Centre Number: _____ **Patient Study Identification Number: _____**

PARTICIPANT INFORMATION SHEET – REFINE-Lung

Full title: A randomised open-label phase III trial of REduced Frequency pembrolizumab ImmuNothErapy for first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) utilising a novel multi-arm frequency-response optimisation design

REFINE-Lung = **R**educed **F**requency pembrolizumab **I**mmu**N**oth**E**rapy: can the frequency of pembrolizumab treatment for non-small cell lung cancer be reduced without reducing its effectiveness?

Introduction

You are invited to take part in our research study. This information sheet will explain why the research is being done and what it would involve for you. **Someone from our team will go through the information sheet with you and answer any questions you have**. Please read the information carefully and talk to others, for example your GP, about the study if you wish.

Part 1 explains the purpose of this study and what it involves.

Part 2 gives more detailed information about how we are conducting the study.

Please ask us if anything is unclear, or if you need more information. Take as much time as you need to decide whether or not to take part. Once you have decided if you want to take part, you will be asked to sign the consent form. You will get a copy of this form.

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

Part 1

1. What is the purpose of the study?

Pembrolizumab is often used to treat people diagnosed with non-small cell lung cancer (NSCLC). Pembrolizumab helps to fight cancer by activating the immune system, the body's natural defence against disease.

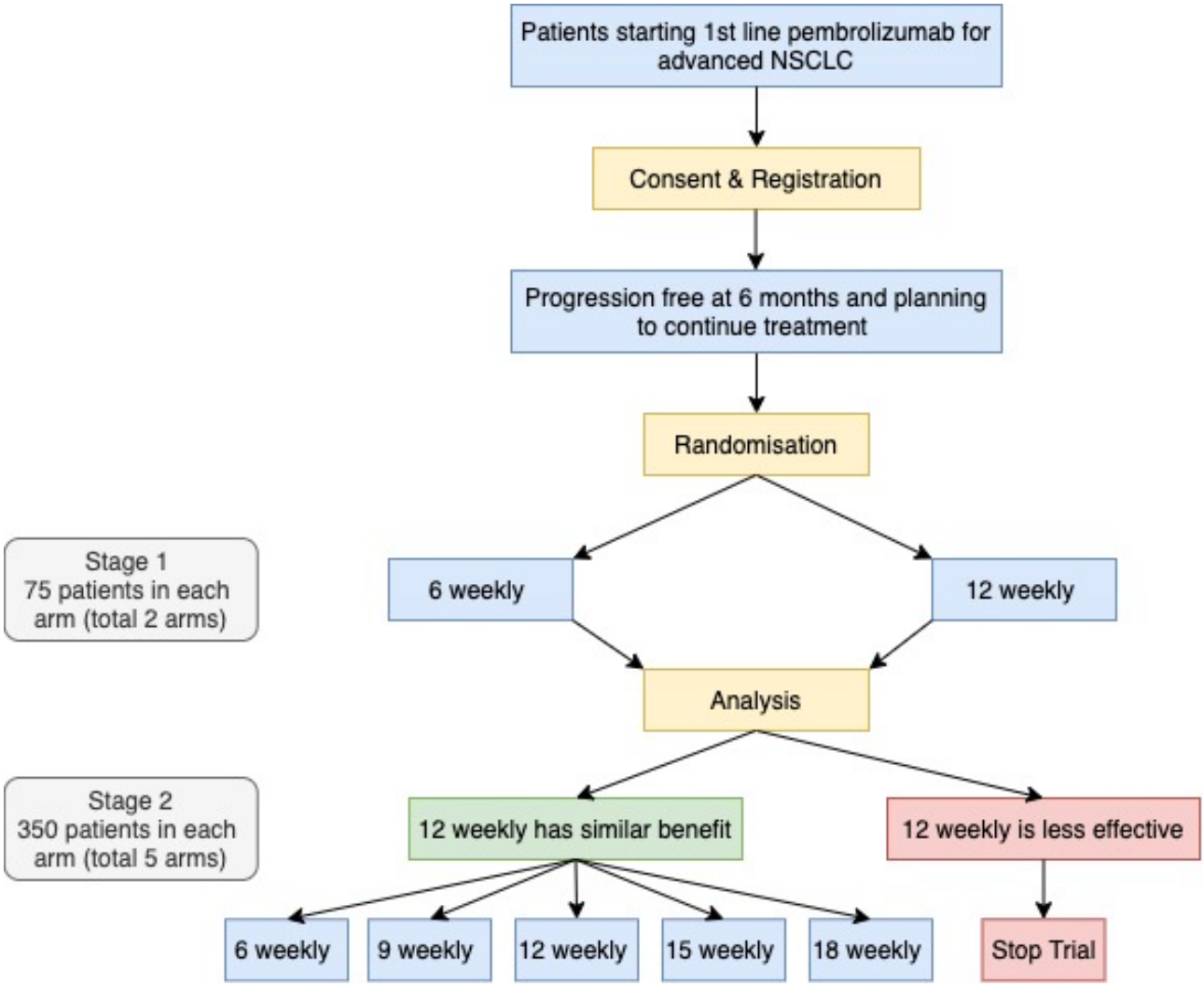
Pembrolizumab is usually given every 3 or 6 weeks for up to 2 years. Our research suggests that standard treatment is too frequent. We think that after 6 months, how often pembrolizumab is given can be given less often without reducing how well the treatment works. For instance, we may be able to give pembrolizumab every 12 weeks instead of 3 or 6 weeks. The main aim of the REFINE-Lung study is to find out if treatment frequency can be safely reduced and the best frequency to use. Giving pembrolizumab less often will have many potential benefits, including:

- The same effectiveness but fewer side effects and hospital visits
- Improved quality of life due to less hospital visits and side effects

This study is being carried out in two stages, Stage 1 and Stage 2. Stage 1 (which you are being invited to take part in) will compare two treatment frequencies – **pembrolizumab given every 6 weeks (the standard treatment) or every 12 weeks.**

Stage 2 will compare an additional three frequencies, pembrolizumab given every 9 weeks, 15 weeks and 18 weeks.

<u>You are only able to take part in the study once. You are being invited to take part in Stage 1 of the study.</u>



2. Why have I been invited to take part?

You have been invited to take part because you have advanced NSCLC and are currently receiving or about to receive pembrolizumab every 3 or 6 weeks with or without chemotherapy. Your oncologist thinks you may be suitable to take part in this research and, if you decide to take part, you will be one of up to 1,750 people recruited into the study from hospitals in the UK.

3. Do I have to take part?

No. It is up to you to decide whether to take part or not. If you prefer not to, you do not have to give a reason. If you do decide to take part after reading this information leaflet, you will be asked to sign a consent form and you will be given a copy to take away with you. You are free to withdraw at any time, without giving a reason. This would not affect the standard treatment you receive.

Your cancer specialist or the study sponsor (Imperial College London) may decide at any time to stop study treatment, even though you may want to continue. This may occur if you have unacceptable side effects or if new information about pembrolizumab becomes available. Your study doctor will explain the reasons why you have to stop and discuss appropriate treatment options with you so that medical care can continue. Full details are included in section 8 and Part 2 of this information sheet.

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

If you take part in this study, you will be asked to follow the study treatment plan, tests and hospital appointments explained below. You should consider how these tests and visits will affect your work and family life and decide if you are able to commit to them. One of the potential benefits of this study is that you may well have less hospital visits.

What will happen before I can enter the trial?

You may be approached about entering the study at any time during the 6 months from starting pembrolizumab. This is to give you an opportunity to consider whether you would like to take part.

Within 6 weeks of reaching 6 months of treatment, if your oncologist thinks you are suitable to enter the study because the treatment is working and you plan on continuing, you will be invited to participate. If you are interested, we will collect some information to check your eligibility (we call this "screening").

If you are **confirmed to be suitable** to take part in the study will then you will continue to Step 2 of this section.

If you are **confirmed not to be suitable** to take part in the study then you will unfortunately not be able to take part, and your oncologist will make alternative arrangements for treatment.

The screening will involve:

- A CT scan to measure and record the size of your tumour(s) to see if it has not grown
- Your consent to enter the study, to collect your previous scans just before and after starting pembrolizumab and your original biopsy. In addition, you will be asked to optionally consent to provide blood for research before each treatment. This will help research to allow us to predict which patients will most likely benefit from immunotherapy
- Collection of other information about you including age; gender including gender reassignment; sexual orientation; marital status; disability; ethnicity, religion; geographical location and socioeconomic status. **All questions will be optional to answer.** The reason we collect this information is to ensure equal opportunity and inclusion

What happens once you are confirmed suitable to take part?

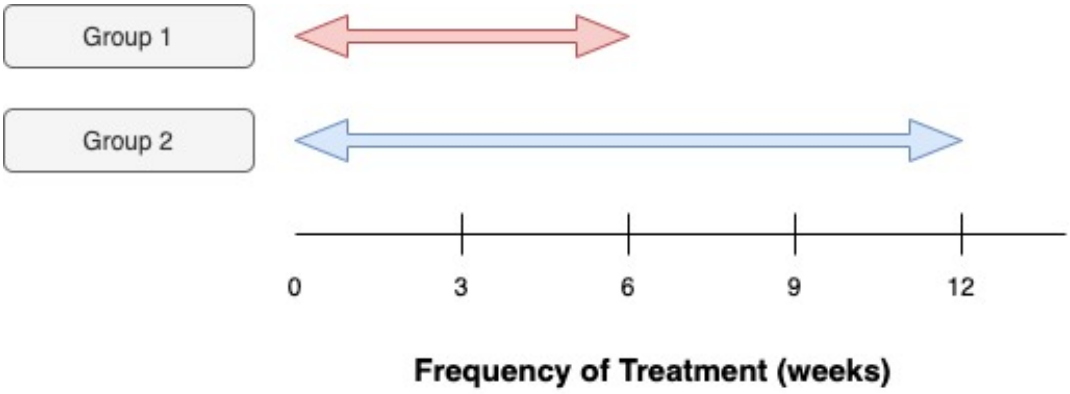
Once you have been confirmed suitable to take part in the study, we will randomly assign you to a treatment frequency. REFINE-Lung is a randomised study. The only way to make sure that people

in the two treatment groups are as similar as possible is to allocate them to a treatment group randomly. This means that if one group does better than the other, it is more likely to be because of the treatment, and not because the people in each group are different from each other in some way. A computer programme is used to perform the randomisation to make sure it is done fairly. You will be told by your study doctor which treatment group you are in.

There are currently two treatment groups Stage 1 of the study:

- **Group 1** – will receive pembrolizumab every 6 weeks for up to 2 years, with or without chemotherapy. This treatment is standard treatment, or the 'control' arm of the study;

- **Group 2** – will receive pembrolizumab every 12 weeks for up to 2 years, with or without chemotherapy.



We will find out how well patients in both groups are doing using CT scans to check if the cancer is growing. If patients in Group 2 do worse with faster cancer growth, we will put patients in this group back onto standard 6 weekly treatment and stop the study. Otherwise, if Groups 1 and 2 are the same, we will start entering patients into the remaining groups as part of Stage 2 (treatment every 9, 15 or 18 weeks).

You will keep stay in the same group as long as scans show the cancer is not growing and you and your doctors are happy for you to continue. You will receive a total of 2 years pembrolizumab treatment which is the current guidelines for standard treatment. If at any point your scans show the cancer is growing, you will have the option of returning to 6 weekly treatment if you are receiving pembrolizumab less frequently than that (in other words, if you are in Group 2). The decision to do this will be guided by your study doctor.

What happens before and during trial treatment?

Once you have been confirmed suitable to take part in the study, a number of procedures and assessments will be completed to check you are fit to receive further treatment with pembrolizumab, such as a physical examination, blood pressure and pulse, blood samples to assess your organ function and fitness for treatment and an assessment of any medications you are taking or have taken recently. These are all part of normal care and would have been completed in your first 6 months of treatment. The tests performed at each visit are the same for everyone, however the number of times you attend hospital will depend on the treatment group you are randomly assigned to.

We will also collect any tissue that is stored at your local hospital for research to better understand NSCLC and why some treatments work for some people and not others.

Extra optional sub-study to predict immunotherapy outcomes

There is an optional sub-study in addition to the main study described below. If you agree to take part in this, we will collect extra blood samples (4 teaspoons, up to 20ml) when you visit hospital for before treatment and at each treatment visit. These are for research to better understand NSCLC and why some treatments work for some people and not others. Your sample will be analysed to study how genetic differences may influence the way different people respond to the study medication. No extra hospital visits will be necessary. If you do not wish to take part in additional blood samples, it does not affect your ability to take part in the study.

5. What do I have to do?

If you take part in this study, you will be asked to follow the study treatment plan, tests and hospital appointments explained above. You must inform your study doctor of any medications you are currently taking or that you intend to use once you have entered the study.

You must not donate blood at any time during the study treatment period.

6. How will we assess whether the treatment is working and its effect on your quality of life?

CT scans to assess your disease will be done every 3 months as part of normal care. In addition, if you are worried you can contact your doctor or nurse at any time to seek advice.

You will also be asked to complete three questionnaires on paper regarding your general health and the cancer usually the same time as your scans. The questionnaires should take approximately 15-20 minutes in total to complete. If you feel uncomfortable answering any of the questions, please talk to your study doctor or nurse. You can leave blank any questions you do not want to answer. This information will help us to understand whether reduced frequency of giving treatment may affect your quality of life.

7. What happens if my cancer is getting worse on the study?

If the cancer progresses and you are receiving treatment less frequently than 6 weekly, you can return to 6 weekly therapy if you and your oncologist agree. If the cancer grows whilst you are on the 6 weekly arm, you will come off the study and your oncologist will guide you regarding the next type of treatment.

8. What happens if I feel unhappy about continuing in the study?

If you were in a reduced frequency arm you could go back to 6 weekly treatment and continue in the study and we will continue to monitor you closely. Alternatively, you could decide to completely withdraw and your local oncologist will carry on your treatment outside of the study.

9. What happens when my treatment stops?

Your trial treatment will be stopped if the cancer grows significantly, you have unacceptable side effects or if you have completed a total of 2 years on therapy (18 months within the study). All patients will have an end of study visit about 1 month after stopping where we will do bloods, review your general health and ensure your CT imaging is up-to-date within the previous 6 weeks. In addition, if you consent, you will be asked to give 4 teaspoons (up to 20ml) of blood for research.

If you stop because of cancer progression or side-effects of treatment we will continue to collect your data until you have completed 18 months from trial entry.

You will not be able to continue receiving treatment after 2 years (18 months within the study) as this is the current recommended maximum treatment time for your cancer with this drug. Your study doctor will discuss a plan for your future care when appropriate.

The research will stop once all patients have completed their last visit for trial procedures. In addition, Imperial College London (the sponsor), the trial's Research Ethics Committee (REC) or Regulatory Authority may decide to stop the study for valid reasons not listed above. If this happens, your study doctor will discuss it with you in full, including a plan for your future care as appropriate.

10. Will I be compensated for taking part in the study?

You will not be paid for taking part in the study. You should not have to attend hospital for any extra visits above those you would for any standard treatment, so you will not be reimbursed for your travel expenses.

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

The treatment itself, blood tests and CT scans you will have on this study are all part of the usual care you would receive if you were not on the study. We do not expect side effects on the study to be worse than what you would otherwise have on pembrolizumab over the last 6 months. If you wish to see details of the expected side effects of pembrolizumab again, please ask your study doctor.

During the time you receive study treatment you will be examined regularly by your study doctor, and several tests will be performed to check for side effects. Your study doctor will help you manage any side effects that you experience. This may be a temporary stop and then restart study treatment when the side effects have improved, or even stop treatment altogether. This will be carefully managed by your study doctor in response to the side effect/s themselves, and also how your body responds to any steps taken to lessen the symptoms e.g., medicine/s. If you experience any side effects, or changes to your general health, it is important that you report them to the study doctor or research staff immediately.

The main possible disadvantage is if reduced frequency treatment is worse for you than standard 6 weekly treatment. To make sure you are not exposed to an unnecessary risk, we will carefully monitor patient outcomes during the course of the study. If there is an indication that less frequent therapy is harmful, we will return you to standard of care treatment.

CT scan

If you have CT scans, a contrast dye will be injected into a vein before the scan is performed. This may result in a slight burning at the injection site, a metallic taste in your mouth, a sensation of wanting to pass urine, or hot flushes. Very rarely, an allergic reaction to the contrast dye may occur. Such reactions can involve itching, a rash or, in severe cases, difficulty in breathing and lowering of blood pressure. You should let your study doctor know if you had any previous allergic reaction to imaging contrast dyes.

These scans would be the same as you would get as part of routine care. These procedures use ionising radiation to form images of your body and provide your doctor with other clinical information. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. In patients with your current clinical condition, the chance of this happening to you is extremely small.

General

You should be aware that certain insurance cover, such as medical or travel insurance may be affected by participation in a clinical study. Please contact your insurance company to see if this applies to you.

12. Pregnancy, contraception and breastfeeding

The study treatment may cause harm to an unborn child and may also affect a mother's milk. Therefore, if you would like to participate in this study and are a woman of childbearing potential, you must:

- tell your study doctor immediately if you become pregnant during this study, or within 4 months of stopping study treatment. Your study doctor will advise you of the possible risks to your unborn child and discuss options for managing the pregnancy with you. The study drug will be stopped immediately and the pregnancy followed until conclusion if you give consent for this;
- use (if you are sexually active with a male partner who has not been sterilised), one highly effective method of birth control and one additional effective barrier method of contraception at the same time. This should be done from the time of signing the informed consent form, throughout the entire study drug treatment period, and for 4 months following the last dose of study treatment. Please discuss effective methods of contraception with your study doctor or nurse.

13. What are the possible benefits of taking part?

The main benefits are that if you are allocated to the reduced frequency arm, you will have fewer hospital attendances, potentially fewer side effects and we hope these will translate into a better quality of life. In general, however, you may not experience any direct health benefits during or following completion of the study. The results of this study will help understand the effectiveness, safety and tolerability of using pembrolizumab in reduced frequencies, and may lead to better management of people with advanced NSCLC in the future.

14. What are the alternatives for treatment?

If you decide not to take part in this study, your doctor will discuss appropriate alternative treatment with you.

15. What if there is a problem?

Your study doctor will be there to answer any questions you might have regarding the cancer, its treatment and your participation in the study. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, then there will be several options available to you. Full details are included in Part 2 of this information sheet.

16. Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. Full details are included in Part 2 of this information sheet

If the information in Part 1 has interested you and you are considering taking part in the study, please read the additional information in Part 2 before making your decision.

Part 2

1. What if new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, your study doctor will tell you and discuss whether you should continue in the study. In addition, we may find other new information about you from your blood and tissue samples or any scans performed during the treatment. If this happens, you will be informed by your study doctor and discuss your options, including whether you 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 your doctor may ask you to sign an updated consent form.

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

You must tell your doctor immediately if you no longer wish to take part in the study. Your doctor will discuss options for further treatment with you.

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 not collect any new information about you, but we will keep the information about you that we have already obtained including any research samples.

To safeguard your rights, we will use the minimum personally-identifiable information possible.

Your study doctor can also stop study treatment at any time e.g., your condition becomes worse, or another condition develops that may mean you are unable to carry on receiving study treatment. If you were to lose the capacity to consent to study procedures during the study, your oncologist, with your family, will decide if it's in your best interest to continue with study treatment. If you do not continue with treatment, you will remain in the study follow-up period to collect data until 18 months from when you started treatment.

3. What if there is a problem?

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 London 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 Imperial clinical trials team by phoning 020 7594 2180. The normal National Health Service mechanisms are also available to you. Details can be obtained from your study doctor or nurse. If you are still not satisfied with the response, you may contact the Imperial College, Research Governance and Integrity Team.

4. Will my taking part in this study be kept confidential?

Imperial College London is the sponsor for this study, based in the United Kingdom, 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. Imperial College 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.

We will need to use information from your medical records for this research project. This information will include your month and year of birth. People will use this information to do the research or to check your records to make sure that the research is being done properly. If you decide to take part in the study, you give individuals from the Imperial College study team and its representatives, the National Institute for Health Research (NIHR), contracted companies conducting review of radiological imaging, regulatory authorities, or the NHS Trust/Health Board where it is relevant to your taking part in this research permission to use, analyse, and evaluate any information gathered about you in this study and share it with others as described in the subsection below.

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 unique code number (study ID) instead.

Archival tissue and copies of CT scans for independent review will be labelled with your study ID, and the month and year of your birth, and not with any personal identifiers such as your name.

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.

LEGAL BASIS

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.

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

INTERNATIONAL TRANSFERS

There may be a requirement to transfer information to countries outside the United Kingdom (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 outside of the United Kingdom, Imperial College London will enter into a data sharing agreement with the recipient organisation to safeguard how your personal data is processed. You will not be able to be identified when sharing this data but it may include demographic information such as the month and year of your birth as well as your study ID.

SHARING YOUR INFORMATION WITH OTHERS

For the purposes referred to in this privacy notice and relying on the bases for processing as set out above, we will share your personal data with certain third parties, including the Medical Research

Council Clinical Trials Unit and University College London who will perform the analysis of the study data.

Other College employees, 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). Our third party service providers are required to enter into data processing agreements with us. We only permit them to process your personal data for specified purposes and in accordance with our policies.

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.

- If you choose to stop taking part in the study, we would like to continue collecting information about your health from your hospital. If you do not want this to happen, tell us and we will stop.
- 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 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 REFINE-Lung@imperial.ac.uk, or
- by ringing us on 020 7594 2180.

COMPLAINT

If you wish to raise a complaint on how we have handled your personal data, 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 are not satisfied 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). The ICO does recommend that you seek to resolve matters with the data controller (us) first before involving the regulator.

5. Involvement of the General Practitioner / family doctor (GP)

With your permission, indicated on the consent form, we will inform your GP about your involvement in this study.

6. Public Involvement

To help the research team in the running of this study, we have a panel made up of 5 members advising us: three people are lung cancer patients, another has breast and ovarian cancer and one person was a carer for a relative who had lung cancer.

When the public gets involved in research, they work alongside researchers to help shape what research gets done, how it's carried out, and how the results are shared and used in practice. Prior

to beginning this research, we discussed the design with several potential patients at conferences. We asked questions about the procedures and tests that we want to carry out, to ensure these were acceptable for patients and collected at appropriate times throughout the study. Our panel has also reviewed all the documents that will be given to you. This was to ensure that the documents are easy to understand and contain the information patients would like to know before signing up. When the study is finished, we will ask our panel to help ensure we share the results using clear language and in patient friendly ways, such as letters, posters, podcasts and videos and that we make them available in places where patients will find them.

Our panel is not the same as taking part in research to test the new frequency of treatment. It's about being a member of the research team that works together to design and run the study.

7. What will happen to any samples that I give?

Routine Samples

Routine blood samples will be taken and tested as part of standard practice and destroyed immediately after testing.

Stored Tissue and Research Blood Samples

Your tissue samples will be looked at for quality control purposes in order to confirm the presence of NSCLC. They will also be kept for future analysis at the Experimental Cancer Medicine laboratory at Imperial College London and Imperial College Healthcare Tissue Bank.

If you consent, additional blood samples will be taken throughout your treatment and kept for future analysis, along with your tissue, at the Experimental Cancer Medicine laboratory at Imperial College London.

If you withdraw your consent after your tissue or blood sample has been sent, the study doctor will ensure that your blood sample and any extracted genetic material is destroyed. Your tissue will be returned to your hospital. However, if genetic research has already been performed the study sponsor is not obliged to destroy results of this research. In this case only the blood sample and extracted genetic material will be destroyed and tissue returned.

8. What rights do I have to see the results of the biomarker research?

These parts of the study are for exploratory research purposes only. You will not be provided with your test results, nor will any results be made available to any insurance company, your employer, your family, your study doctor, your GP, or any other doctor who treats you now or in the future.

Any information derived directly or indirectly from this research, as well as any patents, diagnostic tests, drugs, or biological products developed directly or indirectly as a result of this research, are the sole property of the study sponsor (and its successors and licensees) and may be used for commercial purposes by the collaborators. You will have no right to this property or to any share of the profits that may be earned directly or indirectly as a result of this research. However, in signing the consent form and offering samples for research, you do not give up any rights that you would otherwise have as a participant in research.

9. What will happen to the results of the research study?

Your cancer specialists, the study team and the sponsor Imperial College London, plan to publish the results of this study in a scientific journal and/or present them at national and/or international meetings, so that the information will be widely available to all. Lay summaries will be published on websites as appropriate. You will not be personally identified in any publications or reports.

10. Who is organising and funding the research?

Imperial College London is the legal sponsor of this study and is organising the study through the Imperial Clinical Trials Unit – Cancer (ICTU-Ca). Funding is being provided by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme.

The sponsor of this study will pay your hospital for including you in this study, but your doctor will not receive any personal financial payment if you take part.

11. Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by North West - Haydock Research Ethics Committee.

12. Further information and contact details

If you have any questions or concerns about this study, including study-related injury or study treatment queries, you can talk to *<insert name of doctor and tel.no>* or the study staff *<insert name and tel. no.>*.

Cancer Research UK provides general information about cancer and its treatment on their website www.cancerhelp.org.uk and a confidential information service by specialist nurses on Tel: 0808 800 4040. Macmillan Cancer Support (www.macmillan.org.uk; Tel: 020 7840 7840 also provides support and counselling to help people living with cancer.

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

If you decide you would like to take part, you will be given a copy of this information sheet to keep together with a copy of your signed consent form.