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PRIMROSE CSF Study

A prospective study of the genomic landscape of central nervous system disease secondary to breast cancer utilising cell-free DNA derived from cerebrospinal fluid (CSF).

PRIMROSE

PRIMROSE CSF Study

- You have been invited to take part in The PRIMROSE CSF Study. Before you decide, it is important that you understand what the study is about, why the research is being done and what it will involve for you.
- This information sheet will provide you with these details and help answer some of the questions you may have. Please take time to read the following information carefully.
- We understand that this is a worrying time for patients. You may feel that you have been given lots of information within a short space of time. If there is anything you do not understand, please discuss it with your doctor or specialist nurse involved in your care.
- If you wish you can also discuss it with friends, relatives and/or get independent advice via your local Patient Advice and Liaison Service (PALS) or equivalent.
- The study aims to run for three years and we aim to recruit between 67 to 87 patients depending on sample collection.
- Taking part is voluntary. If you do not want to take part, then you do not need to give a reason.

How to contact the PRIMROSE CSF research team if you have any questions.

PRIMROSE CSF study lead: Professor Carlo Palmieri

<<Add site principle investigator name, site RN name and site contact details for PI/RN below:>>

Principle Investigator: ; Research Nurse: name;

Trust/site address Line 1
Trust/site address Line 2
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Post code

Email: xxxx@xxxx.xx.xx
Telephone: xxxx xxx xxxx

This information sheet is split in two parts:

Part 1 – tells you the purpose of the study and what will happen if you take part.

Part 2 – gives you more detailed information about the conduct of the study

PART 1: Purpose of the study and what will happen if you take part

What is the PRIMROSE CSF Study and Why are we doing it?

The PRIMROSE CSF Study aims to study **cerebrospinal fluid (CSF)** in patients with breast cancer that has spread to the brain (brain metastasis) or the lining surrounding the brain (leptomeningeal disease).

What is CerebroSpinal Fluid (CSF)?

This is the liquid that surrounds and protects the brain and spinal cord. CSF is constantly produced by our body and small amounts removed during extraction procedures are rapidly replaced.

What is a metastasis?

This is when cancer cells break off from the main tumour (in this case – in the breast), enters the blood stream and spreads to another part of the body such as the brain (so called brain metastasis or the thin lining over the brain (so called leptomeningeal disease).

Research into understanding more about breast cancer that has spread to the brain or lining of the brain is limited. This is because it is difficult to get brain tissue containing cancer cells for research. This is normally only obtained if tumours are removed which does not happen in all patients. Research shows that more and more patients with breast cancer are developing disease that spreads to the brain or the lining of the brain as treatments for breast cancer improves. The PRIMROSE CSF Study aims to improve our understanding of breast cancers that spread to the brain/brain lining by collecting and studying the fluid that circulates around the brain and comparing the sample to other cancer samples and blood samples.

Cancer cells that have spread to the brain or the lining of the brain shed their genetic material into the fluid that surrounds the brain. Therefore, by collecting the fluid around the brain we will be able to purify this genetic material that is floating in the fluid from the breast cancer cells. By doing this we will be able to examine the genetic make-up of the breast cancer cells affecting the brain/lining of the brain without having to operate. We will compare the differences between the original cancer and the new cancers in the brain.

This research will help us understand why some breast cancers spread to the brain as well as helping to develop new treatments to treat breast cancers that have spread to the brain or lining of the brain.

Why have I been invited to take part?

You have been invited to participate in this study because you have been diagnosed with brain metastases secondary to breast cancer or have breast cancer cells that have involved the lining surrounding the brain.

Do I have to take part?

No, taking part is voluntary. It is entirely up to you to decide whether you want to take part. If you decide not to take part, then you will still receive the usual treatment

your hospital offers. Your clinical care team, doctor or nurse can provide you with more information on this.

If you decide to take part you can also choose to stop at any time without giving a reason. The decision you make on whether to take part or not will not affect the standard of care you receive now or in the future.

What will I have to do if I agree to take part?

If you agree to take part, you will be asked to sign a consent form confirming you are happy to take part in the study. After we check there is no reason why you cannot have a sample taken, we will ask for consent to the following:

1) **Collection of 10ml – 15ml CSF sample (CSF extraction)**
2) **Collection of 20ml Blood sample**
3) **Collection of Tissue**

Read on for further details on each aspect that we are asking consent for.

Collection of CSF sample: This will occur via one of two procedures - lumbar puncture or aspiration from Ommaya Reservoir (device inserted in your head).

A lumbar puncture will be undertaken to collect the cerebrospinal or fluid that is around the brain (between 10ml to 15ml will be taken). If the team are already planning to undertake a lumbar puncture, then this additional sample will be taken at the same time. If you are having surgery to the brain, the sample will be taken at time of the anaesthetic. If you have a device called an Ommaya Reservoir, then a lumbar puncture would not be carried out and the fluid (10ml to 15ml) will be collected from the Ommaya Reservoir.

If the procedure is an additional one that you would not have normally, the team will inform you. You will continue to receive the routine treatment for patients with breast cancer and brain metastases.

Collection of Blood sample: This will occur immediately before the CSF extraction procedure. A 20ml blood sample will be collected immediately before lumbar puncture or Ommaya Reservoir (whichever procedure you have).

Collection of Tissue: This will occur almost immediately after you consent to the CSF Study. We will organise for the collection of breast cancer material which has been collected and stored or which will be collected, as part of your routine clinical care. Specifically, this includes (all of these may not apply to you):

a. Primary breast cancer tissue
b. Tissue removed by biopsy or surgery from other organs including the brain

Optional CSF sample: Roughly three months after the initial collection of CSF sample, you may be asked to undergo a further CSF extraction as part of your routine care. We would also like to obtain a blood sample for the study, should this happen. This is only applicable to patients who have given

consent to the collection of a second CSF sample regardless of whether your disease has progressed or remains stable.

What will happen before CSF extraction procedure?

A doctor will explain how the lumbar puncture or collection of fluid from the Ommaya Reservoir is performed and you will be given the opportunity to ask questions. Before giving your consent to proceed, the doctor will explain the routine of the procedure, inform you of any possible complications and answer any questions you may have. You can refuse to have the procedure done at any point and for any reason.

There are no special preparations before the procedure. You can take all your usual medication. It is sensible to have a light breakfast and is advisable to drink more fluids than usual in the 12 hours before the procedure to reduce the risk of headache. After the procedure you are also advised to drink more than usual to reduce the risk of headache.

Immediately before the procedure, we will also take 20ml of your blood sample.

What will happen during the CSF extraction procedure?

CSF can be obtained by any of two procedures – Lumbar Puncture or Ommaya Reservoir. They are described below

Lumbar Puncture

Lumbar puncture is performed in your lower back, in the lumbar region. During the procedure, a needle is inserted between two lumbar bones (vertebrae) to remove a sample of cerebrospinal fluid.

The following steps will occur:

- The doctor will usually position you on the left side with your knees curled up to your stomach, but this can be done sitting up.
- The skin of your lower back will be cleaned with an antiseptic – please state if you are allergic to chlorhexidine. The antiseptic may feel wet and cold. A local anaesthetic is then used to numb the skin.
- You may feel a stinging sensation before the local anaesthetic begins to work. You may then feel a pushing sensation as the needle is inserted, and sometimes a brief, sharp pain when the needle is moved forward. This pain should stop in a few seconds.
- Overall, discomfort is minimal to moderate, but it is important to lie still. Once the needle is correctly positioned, the doctor will measure the pressure (if required) and collect the samples.
- The entire procedure usually takes approximately 20 minutes.

Ommaya Reservoir Tap

If you have an Ommaya reservoir in place already the CSF will be collected by inserting a needle into the soft plastic dome. You may have previously had samples collected in this way. This entire process usually takes 20 minutes.

What will happen after the procedure?

Following the lumbar puncture, you may sit up and have something to drink. You should take things easy for a couple of days and drink more fluids than usual for 24- 48 hours. You are usually free to leave the ward after a few hours when ward staff have assessed you.

Following extraction from the Ommaya reservoir, you are usually free to leave the ward immediately after staff have assessed you.

Roughly a month after your CSF extraction, you will be asked to fill in a questionnaire that will record your experience during and after CSF extraction. A member of your clinical care team will contact you via telephone to record your responses to the questionnaire. You will not be asked to come back into clinic specially to fill in the questionnaire. If you have a routine clinical visit, the questionnaire will be done then.

If your cancer worsens or if your cancer is stable over a prolonged period of time, you may be asked to undergo a second lumbar puncture. This is not compulsory.

What are the risks?

All procedures will be carried out by trained medical professionals.

Diagnostic/Routine Tissue Collection - This will only occur as part of procedures that are medically advised for you and thus there are no additional risks introduced as part of the PRIMROSE CSF study.

Lumbar Puncture - There may be risk of the following after the procedure:

- Back Pain at the time of injection (Bleeding, swelling and bruising may occur)
- Post-procedure headache (can be associated with nausea and vomiting)
- Nerve root irritation (tingling or pain down the back of your legs)
- There is a rare risk of increased pressure within the skull (intracranial), due to a brain tumour or other space-occupying lesion, which can lead to compression of the brainstem after a sample of cerebrospinal fluid is removed. Prior to doing a lumbar puncture, your clinician will make a decision using all available information to ensure risks are minimised. Should the clinician deem the risk too high, a lumbar puncture for this study will not be conducted. Risk will be assessed prior to a lumbar puncture being conducted, even if you have given consent.

Ommaya Reservoir – There is a risk of infections, but these are rare. Assessments to ensure your safety will always occur before CSF extraction. If you are deemed to be at high risk of infection, the CSF extraction procedure will not occur.

Once you have healed from the procedure, you can return to all of your normal activities. Ommaya reservoirs do not require any care or maintenance.

What are the benefits?

Research in brain metastases in breast cancer is rare and limited. If we are able to collect enough samples, we will be able to increase the resources for research. We will be able analyse the collected CSF samples to understand more about the diagnosis. This in turn will help with identifying and developing new therapies or treatments for breast cancer patients with brain metastases. It is

likely that patients will not derive any direct benefit from this study. However, it is hoped that this study will provide evidence which will enable the development of future studies and treatments for patients with CNS disease secondary to breast cancer.

What happens if I change my mind?

If you decide to take part in our study, you can also choose to stop at any time without giving a reason. The decision you make on whether to take part or not will not affect the standard of care you receive now or in the future. You can contact your care team to inform us of your decision to withdraw (you do not have to give a reason for withdrawal). Information on how we will handle your information in the event of you withdrawing is detailed in Part 2 of this Information Sheet.

Will my participation be kept confidential?

Yes. All the confidential information about your participation in this study will be kept entirely confidential. Detailed information on this is given in Part 2.

Will I have additional appointments?

This study does require you to have out-of-routine CSF extraction procedure. This may mean additional appointments before the procedure.

What if there is a problem?

Any complaints about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Detailed information is given in Part 2 of this information sheet.

PART 2: Details of the PRIMROSE Study

Who is running the study?

The University of Liverpool is the Sponsor of this study, which means it is responsible for managing it. They are based in the United Kingdom. They have asked that the day to day running of the study is carried out by a team (within the university) based at the Liverpool Clinical Trials Centre (LCTC, part of the University of Liverpool) and any samples collected to be stored at the Good Clinical Practice (GCP) Laboratories (part of the University of Liverpool).

The study has been reviewed by the Health Research Authority and the National Research Ethics Service Committee to make sure that the study is scientifically and ethically acceptable. Patient representatives have also reviewed the study.

What are the aims of the study?

Here is a summary of our aims, which we hope will aid future development of new treatment strategies.

- We want to understand more about the underlying challenges in extracting CSF specifically from patients with brain metastases secondary to breast cancer
- We would like to identify any abnormalities in the CSF on a molecular and genetic level
- We would like to identify molecular differences in CSF and Blood DNA.
- We would like to identify molecular indicators for cancer within CSF.

Is the study funded?

This study is funded by North West Cancer Research, Daiichi Sankyo GmBH Europe, and Make Seconds Count. (Your doctor will not receive any payment for including you in this study).

How will my data or information be collected and handled?

The University of Liverpool is the Data Controller for this study and will need to use information from you and/or your medical records for some aspects of this research project.

This information will include demographic (month and year of birth, broad ethnic group, and sex) disease history and characteristics, prior (top line) cancer therapy, current anti-cancer treatment and concomitant medications, progression details, complications related to lumbar puncture. People will use this information to do the research or to check your records to make sure that the research is being done properly. Trained clinical staff will collect information from you and/or your medical records for this research study. After data collection it will be transferred to the Cancer Research Centre Laboratories (part of University of Leicester) for analysis.

Individuals from the University of Liverpool, the LCTC and regulatory organisations may look at your medical and research records to check the accuracy of the research study. 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. Data will be sent from

your hospital to the LCTC. We will notify your GP that you will be taking part in the study for their information.

We will keep all information about you safe and secure. Once we have finished the study, we will keep the data for 10 years, 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.

What are my choices about how my 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 and may continue to collect limited information for our research. For example, if there are negative experiences after a CSF collection procedure or in specific ways for the research to be reliable. This means that we may not be able to let you see or change the data we hold about you. All data processing will occur in accordance with UK data protection legislation requirements.

If you choose to stop taking part in the study, and you do not want us to use information or samples already collected from you for research or you do not want us to collect limited information even after you withdraw from the study, please tell us and we will stop.

If you wish to withdraw, the value of existing samples will be explained to you, and your permission will be sought to continue retaining and using these samples. Generally, samples will be retained unless you specifically request for them not to be in which case no further samples or data will be collected. Your permission will be sought to use all samples collected thus far in the case of withdrawal. You have the right to request that any samples which have not yet already been used in research to be disposed of. If you explicitly state that this is your wish, then the samples will be destroyed. In some cases however, it will be impossible to destroy the samples without affecting other samples as they will have been irreversibly linked to others. In these cases, the sample itself will not be destroyed; however, information linking the sample to you will be destroyed, deleted or censored as appropriate to eliminate the link and make the sample unidentifiable.

Information sharing for other research

When you agree to take part in a research study, the information about your health and care may be beneficial to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research, or equivalent standards**.**

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.

Will my CSF sample and information be kept confidential?

Yes, your samples and information will be kept confidential at all times. Your NHS number will be used to locate your samples. Your samples and any related

information (collected for research) will also be assigned a unique pseudonymised Study ID. Only specified members of the programme's team will be able to link the codes to the individual patients. This is solely for the purpose of ensuring that we have your permission to allow us to collect and use your samples. When samples are used in research, your name will not be disclosed and only information for which the project has specific ethical approval will be released. Data will be sent from your hospital to the LCTC.

Once we have finished the study, we will keep the data for 10 years, 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. We will notify your GP that you will be taking part in the study for their information. We will keep all information about you safe and secure.

The University of Liverpool will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Liverpool will keep identifiable information about you for 10 years after the study has finished or until your research sample is finished, whichever is longest. 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. Regulatory organisations may look at your medical and research records to check the accuracy of the research study. To safeguard your rights, we will use the minimum of personally-identifiable data possible.

How will my samples be collected?

For your diagnostic/routine tissue collection, once you give consent, clinical care staff will be contacting the relevant members to locate your samples and prepare them to be sent from your hospital to the LCTC.

For your CSF sample collection, once you give consent, your blood and CSF samples will be collected during the lumbar puncture procedure/Ommaya Reservoir procedure.

How will my samples be handled?

All samples collected about you will be kept strictly confidential.

If you decide to give your consent to the study, you will be asked to fill the consent form below. We will then assess your eligibility to be enrolled and, if eligible, enrol you onto the study.

A medical professional trained in lumbar puncture/Ommaya Reservoir will prepare you for the procedure (after you give your consent) and carry out the procedure on you. The sample will be sent to the GCP Laboratories for storage for two years until start of research.

What will happen to the samples I give?

Samples will be sent to the GCP Laboratory at The University of Liverpool for storage until we have collected enough samples to begin research/analysis. After collecting sufficient samples, all samples will be **coded** and sent to Cancer Research Centre Laboratories (part of the University of Leicester) for analysis. The researchers carrying out tests on the samples will not be given

information they do not need to carry out the tests and analyse the results.

'Coded' is not the same as anonymous. It will be possible to use the codes to identify that a result is from your sample. However, we do not currently plan to do this. We will maintain this information so that we can properly manage the samples. For instance, sometimes we may need to update our record of your clinical details to help us interpret the results of tests.

The samples will be kept in a secure place until we need them; nobody outside of the study will have access to **any** confidential information that you give to us. Confidential details will be kept locally at your hospital by your care team. Any confidential details sent from your hospital to LCTC (e.g. your name) will be kept in a secure location and will not be made available to collaborators, in this case the University of Leicester (Cancer Research Centre Laboratories).

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with one of your research team who will do their best to answer your questions.

If you remain unhappy and wish to complain formally, you can do this by contacting local NHS Patient Advice and Liaison Service (PALS) or equivalent. Members of your local hospital team should be able to provide this information to you.

Every care will be taken in the course of this clinical study. However, in the unlikely event that you are harmed by taking part in this research project of the study Sponsor – the University of Liverpool - compensation may be available and you may have to pay your related legal costs. Your hospital where you receive your treatment has a duty of care to you whether or not you agree to participate in the study and the study Sponsor accepts no liability for negligence on the part of your hospital's employees. However, if you are harmed and this is due to someone's negligence at the hospital, then you may have grounds for a legal action for compensation against the NHS Trust where you are being treated but you may have to pay for your legal costs. The normal National Health Service complaints procedures should be available to you. You have the right to lodge a complaint with the Information Commissioner's Office (ICO).

What happens when the study stops?

It is intended that the results of the study will be presented at patient forums, conferences and published in medical journals so that we can explain to the medical community what our research results have shown. **Confidentiality will be ensured at all times and you will not be identified in any publication.**

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 may be used for commercial purposes. You 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 this form and donating tissue and/or blood samples for this research, you do not give up any rights that you would otherwise have as a participant in research.

What if new information becomes available?

Sometimes during the course of a research project, important new information becomes available about the cancer that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want to or should continue in the study. If you decide to withdraw your 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.

On receiving new information your doctor might consider it to be in your best interests to withdraw you from the 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.

Where can I find out more about how my information is used?

Thank you for taking the time to read and consider this information sheet. Should you decide to take part in the study, you will be given a copy of the information sheet and a signed consent form to keep.

You can find out more about how we use your information: at www.hrs.nhs.uk/information-about-patients

- At the LCTC website: http://lctc.org.uk/privacy
- in the Health Research Authority leaflet available from www.hra.nhs.uk/patientdataandresearch
- by contacting the University of Liverpool Data Protection Officer on LegalServices@liverpool.ac.uk
- by asking one of the clinical research team

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The PRIMROSE CSF Study

<Trust/Site address 1>
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<Trust/Site address 3>
<postcode>
Tel: <telephone number>

FOR SITE USE ONLY:

Site Name:			
Patient Study ID:			
Participant Initials:		Participant DOB:	/ /

Adult Consent Form

To be completed by the participant:

Once you have read and understood each statement please enter your initials in each box.	Initial
1. I have read and understood the information sheet for this study. I have had the opportunity to ask questions and have had these answered satisfactorily.	
2. I understand that participation is voluntary and that I am free to withdraw from the study at any time, without giving a reason, and without my care or legal rights being affected. However, the study team may need to collect some limited information for safety reasons.	
3. I give permission for a copy of this fully completed consent form to be sent to the LCTC (where it will be kept in a secure location) to allow confirmation that my consent was given.	
4. I understand that relevant sections of my medical notes and any data collected during the study may be looked at by authorised individuals from the central study team and representatives of the Sponsor, regulatory authorities, the local NHS Trust and international research collaborators. I give permission for these individuals to have access to my records and data.	
5. I agree to my GP being informed of my participation in the study.	
6. I agree for the relevant data to be collected from my medical records for the purposes of this study.	
7. I understand that my data will be kept by the University of Liverpool, GCP Laboratories or Cancer Research Centre at the University of Leicester research site in a confidential manner for 10 years from the end of the study.	
8. I consent to samples of between 10ml-15ml of cerebrospinal fluid, 20ml sample of blood (pre-lumbar puncture/Ommaya Reservoir aspiration procedure) and diagnostic/routinely collected tissue (breast cancer, breast cancer spread to other organs including the brain and non-brain tissue if available) to be taken and used for this study.	
9. I consent to samples being analysed for genetic analysis (analysis of the DNA) within the samples.	

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The PRIMROSE CSF Study

<Trust/Site address 1>
<Trust/Site address 2>
<Trust/Site address 3>
<postcode>
Tel: <telephone number>

FOR SITE USE ONLY:

Site Name:			
Patient Study ID:			
Participant Initials:		Participant DOB:	/ /

Adult Consent Form

10. I agree for samples collected for future research to be transferred along with a copy of this Consent Form to GCP Laboratories for future ethically approved research for any intended special use (genetic, xenotransplantation, commercial, international). ☐

11. I agree to allow information or results arising from this study to be used in future healthcare and/or medical research providing my confidentiality is maintained. ☐

12. I agree to take part in the above study. ☐

The statement below is optional (you can still take part in the study even if you do not wish to agree to the below):

13. If your cancer worsens or if your cancer is stable over a prolonged period of time, you may be asked to undergo a second lumbar puncture. I consent to samples of between 10ml-15ml of cerebrospinal fluid, 20ml sample of blood (pre-lumbar puncture/Ommaya Reservoir aspiration procedure) and diagnostic/routinely collected tissue (breast cancer, breast cancer spread to other organs including the brain and non-brain tissue if available) to be taken and used for this study. ☐

14. I agree to be contacted by my hospital with the results of this study, when they become available. ☐

15. If you choose to stop taking part in the study, we may need to continue collecting limited information for example, if we need to manage your records in specific ways for the research to be reliable. I agree for the limited information about my health to be collected after I stop taking part in the study for the reason mentioned. ☐

16. I agree to allow the usage of already collected tissue or samples for research even after I stop taking part in the study. ☐

To be completed by the participant:

Your full name (please print):			
Your signature:		Date:	

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The PRIMROSE CSF Study

<Trust/Site address 1>
<Trust/Site address 2>
<Trust/Site address 3>
<postcode>
Tel: <telephone number>

FOR SITE USE ONLY:			
Site Name:			
Patient Study ID:			
Participant Initials:		Participant DOB:	/ /

Adult Consent Form

To be completed by the Researcher (after participant has completed the form):

Researcher full name (please print):			
Researcher signature:		Date:	

Please file the original wet-ink copy in the PRIMROSE Investigator Site File, and make three copies: one for the participant, one for the medical notes and one to be sent to the LCTC.