CLINICAL STUDY PROTOCOL

GIM29-GIMOMIC

TITLE: Observational, retrospective and prospective, non-interventional, multicentre national registry-based study to collect information on the use of genomic testing in the management of early stage HR+/HER2- breast cancer

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PROTOCOL APPROVAL

CLINICAL STUDY PROTOCOL

GIM 29- GIMOMIC

Observational, retrospective and prospective, non-interventional, multicentre national registry-based study to collect information on the use of genomic testing in the management of early stage HR+/HER2- breast cancer

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to principles of Good Clinical Practices and local regulations and requirements.

Investigator:

Site Number: _____

Name: _____

Signature: _____

Date: _____

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADCC	Antibody-dependent Cell-mediated Cytotoxicity
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CE	Conformitè Europëenne
CI	Confidence Interval
CRO	Contract Research Organization
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
eBC	Early Breast Cancer
CNS	Central Nervous System
DRFI	Distant Recurrence-free Interval
DFS	Disease-free Survival
ECD	Extracellular Domain
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EoT	End of Treatment
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HER2	Human Epidermal growth factor Receptor 2
HR	Hazard Ratio
ICH	International Council for Harmonisation
iDFS	Invasive Disease-free Survival
IEC	Independent Ethic Committee
Ig	Immunoglobulin
ISH	In Situ Hybridization
ITT	Intention-to-treat
IV	Intravenous

IVD	In Vitro Diagnostic
KM	Kaplan Meier
LVEF	Left Ventricle Ejection Fraction
MAH	Marketing Authorization Holder
MCC	4-[N-maleimidomethyl] Cyclohexane-1-carboxylate
MedDRA	Medical Dictionary for Regulatory Activities
MoH	Ministry of Health
MRI	Magnetic Resonance Imaging
MUGA	Multiple-gated Acquisition
NCI	National Cancer Institute
OS	Overall Survival
pCR	Pathological Complete Response
PET	Positron Emission Tomography
PgR	Progestinic Receptor
PI3-K	Phosphatidylinositol 3-kinase
PT	Preferred Term
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
T-DM1	Trastuzumab Emtansine
WHO	World Health Organization

TABLE OF CONTENTS

PROTOCOL SYNOPSIS

Study Title	Observational, retrospective and prospective, non-interventional, multicentre national registry-based study to collect information on the use of genomic testing in the management of early stage HR+/HER2- breast cancer
Study ID	GIM29-GIMOMIC
Number of participating Sites	Approximately 25 Italian sites
Study aim	The study aims to establish an Italian registry for the implementation of the use of genomic tests in patients with HR +/HER2- breast cancer at intermediate risk of recurrence after the entry into force of the Ministerial Decree of 18/05/2021. The decree has established the reimbursability of genomic testing for breast cancer patients, thereby influencing clinical decision-making and patient management within Breast Units. In addition, the study aims to evaluate the clinical impact of the use of genomic testing on the type of adjuvant treatment, in terms of change of treatment indication by breast units according to the test result. The retrospective cohort will contribute to expanding our knowledge of the clinico-pathological characteristics of patients who underwent genomic testing. This comprehensive understanding of the clinico-pathological profile of patients undergoing genomic testing will enable a more thorough assessment of the clinical dynamics and therapeutic decisions associated with genomic testing results, including the analysis of their possible evolution over the years.
Study Design	The study is a retrospective and prospective, non-interventional, observational registry-based study that will enroll all patients with ER +/HER2-negative, T1-3 breast cancer with negative axillary lymph nodes or up to 3 positive axillary lymph nodes for whom Breast Units require genomic test to support adjuvant therapy decisions, according to current clinical practice. For prospective cohort: genomic tests will be performed on all patients who meet the criteria for access to testing as set out in the Ministerial Decree of 18/05/2021, unless otherwise agreed by the reference Breast Unit, in accordance with the specific diagnostic pathways activated by each site. For retrospective cohort: data for patient referred for genomic testing following Ministerial Decree 18/05/2021 will be collected. The patient's baseline demographic characteristics, tumor clinicopathological features, pre and post-test therapeutic indication (CET vs ET), the test results, the actual adjuvant treatment received and time around data will be recorded in a dedicated registry.
Duration of the study	18 months
Primary endpoints	1. Establishment of a prospective Italian observational registry for the implementation of genomic tests in patients with HR +/HER2- breast cancer at

	intermediate risk of recurrence after the adoption of the Ministerial Decree of 18/05/2021 2. Measurement of the impact of genomic testing on adjuvant treatment choice (CET vs ET only) in terms of: - Rate of adjuvant treatment choice's change following the genomic test result (Breast Unit's pre-test vs post-test indication) - Saving in adjuvant chemotherapy compared to the pre-test indication - Addition of adjuvant chemotherapy to endocrine therapy alone compared to the pre-test indication - Type of adjuvant treatment the patient actually received
Secondary Endpoints	- Record the predominant demographic and clinical characteristics of the patients for whom genomic testing was indicated. - Describe which genomic tests are used and the factors involved in the selection of genomic tests. - Identify any inequalities in access to the genomic tests in different geographical areas of the country. - Analyse the prescriptive adequacy and the compliance with the inclusion criteria for genomic tests. - Record the distribution of demographic and clinical characteristics (e.g., patient age, comorbidities, tumour size, number of positive lymph nodes, tumour grade) in the group of patients with changed treatment recommendation compared to the group of patients with unchanged indication after genomic test. - Evaluate the impact of the test on the timing of activation of adjuvant treatment, in terms of: o Time from diagnosis to request for genomic test o Time from request for the genomic test to result o Time from test result to activation of adjuvant chemotherapy, if indicated o Time from diagnosis to activation of adjuvant chemotherapy, if indicated
Patients number	1.000 patients
Study Population	**Inclusion Criteria** All male and female patients meeting these criteria: 1. Age ≥ 18 years 2. PS ECOG 0-1 3. Histologically confirmed early breast carcinoma with positivity for hormone receptors (ER+ IHC >10%) and HER2 negative (IHC value 0-1+ and/or FISH not-amplified) 4. Primary resective surgery for early breast cancer with adequate assessment of lymph node status (sentinel lymph node biopsy or complete axillary dissection), with one of the following diagnostic stages: • T1-3, N0, M0 • T1-3, pN1mic, M0 • T1-3, pN1a, M0

	5. Indication for adjuvant treatment with endocrine therapy (ET) or chemo-endocrine therapy (CET), according to the decision of the reference Breast Unit 6. Meeting the criteria for "intermediate" risk, i.e., no “low” or “high” risk of recurrence, as defined in the ministerial decree of 18/05/21: • Low risk defined by at least 5 of the following: G1, T1a-b, KI67 < 15, N neg, ER > 80% • High risk, defined by at least 4 of the following: G3, T > 2, Ki67 > 30, N pos, ER < 30% 7. Indication for genomic test (Oncotype DX®, Mammaprint®, PAM50-Prosigna®, Breast Cancer Index®, EndoPredict®) by the Breast Unit 8. Ability to provide written informed consent to participate in the registry study, approved by the local Ethics Committee. 9. The patient underwent genomic testing starting from September 2021 **Exclusion criteria** 1. Low-risk and High-risk patients as defined in the Ministerial Decree of 18/05/21 2. ER negative and/or HER2 positive tumours 3. More than 3 lymph nodes involved at clinical/pathological staging 4. Invasive tumours <2mm evaluated by local pathologists 5. Previous history of breast cancer 6. Synchronous breast cancers 7. Multifocal tumours 8. Metastatic disease 9. Contraindications to adjuvant treatments 10. Performance status (PS ECOG) > 1 and / or other clinical factors that would make the patient a candidate and unsuitable for systemic adjuvant treatment or have received an exclusive indication for precautionary hormone therapy as part of the Breast Unit collegial assessment. 11. Psychiatric diagnosis that may affect the ability to participate in this study
Statistical methods	Although the true nature of this registry does not define apriori the number of patients ultimately expected, one of the main factors driving the sample size of this study is the clinical impact analysis and focuses on the accuracy of the estimate of the proportion of changes in planned adjuvant therapy pre and post genomic results.
Study Duration	Duration of the Project: 18 months Ethics committee submission: June 2023 Patient enrolment: May 2024-May 2025 End of Follow-up: November 2026

1 BACKGROUND AND INTRODUCTION

Breast cancer (BC) is the most common cancer in women, with approximately 55,000 new diagnosed cases per year in Italy and 13,000 BC specific deaths. After BC surgery, adjuvant treatment with radiotherapy, endocrine therapy and chemotherapy in selected cases, represents the standard of care for hormone-positive (HR +), HER2-negative early breast cancer (eBC).

The choice of the type of adjuvant treatment generally takes into account the clinicopathological characteristics of the patient and the tumour, including age, menopausal status, tumour size, grading and Ki67 labelling index, number of lymph nodes involved and hormone receptor expression. These characteristics configure specific and different BC risk profiles and drive the individual adjuvant BC treatment as for recommended international guidelines.

However, some ambiguity still remains in the optimal adjuvant treatment in HR+/HER2- eBC, particularly regarding whether patients should receive or not adjuvant chemotherapy (CT) in addition to endocrine treatment (ET). Considering the absolute clinical benefit of adjuvant CT in addition to ET in HR + eBC with negative lymph nodes (N0) is modest (4% absolute recurrence risk reduction at 10 years), and considering that currently about 50% of patients with HR+/HER2- eBC still receive adjuvant CT, the proper patient selection for CT is a major clinical unmet need. The same applies to older patients (post-menopausal) with HR +/HER2- eBC with limited lymph node involvement (N1a), for whom the use of adjuvant CT is often associated with increase toxicity and avoidable side-effects.

Consequently, there is an urgent clinical need to support the optimal decision-making process for determining the best postoperative therapy, especially for "intermediate" risk patients for whom it is unclear whether they should receive endocrine therapy alone (ET) or chemotherapy (CT).

In recent years, the role of molecular classifiers in prognosis and prediction has increased considerably. Indeed, several tests have been developed that assess the expression of panels of genes involved in the cellular replication of tumour cells and their metastatic ability, revealing specific genomic profiles associated with different risk of recurrence. Eventually, these tools can be used to refine the individual patients' prognosis and to estimate the benefit expected of adjuvant treatment. Accordingly, these tests provide critical support for therapeutic choice in patients with HR +/HER2- eBC (stage I-IIIA) at intermediate risk of recurrence according to clinical and histopathological factors, and help define whether adjuvant chemotherapy is appropriate in addition to endocrine therapy alone.

Several clinical trials have investigated the impact of these molecular classifiers on the choice of therapy. Multigenic tests have significantly changed the choice of treatment in a substantial proportion of patients, largely sparing the need for additional chemotherapy in favour of endocrine therapy alone.

Currently, some of these classifiers are available for routine clinical use in Italy, including OncotypeDX, Endopredict, Prosigna and Mammaprint. In line with the growing scientific evidence, the Ministry of Health, by decree of 18 May 2021, recognised the utility of genomic breast genomic tests and established their reimbursement according to some clinical criteria that can define the intermediate risk of recurrence, as derived from the scientific literature and the results of 3 prospective Italian experiences with the use of OncotypeDX.

The Ministry estimates that approximately 10,000 patients per year are expected to have access to the tests, resulting in a potential saving in chemotherapy prescription > 50% compared to what is currently proposed. Conversely, it is estimated that in about 10% of patients eligible for adjuvant endocrine therapy alone, the genomic test result will change the therapeutic approach and indicate the need to associate chemotherapy.

2 RATIONALE

With the receipt of the ministerial decree, Italian Breast Units have made genomic tests available to patients according to national indications, although availability varies from region to region. Irrespective of the estimates of the expected use of genomic tests, it is crucial to assess the actual degree of implementation of the use of genomic tests in accordance with ministerial indications, their prescriptive suitability and, finally, the clinical-therapeutic impact since the decree came into force.

Understanding the clinico-pathological characteristics of patients undergoing genomic tests is crucial for personalized cancer care. This understanding enables clinicians to tailor treatment plans effectively by identifying specific patient characteristics that correlate with certain genomic profiles. This approach improves treatment outcomes and reduces adverse effects. Additionally, integrating clinico-pathological characteristics with genomic data enhances prognostication, providing patients with more accurate prognostic information and enabling better long-term management strategies.

Furthermore, this comprehensive understanding facilitates the identification of predictive biomarkers, guiding the selection of effective therapeutic interventions and driving the development of innovative targeted therapies. By assessing the evolution of clinico-pathological characteristics and treatment decisions over time, the study provides insights into the long-term effectiveness of genomic testing, allowing for continuous quality improvement and optimization of treatment protocols.

Ultimately, findings from this study inform the development of clinical practice guidelines and health policies, guiding evidence-based decisions on resource allocation, reimbursement policies, and the integration of genomic testing into standard clinical practice. This comprehensive approach to understanding clinico-pathological characteristics in patients undergoing genomic testing contributes to the delivery of more effective, personalized cancer care, thereby improving patient outcomes and quality of life.

3 OBJECTIVES OF THE STUDY

The study aims to establish an Italian registry for the implementation of the use of genomic tests in patients with HR +/HER2- breast cancer at intermediate risk of recurrence after the entry into force of the Ministerial Decree of 18/05/2021. The decree has established the reimbursability of genomic testing for breast cancer patients, thereby influencing clinical decision-making and patient management within Breast Units.

In addition, the study aims to evaluate the clinical impact of the use of genomic testing on the type of adjuvant treatment, in terms of change of treatment indication by breast units according to the test result.

The retrospective cohort will contribute to expanding our knowledge of the clinico-pathological characteristics of patients who underwent genomic testing. This comprehensive understanding of the clinico-pathological profile of patients undergoing genomic testing will enable a more thorough assessment of the clinical dynamics and therapeutic decisions associated with genomic testing results, including the analysis of their possible evolution over the years.

4 ENDPOINTS

4.1 Co-primary endpoints

1. Establishment of a prospective Italian observational registry for the implementation of genomic tests in patients with HR +/HER2- breast cancer at intermediate risk of recurrence after the adoption of the Ministerial Decree of 18/05/2021
2. Measurement of the impact of genomic testing on adjuvant treatment choice (CET vs ET only) in terms of:
   - Rate of adjuvant treatment choice's change following the genomic test result (Breast Unit's pre-test vs post-test indication)
   - Saving in adjuvant chemotherapy compared to the pre-test indication
   - Addition of adjuvant chemotherapy to endocrine therapy alone compared to the pre-test indication
   - Type of adjuvant treatment the patient actually received

4.2 Secondary endpoints

- Record the predominant demographic and clinical characteristics of the patients for whom genomic testing was indicated.
- Describe which genomic tests are used and the factors involved in the selection of genomic tests.
- Identify any inequalities in access to the genomic tests in different geographical areas of the country.
- Analyse the prescriptive adequacy and the compliance with the inclusion criteria for genomic tests.
- Record the distribution of demographic and clinical characteristics (e.g., patient age, comorbidities, tumour size, number of positive lymph nodes, tumour grade) in the group of patients with changed treatment recommendation compared to the group of patients with unchanged indication after genomic test.
- Evaluate the impact of the test on the timing of activation of adjuvant treatment, in terms of:
  - Time from diagnosis to request for genomic test
  - Time from request for the genomic test to result
  - Time from test result to activation of adjuvant chemotherapy, if indicated
  - Time from diagnosis to activation of adjuvant chemotherapy, if indicated

5 PATIENT SELECTION CRITERIA

5.1 Inclusion Criteria

All male and female patients meeting these criteria:

1. Age ≥ 18 years
2. PS ECOG 0-1
3. Histologically confirmed early breast carcinoma with positivity for hormone receptors (ER+ IHC >10%) and HER2 negative (IHC value 0-1+ and/or FISH not-amplified)

4. Primary resective surgery for early breast cancer with adequate assessment of lymph node status (sentinel lymph node biopsy or complete axillary dissection), with one of the following diagnostic stages:
   T1-3, N0, M0
   T1-3, pN1mic, M0
   T1-3, pN1a, M0
5. Indication for adjuvant treatment with endocrine therapy (ET) or chemo-endocrine therapy (CET), according to the decision of the reference Breast Unit
6. Meeting the criteria for "intermediate" risk, i.e., no “low” or “high” risk of recurrence, as defined in the ministerial decree of 18/05/21:
   - Low risk defined by at least 5 of the following: G1, T1a-b, KI67 < 15, N neg, ER > 80%
   - High risk, defined by at least 4 of the following: G3, T > 2, Ki67 > 30, N pos, ER < 30%
7. Indication for genomic test (Oncotype DX®, Mammaprint®, PAM50-Prosigna®, Breast Cancer Index®, EndoPredict®) by the Breast Unit
8. Ability to provide written informed consent to participate in the registry study, approved by the local Ethics Committee.
9. The patient underwent genomic testing starting from September 2021

5.2 Exclusion criteria

1. Low-risk and High-risk patients as defined in the Ministerial Decree of 18/05/21
2. ER negative and/or HER2 positive tumours
3. More than 3 lymph nodes involved at clinical/pathological staging
4. Invasive tumours <2mm evaluated by local pathologists
5. Previous history of breast cancer
6. Synchronous breast cancers
7. Multifocal tumours
8. Metastatic disease
9. Contraindications to adjuvant treatments
10. Performance status (PS ECOG) > 1 and / or other clinical factors that would make the patient a candidate and unsuitable for systemic adjuvant treatment or have received an exclusive indication for precautionary hormone therapy as part of the Breast Unit collegial assessment.
11. Psychiatric diagnosis that may affect the ability to participate in this study

6 STUDY DESIGN

The study is a retrospective and prospective, non-interventional, observational registry-based study that will enrol all patients with ER +/HER2-negative, T1-3 breast cancer with negative axillary lymph nodes or up to 3 positive axillary lymph nodes for whom Breast Units require genomic test to support adjuvant therapy decisions, according to current clinical practice.

Only patients who fulfill certain criteria specified in Ministerial Decree 18/05/2021 will be included unless otherwise agreed by the reference Breast Unit, in accordance with the specific diagnostic pathways activated by each site.

Data will be collected from September 2021 onwards. The tests are conducted as part of routine clinical care, independent of this observational clinical study.

The patient's baseline demographic characteristics, tumour clinicopathological features, pre and post-test therapeutic indication (CET vs ET), the test results, the actual adjuvant treatment received and time around data will be recorded in a dedicated registry.

7 VISITS

7.1 Schedule

Due to the observational nature of the study, no predetermined visit schedule can be planned, as patients performed visits at the clinic according to common clinical practice as programmed with the study physicians and staff.
Therefore, data from all assessments detailed in Section 7.2 will be collected if and where available at the study visits.

7.2 Assessments

The main data for this study will come from the medical records of each patient who participates. All information entered into the electronic Case Report Form (eCRF) should have corresponding documentation in the patients' medical records.

Throughout the observational period, data collection will adhere to standard clinical practices, whenever possible. This includes tests, procedures, and visits, which are conducted based on the usual clinical protocols at each site and at the discretion of the site physician.

Upon obtaining informed consent from the patients, the following data will be collected during the enrollment period, provided it is available:

- ✓ Enrollment and screening

- General demography: sex, date of birth, age at the time of signing the consent, region of origin;
- Menopausal state, previous surgery, previous threpapies (including start and stop date, type of therapy).
- Tumor characteristics: histology, grading, size of primary tumor, lymphnode status and number of metastatic lymphnodes, receptor status (ER, HER, PgR, Ki67)
- Physical examination: weight, height, BMI
- Prior and concomitant comorbities and medication.

- ✓ Visit prior test

- Therapy prior test

- ✓ Visit prior test

- Test Type, test result, post therapeutic recommendation, patient decision

- ✓ End of study: specify reason

8 STATISTICAL CONSIDERATION

Although the true nature of this registry does not define apriori the number of patients ultimately expected, one of the main factors driving the sample size of this study is the clinical impact analysis and focuses on the accuracy of the estimate of the proportion of changes in planned adjuvant therapy pre and post genomic results.

8.1 Sample size

For the clinical impact analysis, 1000 patients, stratified in 60% of N0 and 40% of N1a patients, corresponding to 600 node-negative and 400 node-positive patients were enrolled.

After reaching the first 400 patients, an interim analysis is planned to check the accuracy of the assumed estimates and the feasibility of the study.

Moreover, to increase the accuracy of the results of this registry, enrolment and data collection will continue beyond the planned number of 1000 participants and will include all patients who meet the inclusion criteria throughout the whole study period.

8.2 Statistical analysis

It is assumed that the proportion of patients changing from chemotherapy (CT) followed by endocrine therapy (ET) to ET alone may be 50%, while the proportion of patients who change from ET to CT (followed by ET) is 10%. Therefore, the net change from CT to ET is expected to be 40%.

To demonstrate this expected impact in clinical practice, with a sample size of 1000 patients, the confidence intervals for these three estimates are expected to be 46.9%-53.1% (C.I. width of 6.2%) for changes from CT to ET; 8.3%-12.0% (C.I. width of 3.7%) for changes from ET to CT and 37.0%-43.1% (C.I. width of 6.1%) for the net change from CT to ET.

9 FORMS AND PROCEDURES FOR COLLECTING DATA AND DATA MANAGING

All patient's data will be recorded in a dedicated Case report form (CRF). All the information will be extracted from the medical records.

CRF is the primary data collection instruments for the study. All data requested on the CRF must be recorded, and any missing data must be explained. If a space is left blank because the procedure was not done or the question was not asked, "N/D" must be noted. If the item is not applicable to the individual case "N/A" must be noted.

The registry will be implemented on a web-based platform to capture and update patient recruitment in real time by regularly monitoring the number of patients enrolled as well as geographic and demographic information. In addition, the platform will be able to generate quarterly reports that will be available to those involved in the management and support of the study.

10 QUALITY CONTROL

The Study will be conducted according to applicable ICH and GCP guidelines. The monitoring visits will be conducted to ensure protocol adherence, quality of data, and compliance with regulatory requirements. As required by GCP and local regulations, the investigator will provide direct access to source data / documents for trial-related monitoring, audit, review by representatives of the sponsor, to CE and for inspections by regulatory authorities.

Clinical Monitor(s) will visit the Investigator(s) at regular intervals during the course of the study and after the study has completed, if required. They can be both on-site and/or remote visits. During on-site visits, eCRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved. Furthermore, electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system or via e-mail.

11 DATABASE RETENTION AND ARCHIVING OF STUDY DOCUMENTS

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor (25 years), whichever is longer.

The investigator must contact the sponsor prior to destroying any records associated with the study. Location of database and supporting documentation will be outlined in the final observational study report.

12 ETHICAL CONSIDERATION

This study will be conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong and Somerset West amendments) and the laws and regulations of the country, whichever provides the greatest protection of the patients. The protocol has been written and the study will be conducted according to the ICH guidelines for good clinical practice (ICH / GCP).

12.1 Patient Protection

All parties involved in the registry development will maintain the strict confidentiality to assure that neither the person nor the family privacy of the patient participating in the registries is violated.

Data will be processed exclusively by authorized personnel who participate in the definition of the GIMOMIC Study (data processor will be identified in each HCP involved). Access to computer systems and premises where they are kept will be controlled by means of appropriate security measures that comply with the requirements of the privacy regulations. The processing of the personal data of patients taking part in the GIMOMIC Study, and in particular regarding data concerning consent, will comply with local law on the privacy and with the General Data Protection Regulation 2016/679 (GDPR) of the European Union.

The registry protocol will be submitted to the Ethic Committee (EC) of the HCPs involved. Furthermore, ECs of the HCP involved, will authorize in advance any research carried out with the GIMOMIC Study data.

12.2 Informed Consent

The informed consent is the legal basis of the GIMOMIC Study. The investigator must explain to each patient (or legally authorised representative) the nature of the GIMOMIC Study, its purpose, the type of data collected, the expected duration, the potential risks and benefits involved. Each patient must be informed that consenting to have her/his data in the GIMOMIC Study is voluntary and that she/he may withdraw from the registry at any time and that withdrawal of consent will not affect her/his subsequent medical treatment or relationship with treating physician. The informed consent will be given by means of standard written statement, using non-technical language. The patient should read and consider the statement before signing and dating it, and should be given an original copy of the signed document. If the subject cannot read or sign the document, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the registry, mentioning that the patient could not read or sign documents. Information about a patient cannot be entered in the GIMOMIC Study before her/his informed consent has been obtained.

A separate informed consent for the analysis of biological samples, not mandatory to be part of the main study, will be signed by the patient. The informed consent must explain to the patient that no additional samples will be required for the purpose of GIMOMIC Study, but only results coming from the genomic test on biological samples already available at the site will be used.

The informed consent is part of the protocol and must be submitted to the local ECs.

The patient can withdraw the consent in any moment during the study.

The investigator should maintain a copy of the informed consent in the Trial Investigator File of the study and he/she should release an original copy to the patient.

For patients who will no longer be traceable, the data collected up to the last observation date will be analysed.

12.3 Insurance

Given the observational nature of the study, no additional insurance policy will be required compared to those already provided in normal clinical practice (AIFA Determination, 20 March 2008). The insurance is included in the general insurance coverage of the Hospital for clinical and research activities.

13 RISK/BENEFIT STATEMENT

There are no identifiable physical, psychological and/or social risks directly derived from the procedures that will be followed for the enrolment of patients in the study and the collection of the related data.

This study does not represent a direct benefit for the patient involved, however the collection of information regarding breast cancer may help the future treatment of patients affected by this disease.

14 FARMACOVIGILANCE/ADVERSE REACTION REPORTING

Since this is an observational study, medicinal products are prescribed in accordance with the terms of the marketing authorization (AIC) and in any case the assignment of the patient to a specific therapeutic strategy is not decided in advance by this trial protocol, but falls within current practice and the decision to prescribe the medicinal product is completely independent of that of including the patient in the study. No additional diagnostic or monitoring procedures should be applied to the patients and, and epidemiological methods will be used for the analysis of collected data, according to the provisions of AIFA Determination 20 March 2008 on "Guidelines for classification and conducting observational studies on medicinal products" published in the OJ 31 March 2008 No. 76.

For these reasons, any adverse reaction must be notified to the local authority as required by Italian Legislative Decree no. 219 dated 24 April 2006, Implementation of directive 2001/83/EC (and subsequent amending directives) relating to a community code concerning medicinal products for human use, as well as directive 2003/94/EC, and subsequent amendments

15 STUDY TIMETABLE

Duration of the Project: 18 months
Ethics committee submission: June 2023
Patient enrolment: May 2024-May2024
End of Follow-up: November 2026

16 REFERENCES

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