wider study or the accuracy of the data collected.

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- If data will be used for future research: If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.

WHERE CAN YOU FIND OUT MORE ABOUT HOW YOUR INFORMATION IS USED

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- by asking one of the research team
- by sending an email to pelican-trial@imperial.ac.uk, or
- by ringing us on 0208 383 1362

20. What will happen to any tissue or other samples I give?

Most blood and urine samples collected from you will be tested within the NHS organisation hosting the study, to check your health and monitor your disease.

Tumour tissue samples, and optional blood, urine and stool samples, will be transferred to the research sponsor, Imperial College London. These samples will be labelled with a unique code instead of your name and analysed in order to study your disease. Information derived from these samples will be handled by Imperial College London as described in Section 19 above.

At the end of the study, if there are any samples left over, they may be transferred for indefinite, long-term storage in the Imperial College Healthcare Tissue Bank, which is licensed by the UK Human Tissue Authority. Your samples will be labelled with a unique code instead of your name or other details that could readily identify you. They may be used in future, ethically approved research to study liver cancer or other diseases. This future research may involve transfer of samples to Imperial College London's agents, collaborators and business partners who may be located outside of the country or region (e.g., the European Union) in which you live. However, your samples and data they provide will be kept confidential and secure.

If you withdraw from the study, any stored blood or tissue samples that can still be identified as yours will be destroyed if you wish. If you wish to withdraw your consent for such samples to be retained, you should let your study doctor know.

21. Will any genetic tests be done?

Yes. As part of this study, the sponsor would like to see if there is anything within your genes/proteins which may help them to understand or treat neuroendocrine cancer. This analysis will be completed on the sample of your tumour that was taken at the time of diagnosis, or during other surgical procedures, and on some of the blood samples that are taken from you. The future research mentioned in Section 20 might involve genetic tests also. You will not be contacted by the sponsor in

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connection with the research or given any information about the results of genetic tests performed on the samples that you provide for this research.

22. What will happen with the results of the research study?

The data collected will be used for the evaluation of the study and may be used in the future in related or other studies. The data may be submitted in coded form to health authorities for registration purposes. Members of health authorities, such as the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK, Food and Drug Administration (FDA) and Research Ethics Committees or other persons required by law may review the coded data provided. This data may also be used in publications about the study drug, but the data will remain coded. Your identity will not be revealed in any compilation, study report or publication at any time.

23. Who is organising and funding the research?

The academic institution organising ('sponsoring') this study is Imperial College London. The funding is from the pharmaceutical company, Merck Sharp & Dohme Limited.

The NHS organisations hosting the study will be paid for including you in this study.

24. Who has reviewed the study?

An NHS Ethics Committee*, to add REC name* has reviewed the objectives and the proposed conduct of the study and has given a favourable opinion of it. The study has also been reviewed and authorised by the UK Medicines and Healthcare products Regulatory Agency and approved by the UK Health Research Authority.

25. Further information & Contact details:

If you have any questions regarding the study or in case of study related injury you should contact your study doctor – *Local Doctor 's name and Tel contact number*.

Please contact Chynna, Clinical Trials Manager on the following 24-hour contact details:
Telephone: 0203 313 1362
Email: pelican-trial@imperial.ac.uk

A description of this clinical trial will be publicly available on https://clinicaltrials.gov.

Thank you for taking time to read this sheet.

You will receive a copy of this information sheet and the signed informed consent form should you wish to participate in this study

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(To add on hospital headed paper)

Informed Consent Form – Main Study

PELICAN: A phase II study of etoposide-carboplatin chemotherapy in combination with pembrolizumab and lenvatinib maintenance in advanced high-grade neuroendocrine tumours (HG-NETs).

	Patient initials in each box
I confirm that I have read and understand the participant information sheet version 1.0 dated 10/05/2023 for the PELICAN study: A phase II study of etoposide-carboplatin chemotherapy in combination with pembrolizumab and lenvatinib maintenance in advanced high-grade neuroendocrine tumours (HG-NETs), and have had the opportunity to ask questions which have been answered fully.	
I understand that my participation is voluntary, and I am free to withdraw at any time, without giving any reason and without my legal rights nor treatment / healthcare being affected.	
I understand that sections of any of my medical notes may be looked at by responsible individuals from [company/institution name], from NHS Trust or from regulatory authorities where it is relevant to my taking part in this research.	
I agree to have a tumour biopsy at screening.	
I give consent for information collected about me to be used to support other research or in the development of a new test, medication, medical device or treatment (delete as applicable) by an academic institution or commercial company in the future, including those outside of the United Kingdom (which Imperial has ensured will keep this information secure).	
I give / do not give (delete as applicable) consent for samples (human tissue) collected about me to be used to support other research or in the development of a new test, medication, medical device or treatment (delete as applicable) by an academic institution or commercial company in the future, including those outside of the United Kingdom (which Imperial has ensured will keep this information secure).	
I understand that tissue samples and / or data collected from me are a gift donated to Imperial College and that I will not personally benefit financially if this research leads to an invention and/or the successful development of a new test, medication treatment, product or service.	
I agree that my coded study data and samples may be transferred both within and outside of Europe.	
I confirm that I have received a patient alert card providing the contact details of the study doctor. I agree to carry this card with me at all times.	
I agree to my GP being informed of my participation in the study.	
I agree that tissue samples that have already been taken from me and are in storage can be used for the purposes of the study.	

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I confirm that the information on pregnancy prevention has been reviewed with me. (If applicable)	
I consent to take part in PELICAN: A phase II study of etoposide-carboplatin chemotherapy in combination with pembrolizumab and lenvatinib maintenance in advanced high-grade neuroendocrine tumours (HG-NETs).	
I give / do not give (delete/mark as applicable) consent to being contacted about the possibility to take part in other research studies.	
I agree / I do not agree to my tissue samples being used to undertake genetic research which may have the potential to generate data that can be tracked back to me.	

Name of participant	Signature	Date
Name of person taking consent	Signature	Date

1 copy for participant; 1 copy for Principal Investigator 1 copy for hospital notes

To ensure confidence in the process and minimise risk of loss, all consent forms must be printed, presented and stored in double sided formal.

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(To add on hospital headed paper)

Informed Consent Form – Optional Sampling

PELICAN: A phase II study of etoposide-carboplatin chemotherapy in combination with pembrolizumab and lenvatinib maintenance in advanced high-grade neuroendocrine tumours (HG-NETs).

Name of Principal Investigator: _____

	Patient initials in boxes
I agree to give the optional blood samples.	
I agree to give the optional urine samples.	
I agree to give the optional stool samples.	
I agree to give the optional biopsy samples.	

To be signed simultaneously, (i.e. same date), by all parties:

_____	_____	_____
Name of patient	Date	Signature of patient
_____	_____	_____
Name of person taking consent	Date	Signature of person taking consent

When completed, place original in site file, give copy to participant and place another in his/her medical record.