PARTICIPANT INFORMATION SHEET

1. Study Information
Protocol Title:

Optimising Hormonal Therapy In Hormone Responsive Breast Cancer

Principal Investigator & Contact Details: Dr Tan Ern Yu (6357 7807); TTSH 24h main line (6256 6011)

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2. Purpose of the Research Study
You are invited to participate in a research study. It is important to us that you first take time to read through and understand the information provided in this sheet. Nevertheless, before you take part in this research study, the study will be explained to you and you will be given the chance to ask questions. After you are properly satisfied that you understand this study, and should you wish to take part in this study, you must sign this informed consent form. You will be given a copy of this consent form to take home with you.

You are invited because you require hormonal therapy for breast cancer.

This study aims to determine whether the choice of hormonal agent (tamoxifen or aromatase inhibitor, AI) should be determined by variations in the CYP2D6 gene. The CYP2D6 gene determines how effective tamoxifen is expected to be. Certain variations of this gene make tamoxifen less effective; this study aims to determine whether women with these variations should be given AI instead of tamoxifen.

This study will recruit a total of 100 patients from Tan Tock Seng Hospital over a period of approximately 12 months. This study will last for a period of 24 months.

Study Procedure and Visit Schedule

If you agree to take part in this study, 1 saliva sample and 2 tubes of blood (about 12ml of blood) will be taken from you and tested for variants of the CYP2D6 gene, as well as serum estradiol levels. The CYP2D6 gene determines how well tamoxifen is expected to work for you. If you are found to have a gene variant that predicts a poor response to tamoxifen, you will be recommended an AI (either anastrozole or letrozole). Should you opt to receive tamoxifen instead, we will continue to keep you on the study since this allows us to find out whether such women truly have a higher risk of disease relapse. This remains controversial; some studies have suggested that CYP2D6 variants is related to disease relapse, while other studies have found no relation. If you are found to have a gene variant that predicts a good response to tamoxifen, you will be offered a choice between AI (either anastrozole or letrozole) and tamoxifen. Both AI and tamoxifen are hormonal agents that are currently used in routine clinical practice. Currently, we allow patients to choose between these agents after discussing the benefits and side effects. Tamoxifen and AIs work by reducing serum estradiol levels. Measuring these levels will help us determine how changes in these levels affect your condition.

In this study, you will receive either AI or tamoxifen for the standard period of 5 years, unless advised otherwise by your doctor. The treatment will last beyond the duration of this study.

Schedule of visits:

i. Screening visit (Visit 1): a detailed medical history and physical examination are done to make sure that you are suitable for this study prior to informed consent. Blood and saliva will be taken at this visit after you have been counseled regarding the procedure.

ii. Visit 2: the blood test results will be explained. Your doctor will also discuss the benefits and side effects of AI and tamoxifen. You will be started on the allocated medication at

this visit, or at a later visit if you have not completed your other post-surgery treatments.

iii. You will be reviewed every 3 months in the first year, and every 4 months in the second. At each visit, a detailed clinical history and physical examination will be carried out to monitor your health status and the effects of the hormonal therapy. These visits coincide with the regular follow-up for all breast cancer patients in our institution.

iv. Blood will be taken to measure estradiol levels before you start the medication and 3 months later. You will be scheduled for mammography every year (starting 6 months after the completion of radiotherapy treatment if you are receiving it, or 1 year after the mammography done prior to surgery).

v. If you are taking AI, you will be scheduled for a bone mineral density test within the first 3 months of starting treatment, and every subsequent year thereafter.

vi. If you are taking tamoxifen, you will be scheduled for a gynaecology review within the first 3 months of starting treatment, and every subsequent year thereafter.

Additional investigations and procedures may be required depending on your response to treatment. The timing of the mammography and bone mineral density tests may differ depending on the results. You may be withdrawn from the study and the hormonal agent initially offered may be changed if your doctor feels it necessary.

At each visit, you must notify your doctor of any other drugs you may be taking, including any complementary treatments. You must also notify your doctor if you experience new changes in your health or condition. You must also notify your doctor if you have sought treatment elsewhere during this study period.

3. Your Responsibilities in This Study

If you agree to participate in this study, you should follow the advice given to you by the study team.

a. You will be required to have saliva and blood taken for genotype testing and estradiol levels.

b. You will be required to adhere to the dosage and frequency of the medication prescribed.

c. You will be required to take the prescribed medication unless otherwise advised by your doctor.

c. You will be required to return for regular follow-up visits at our institute. If you miss a visit, you must contact the study staff as soon as possible.

d. You will be required to adhere to routine follow-up investigations which include mammography, bone mineral density tests (for those on AI) and gynaecological assessment (for those on tamoxifen).

e. You must inform the study staff of any change in your health or condition immediately.

f. You will be asked to return for a mandatory follow-up clinic visit if you are prematurely discontinued from this study.

4. What Is Not Standard Care or Experimental in This Study

The collection of blood and testing for CYP2D6 gene variants and serum estradiol measurements. The standard therapy is to incorporate an AI in the absence of contraindications. The current standard treatment for patients only with tamoxifen is considered inferior treatment compared to treatment that incorporates at least some duration of AIs. While it is theoretically possible that extensive or ultra-fast CYP2D6 metabolizers may derive equivalent benefit from tamoxifen (compared to AIs), this has not been shown in randomized trials.

5. Possible Risks and Side Effects

There are no potential risks from taking a saliva sample.

Possible side effects from blood taking include discomfort at the injection site during the procedure, bruising, swelling and very rarely an infection at the injection site.

Possible side effects of AI include muscle and bone aches, bone loss and fracture, cardiovascular events, hypertension, hot flushes, nausea and a sense of tiredness

Possible side effects of tamoxifen include blood clot formation in the legs (deep venous thrombosis), blood clot formation in the lungs (pulmonary embolism), stroke, vaginal bleeding, uterine cancer, hot flushes, nausea and a sense of tiredness.

These side effects of AI and tamoxifen will be discussed with you in detail.

6. Possible Benefits from Participating in the Study

You may not benefit from this study. It has been proposed that those with certain CYP2D6 gene variants may do less well if using tamoxifen. Disease relapse may be reduced if AIs are used instead. This, however, has not yet been proven in any large clinical study. There is a recently published report that CYP2D6 gene variants is not related to disease relapse. This study will help clarify the conflicting evidence.

7. Costs & Payments if Participating in the Study

There are no additional costs involved other than those related to your routine treatment. Blood taking, CYP2D6 gene and estradiol level analysis will not be charged to you. You will pay for the medication, follow-up visits, mammography, bone mineral density tests, gynaecological reviews and all other routine treatments.

8. Voluntary Participation

Your participation in this study is entirely voluntary. Your decision not to take part in this study will not affect your medical care or any benefits to which you are entitled. Your doctor will exclude you from this study if you are not suitable.

In the event of any new information becoming available that may be relevant to your willingness to continue in this study, you *(or your legally acceptable representative, if relevant*) will be informed in a timely manner by the Principal Investigator or his/her representative.

You are free to withdraw your consent and discontinue your participation at any time without prejudice to you or effect on your medical care. If you should decide to stop taking part in this study, please inform the Principal Investigator. If you stop taking part in this study, you will continue to receive the standard of care offered to all our patients. You will not have to stop the medication or switch to another medication should you stop taking part in this study, unless medically indicated.

9. Alternatives to participation

You may not wish to participate in this study. In which case, you will still be able to receive either tamoxifen or any of the AIs (anastrozole, letrozole or exemestane). You may, however, choose neither. There is no equivalent alternative to hormonal therapy. Without hormonal therapy, there is a higher chance of developing disease recurrence or a new breast cancer.

10. Compensation for Injury

Tan Tock Seng Hospital without legal commitment will compensate you for the injuries arising from your participation in the study without you having to prove that Tan Tock Seng Hospital is at fault. There are however conditions and limitations to the extent of compensation provided. You may wish to discuss this with your Principal Investigator. By signing this consent form, you will not waive any of your legal rights or release the parties involved in this study from liability for negligence. Payment for the management of the normally expected consequences of your treatment will not be provided by Tan Tock Seng Hospital.

11. Confidentiality of Study and Medical Records

Information collected for this study will be kept confidential. Only those directly involved in the study will have access to your records. The blood collected from you will be identified by a code. This code ensures that the blood samples cannot be linked back to any individual person. Only the principal investigator will maintain the database linking the codes to the person from whom the blood sample was taken from. All other people in the study will only have access to the codes.

Your records, to the extent of the applicable laws and regulations, will not be made publicly available. However, NHG Domain-Specific Review Board and Ministry of Health will be granted direct access to your original medical records to check study procedures and data, without making any of your information public. By signing the Informed Consent Form attached, you (*or your legally acceptable representative, if relevant*) are authorizing such access to your study and medical records.

The regulatory authorities (Health Sciences Authority) will be granted direct access to your medical records for verification of clinical trial procedures and/or data, to the extent permitted by applicable

laws and regulations. Data collected and entered into the Case Report Forms are the property of Tan Tock Seng Hospital. In the event of any publication regarding this study, your identity will remain confidential.

12. Use of these samples for future research

We expect there to be leftover material (genomic DNA) after the DNA analysis for this study is completed. As genomic DNA is a very valuable source of clinical material, we seek your consent to store these leftover samples for future research. Ethics approval will be obtained. These samples will be annonymised and cannot be linked back to you. You reserve the right to withdraw your consent for use of these samples if they are not annoymised. The samples will be stored for a maximum of 10 years and will be afterwards disposed of according to standard biohazard protocols. Only the study PI (Dr Tan Ern Yu) will have access to these samples. Future studies utilising these samples will include those to identify yet unknown gene variants that may predict a risk of developing breast cancer or that predict treatment response. The information from these studies will have no relevant impact on your management since these gene variants are yet unknown and your treatment will have been completed before their clinical relevance can be confirmed. No drug or biotechnology companies will have access to these samples.

13. Who To Contact if You Have Questions

If you have questions about this research study, or in case of any injuries or changes to your health and condition, you may contact the Principal Investigator, *(Dr Tan Ern Yu. Contact number 6357 7807. Contact email <ern_yu_tan@ttsh.com.sg>)*

The study has been reviewed by the NHG Domain Specific Review Board (the central ethics committee) for ethics approval. If you want an independent opinion of your rights as a research subject you may contact the NHG Domain Specific Review Board Secretariat at 6471-3266. If you have any complaints about this research study, you may contact the Principal Investigator or the NHG Domain Specific Review Board Secretariat.

Procedure	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	
	Screening	Baseline	Year 1	Year 1	Year 1	Year 1	Year 2	Year 2	Year 2	
Timing		Day 1 *2 to 3 weeks after Visit 1 if not for chemotherapy; 6 months after Visit 1 if for chemotherapy*	3 mth	6 mth	9 mth	12 mth	16 mth	20 mth	24 mth Study completion	Premature discontinuation
Informed consent	X									
Medical history	X	X	X	X	X	X	X	X	X	X
Clinical exam	X	X	X	X	X	X	X	X	X	X
Blood and saliva taken for CYP2D6 genotyping	X									
Blood taken for serum estradiol levels	X (baseline) *If not for chemotherapy*	X (baseline) *If to complete chemotherapy first*	X							
Allocation into treatment and control groups		X								
BMD*			X				X			
Gynaecological exam+			X				X			
Mammogram						X *If no RT received; otherwise 6 months after completion*			X	

						of RT				

Table of scheduled visits and procedures.
*For patients on AI, [+]For patients on tamoxifen

CONSENT FORM

Protocol Title:

Optimising Hormonal Therapy In Hormone Responsive Breast Cancer

Principal Investigator & Contact Details:

Dr Tan Ern Yu. Contact number 6357 7807. Contact email <ern_yu_tan@ttsh.com.sg>

I voluntarily consent to take part in this research study. I have fully discussed and understood the purpose and procedures of this study. This study has been explained to me in a language that I understand. I have been given enough time to ask any questions that I have about the study, and all my questions have been answered to my satisfaction.

☐ I agree to have my samples used in other research studies
☐ I do not agree to have my samples used in other research studies

_____	_____	_____
Name of Participant	Signature	Date

<Consent should be taken from the subject, unless consent from Legally Acceptable Representative has been specifically approved for the study by DSRB>

< Please include "Translator Information" if the participant / legally acceptable representative is unable to understand English and read any of the translated consent document or short form consent forms available>

Translator Information
The study has been explained to the participant / legally acceptable representative in *<language>*_____ by _____

< Please include "Witness Statement" if the participant / legally acceptable representative is unable to read any of the translated consent document or short form consent documents available. An impartial witness should be present during the entire informed consent discussion.>

Witness Statement
I, the undersigned, certify to the best of my knowledge that the participant signing this informed consent form had the study fully explained in a language understood by him / her and clearly understands the nature, risks and benefits of his / her participation in the study.

_____	_____	_____
Name of Witness	Signature	Date

Investigator Statement
I, the undersigned, certify that I explained the study to the participant and to the best of my knowledge the participant signing this informed consent form clearly understands the nature, risks and benefits of her participation in the study.

_____	_____	_____
Name of Investigator / Person administering consent	Signature	Date