This page is an integral part of the information text

Dear Ms, the information contained in the following information form is detailed and may be

VERY COMPLEX.

We ask you to accept participation in the study ONLY after you have carefully read this information form and had an EXHAUSTING MEETING with the investigating doctor, who will give you the

TIME REQUIRED

to fully understand what is being proposed to you

Title of study:

ExclUsive endocrine therapy Or radiation theraPy for women aged ≥70 years with luminal A-like early stage breast cancer (EUROPA): a randomised phase 3 trial.

Protocol code, version and date: Version 2.1, 15 March 2022

Study sponsor: Department of Experimental and Clinical Biomedical Sciences 'Mario Serio', University of Florence.

Principal Investigator:

Dr./Prof. _____

Trial Centre: (*insert Department, Hospital, Address, Tel, Fax*):

_____

Study coordinators:

Prof. Lorenzo Livi

SOD Radiotherapy AOUC

University of Florence

Prof. Philip M. P. Poortmans

Iridium Kankernetwerk; University of Antwerp, Faculty of Medicine and Health Sciences; Wilrijk-Antwerp, Belgium

Dear Madam,

In this Institute, a medical and scientific research project is being planned under the title **"ExclUsive endocrine therapy Or radiation theraPy for women aged ≥70 years with luminal A-like early stage breast cancer (EUROPA): a randomised phase 3 trial".**

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This research is multicentric, which means that several hospitals and care centres are taking part. In order to carry out this research we need the collaboration and availability of people who, like you, meet the appropriate scientific requirements. However, before you make the decision to accept or refuse to participate in the study, we ask you to read these pages carefully, taking as much time as you need, and to ask us for clarification if you do not understand or need further details. You can also ask your family or doctor for advice before making your decision if you wish.

What is the aim of the study?

The current standard of care for all patients with luminal-A breast cancer after conservative surgery is radiotherapy and endocrine therapy for at least 5 years. There is no unequivocal indication for postoperative treatment of patients over 70 years of age with a very low risk of early recurrence. This fragile patient population is in fact poorly represented in literature studies that have validated adjuvant therapeutic strategies. National and international guidelines vary widely, and depending on the oncological judgement both the omission of endocrine therapy and postoperative radiotherapy is considered after adequate multidisciplinary discussion and sharing with the patient. The primary goal to be achieved for these patients seems to be quality of life and toxicity profile as well as survival, but unfortunately the data available in the literature are very limited.

In patients aged ≥70 years undergoing conservative surgery, exclusive breast irradiation may be better in terms of preservation of quality of life when compared to endocrine therapy alone, with an equivalent local recurrence rate with the two treatment modalities. Therefore, this study aims to measure quality of life using the QLQ-C30 questionnaire and the QLQ-BR45 and ELD-14 forms in patients aged ≥70 years with early luminal A breast cancer undergoing conservative surgery and exclusive breast radiotherapy or exclusive endocrine therapy.

Participation in the study

Based on your previous examinations and clinical evaluation, you may meet the criteria for participation in this study. The study is a randomised, prospective, multicentre, quality of life monitoring study for patients with early stage luminal A breast cancer treated with breast radiotherapy or endocrine therapy after conservative surgery. All patients with these disease characteristics will be

randomised to receive exclusive breast radiotherapy or endocrine therapy for 5 years. In practice, 50% of patients will receive breast radiotherapy only, and the remaining 50% will receive endocrine therapy with an aromatase inhibitor (letrozole, anastrozole, exemestane) or tamoxifen only. Assignment to one of the two treatment groups will be random. The project will collect data on quality of life.

If you agree to take part in this study, you will have an initial visit to check that your condition meets the criteria. You will also be given questionnaires periodically during the study to assess the presence of any symptoms and side effects and your quality of life, in order to collect data on these aspects.

Participation in the study does not involve any additional costs for you, all of which will be borne by this structure. If you agree to take part in this study, you will undertake to inform your general practitioner and any other doctors with whom you are treated of your enrolment in the trial, who may be contacted by the investigator.

How long will I stay in the study? What will happen during the study?

The duration of participation in the study is 5 years. During this period, clinical and instrumental evaluations will be scheduled periodically, as per clinical practice, and quality of life questionnaires will be administered after 3, 6, 12, 24 months and 5 years, and a geriatric evaluation will be carried out at the beginning and end of the study. No additional examinations to the standard of care are planned.

What benefits and risks will I receive from participating in the study?

To test the benefit in terms of improved quality of life with breast irradiation alone compared to 5 years of hormone therapy alone without radiotherapy, patients included in the study will be divided into 2 groups. One group will receive treatment with breast irradiation alone, the other group will receive treatment with endocrine therapy alone to be taken for a total of 5 years. The groups should be similar, and the best way to group people similarly is to use randomisation. Randomisation is a methodology that randomly assigns participants in a study to one treatment or another. After you have given your consent to participate in this study, the randomisation process will have started. Only then you will know which group you have been included in. In inviting you to take part in this study, we hope that you will derive the expected clinical benefits in terms of improved quality of life with a favourable cost/benefit ratio from the planned treatment in your case. It is possible that you will not benefit from participation in this study. Your condition may remain the same or worsen and there is a risk that you may be harmed. If you are harmed by research-related procedures, your injury will be treated.

We would like to inform you that the Promoter, in accordance with the Ministerial Decree of 14 July 2009, has taken out insurance cover with HDI-GLOBAL SE, for any damages arising from this study in accordance with current legislation. The maximum coverage provided by the insurance certificate is € 7,500,000.00 for the protocol and € 1,000,000.00 for the patient.

The insurance policy covers damage which has occurred within 24 months of the end of the trial and for which the claim is made within 36 months of the end of the trial.

However, the insurance policy, which provides coverage for damages from liability arising from the trial, does not cover the value in excess of the maximum amount and only applies to damages for which a claim is made no later than the period provided for in the policy. This limitation does not affect your right to compensation from the party responsible for the damage.

The above insurance policy provides for the following exclusions from the insurance cover:

a) For trials not duly authorised and/or intentionally carried out in a manner contrary to that authorised by the competent authorities;
b) For damage that is not accidentally related, under the terms of the applicable Laws and Decrees, to the insured trial;
c) For complaints due to the fact that the product and/or the therapeutic investigation and/or the medical device does not fulfil the intended healing purposes;
d) For damage to pregnant women, for congenital damage, for genetic damage and/or for malformations caused to the foetus;
e) For claims arising from the use of systems, machinery and chemical and nuclear substances that do not comply with the law;
f) For claims due to acquired HIV immunodeficiency or misdiagnosis of this syndrome;
g) For damage resulting from the use of surgical activities;
h) The cover does not apply to damage arising from the use of invasive and surgical activities, except for intramuscular, intravenous, intradermal, subcutaneous injections and blood samples;
i) Exclusion of Coronavirus, Fllovirus, epidemic and/or pandemic

Exceeding these limits and the foregoing restrictions shall not affect your right to seek compensation directly from the party responsible for the damage. By signing this informed consent you are not waiving any of your legal rights.

If you have an insurance policy, you should check with your insurer that your participation in the trial will not affect your policy.

All hospitals and centres conducting research on human subjects refer to an independent ethics committee, which is responsible for reviewing all new research studies to ensure that the rights and

welfare of patients are protected. This study has been reviewed and approved by this hospital's Ethics Committee.

The aim of the study is to define the treatment that, with equal efficacy, allows women aged 70 years and older who have been operated on for early-stage luminal-A breast cancer to achieve a significant improvement in quality of life, with a reduction in the overall duration of post-operative treatment and consequently in side effects. Your participation could provide very important information in this regard. This information will be very useful for patients with early stage luminal-A breast cancer in the future.

What are the possible side effects of the treatment?

The side effects most commonly associated with breast radiotherapy are: dermatitis, oedema with a feeling of "breast tightness", increased breast firmness, fatigue. The side effects most commonly associated with endocrine therapy may be: insomnia, hot flushes, fatigue, nausea, headache, musculoskeletal and joint pain, increased sweating, osteoporosis, depression, abdominal pain, vomiting, constipation, dyspepsia, diarrhoea, peripheral oedema, rash, alopecia, urticaria, itching (aromatase inhibitors). For tamoxifen, additional risks are: endometrial hyperplasia with increased risk of developing endometrial adenocarcinoma, stroke, pulmonary embolism, deep vein thrombosis, dizziness, muscle cramps.

Tell the study doctor about any side effects, problems or unusual experiences you may have while taking part in this study. This may reduce the chance of side effects continuing or getting worse.

There may be other medicines that your doctor may give you to make any side effects more bearable or to make you feel better. If serious side effects occur, you and your doctor may decide it is in your best interest to stop taking part in the study.

What happens if I decide not to participate in the study?

You are free not to participate in the study. In this case, the doctors will continue to provide you with the necessary care. Regardless of your decision to participate in the study, you will undergo the standard in-therapy and in-therapy follow-up, i.e. instrumental examinations and medical examination, as required by your centre.

Interruption of the study

Your participation in this clinical research programme is completely voluntary and you may withdraw from the study at any time. Similarly, the trial may be terminated if the doctor determines that unwanted and clinically unacceptable adverse effects have occurred. In this case, you will be

informed in good time about further valid treatments for your disease and can discuss them with your doctor.

Confidentiality of personal data, data collection and use

Pursuant to Legislative Decree no. 196 of 30.6.2003 and subsequent amendments and to European Regulation 679/2016 on the protection of individuals with regard to the processing of personal data, we inform you that your personal data will be collected and stored electronically in anonymised form and will be used exclusively for scientific research purposes. You have the right to know what information will be stored and to update or change erroneous data. Access to this data will be protected by the investigator. Your personal data, in compliance with the requirements of the privacy law, may be inspected, including by validated and certified remote digital means, by regulatory authorities, and by specialised personnel appointed and authorised by the study sponsor. By signing the informed consent form you authorise access to such data. The results of the study in which you participate may be published but your identity will always remain confidential.

DECLARATION OF CONSENT

I, the undersigned _____ hereby declare that I have received from Dr./Prof. _____ full explanations regarding my application to participate in the study in question, as set out in the information sheet attached hereto, a copy of which I have previously been given. I also declare that I have been able to discuss these explanations, have asked all the questions I considered necessary and have received satisfactory answers, as well as having had the opportunity to find out the details of the study from a person I trust.

I also declare that I am aware:

-that participation in the study is voluntary, that I can withdraw at any time and that, in my own interest, the doctor can decide on my withdrawal from the study;

-that my medical records may be examined, but will remain strictly confidential, and that my identity and my data will be used with the utmost confidentiality, in accordance with Legislative Decree no. 196 of 30.6.2003 and subsequent additions;

-that the data will be stored and disseminated for scientific purposes only and in anonymous form;

-that the data will only be accessible to expressly authorised personnel;

-that the data can be rectified at my request;

-that I will be informed of any new data that may cast doubt on the validity and safety of the proposed study protocol;

I therefore freely agree to participate in the trial, having fully understood the meaning of the request and having understood the risks and benefits involved.

I was also informed of my right to have free access to the documentation relating to the trial (insurance, clinical-scientific, pharmaco-therapeutic) and to the evaluation expressed by the Ethics Committee.

I undertake to inform my medical officer, and all other doctors with whom I am treating, of my enrolment in the trial and I authorise the investigator to contact my other treating doctors.

_____ _____

Date Signature

TO BE COMPLETED BY THE DOCTOR WHO CONDUCTED THE INTERVIEW

I confirm that I have explained to the patient the characteristics, nature, purpose and potential benefits/risks of the study and the possibility for the patient to discontinue the study on request, and I believe in good conscience that these have been understood. I confirm that the patient has freely agreed to participate in the study by signing the consent form, that the consent form will be kept on file at our research centre in accordance with current regulations and that I have given a copy to the patient.

_____ _____

Date Signature of the doctor who informed the patient

If you have any questions about your rights as a research subject, or any questions about this study, please contact the doctor in charge of the project, Dr./Prof._____, at _____.

INFORMATION AND EXPRESSION OF CONSENT TO THE PROCESSING OF PERSONAL DATA

Purpose of processing. Data controller and processor

The Company ..... at which the study is carried out and the Promoter University of Florence, which commissioned the study "Endocrine therapy or radiotherapy of the breast as exclusive postoperative treatment in women aged ≥70 years with luminal-A breast cancer at an early stage: a randomised phase 3 study" presented to you, will use your personal data as autonomous data controllers, in accordance with the responsibilities provided for by the rules of good clinical practice (d. l. 211/2003) and the provisions on the protection of personal data (d. l. 196/2003).l. 211/2003) and the provisions on the protection of personal data (d.l. 196/2003). The Principal Investigator, who is following the study at _____ *(insert name of Hospital*), is identified as the person responsible for data processing with reference to the ownership of the trial Centre itself.

Type and nature of data

The following types of data will be covered in the course of the study:

- personal data
- clinical data
- information on origin
- Lifestyle information
- Information about the treatment she will undergo and its outcome, in terms of effectiveness and aesthetic results

Provision of data

The processing of the personal data detailed above is essential for the conduct of the study: refusal to provide them will not allow you to participate in the study.

Processing methods

The data will be processed by means of paper and electronic tools, by means of electronic CRF.

The doctor(s) (investigator(s)) who will follow you in the study will identify you with a code: data about you collected during the study will be recorded, processed and stored for seven years together with this code. Only the doctor and authorised persons will be able to link this code to your name.

The data, coded as indicated above, will be collected by the Trial Centre and transmitted to the Promoter. The data may be disseminated, for example through scientific publications, statistics and scientific conferences, only in a strictly anonymous form.

Monitoring and verification of the study

Your participation in the study implies that, in accordance with the regulations on clinical trials, the staff performing the monitoring and verification of the study, the Ethics Committee and the health authorities will be able to see the data (including identification data) concerning you, possibly including those contained in your original clinical documentation.

Exercise of rights

You may terminate your participation in the study at any time and without giving any reason; as a result, no further data concerning you will be collected, without prejudice to the use of any data already collected to determine, without altering, the results of the research.

You may exercise your rights under Article 7 of the Code (e.g. access your personal data, supplement them, update them, correct them, oppose their processing for legitimate reasons, etc.) by contacting the Testing Centre directly (insert Hospital, Department, tel, e-mail), _____, or, through it, the Promoter.

Consent

By signing this form I consent to the processing of my personal data for research purposes within the limits and in the manner indicated in the information provided to me herein.

I certify that my consent has been freely given and that I am aware that it can be revoked at any time without disadvantage or prejudice, and that I can always oppose the processing of such data for legitimate reasons (such data will then no longer be usable, unless the data, either originally or as a result of processing, no longer allow me to be identified).

Signature of the person concerned _____

Date _____

Further information

There are no additional costs to you arising from participation in the study, and you will not receive any financial compensation for participating in the study.

The study protocol proposed to you has been approved by the Ethics Committee of the hospital where the study is being conducted. The Ethics Committee has, among other things, verified that the study complies with the European Union's Standards of Good Clinical Practice and the ethical principles expressed in the Declaration of Helsinki.

You may report any facts you feel are relevant to the research that concerns you to the Ethics Committee and/or the Medical Directorate of this hospital.

Dr./Prof.	..... (Surname)	..... (Name)
Phone	.....	.....
Email	.....	

.....

Full name of the doctor who delivered the information sheet

_____ _____ _____

Date Time Signature

All references to D. L.vo 196/2003 are understood to be updated by EU Regulation no. 2016/679. We list below what is provided for by the GDPR n. 2016 / 679: Your consent represents the basis of legitimacy of the processing carried out on your personal data for the purposes listed in the above information. In addition, in order to comply with legal obligations, regulations and EU legislation, to assert or defend rights in court, to pursue legitimate interests and in all the cases provided for by Articles 6 and 9 of the Regulation, where applicable, your data may be processed even without your prior consent.

All data concerning you and the biological samples taken from you will be processed and transferred in accordance with the security measures laid down in EU Regulation 2016/679.

The EU Regulation 2016/679 provides some tools to protect and guarantee the rights listed in Chapter III. In particular, you have the right, at any time, to obtain confirmation of the existence or otherwise of data concerning you, to access such data, to verify its content, origin, accuracy, location (including in relation to third countries where the data is located), to request a copy, integration, updating, rectification and, in the cases provided for by law, the portability, limitation, transformation into anonymous form, opposition to processing for legitimate reasons. Finally, you may lodge a complaint with the Italian Data Protection Authority.

You may exercise these rights by contacting the Trial Centre directly _____ [please indicate the name of a responsible individual or office and an address] or, through the Trial Centre, the Trial Promoter.

_____ _____

Date Patient's signature

INFORMED CONSENT FORM

Endocrine therapy or breast radiotherapy as exclusive postoperative treatment in women aged ≥70 years with early-stage luminal-A breast cancer: a randomised phase 3 study.

ExclUsive endocrine therapy Or radiation theraPy for women aged ≥70 years with luminal A-like early stage breast cancer (EUROPA): a randomised phase 3 trial.

Protocol code, version and date: Version 2.1, 15 March 2022

Study sponsor: Department of Experimental and Clinical Biomedical Sciences 'Mario Serio', University of Florence.

Principal Investigator:

Dr./Prof. _____

Trial Centre: (*insert Department, Hospital, Address, Tel, Fax*):

_____

Study coordinators:

Prof. Lorenzo Livi

SOD Radiotherapy AOUC

University of Florence

Prof. Philip M. P. Poortmans

Iridium Kankernetwerk; University of Antwerp, Faculty of Medicine and Health Sciences; Wilrijk-Antwerp, Belgium

I, the undersigned _____, born on ____/_____, residing at _____Tel. _____, domicile (if different from residence)_____

I DECLARE

-that I have received from Dr. _____ full explanations regarding the request to participate in the research in question, as set out in the information sheet, which forms part of this consent, a copy of which I was given on the date

-at _____ (indicate date and time of delivery);

-that have been clearly explained to me and that I understand the nature, purpose, procedures, expected benefits, possible risks and drawbacks, and alternatives of the clinical trial;

-of having had the opportunity to ask clarifying questions and having received satisfactory answers;

-of having had ample time before deciding whether or not to participate;

-that there was no undue coercion in the request for Consent;

-that it was clearly explained to me that I was free to decide not to take part in the study or to leave it at any time without giving reasons, and that these decisions would not in any way alter my relationship with my treating doctors and the facility where I was being treated;

-that I am aware of the importance (and my responsibility) of informing my general practitioner of the trial in which I agree to participate; if I decide not to inform my general practitioner, I release both my general practitioner and the doctors involved in the trial from liability for any harm that may arise from incompatibility between the investigational medicinal product(s) and other medical treatments.

I therefore DECLARE

⬭ **Want** ⬭ **NOT to want**

participate in the study

⬭ **Want** ⬭ **NOT to want**

be informed about the results of this research by the study doctor

⬭ **Want** ⬭ **NOT to want**

be informed of the results of the research by the study doctor, also in relation to any unexpected information that may accidentally be found during the investigations foreseen in the study

⬭ **Want** ⬭ **NOT to want**

informing the general practitioner of participation in the study

.....

Full name of patient

_____ _____ _____

Date Time Signature

Full name of legal representative

_____ _____ _____

Date Time Signature

By signing this form I consent to the processing of my personal data and their transfer outside the European Union (to be inserted if done by specifying the identification details of the recipients) for research purposes within the limits and in the manner indicated in the information provided to me herein.

Full name of patient

_____ _____ _____

Date Time Signature

Full name of legal representative

_____ _____ _____

Date Time Signature

I, the undersigned Prof./Dr. .....

I declare that the Patient has voluntarily signed her participation in the study.

I also declare that:

-provided the patient with a full explanation of the purpose of the study, the procedures, the possible risks and benefits and the possible alternatives;

-checking that the patient has sufficiently understood the information provided.

-allowing the patient time and the possibility to ask questions about the study

-not having exercised any coercion or undue influence in the request for Consent

.....

Full name of the doctor who provided the information and collected the informed consent

_____	_____	_____
Date	Time	Signature