PROTOCOL SYNOPSIS

Background and Rational	Breast cancer represents the most common diagnosed tumour among Italian women and it is the first leading cause of death for cancer disease in the female sex (12.000 deaths in 2012). The risk of developing breast cancer has been associated to a group of genetic and familiar, endocrine, dietary, environmental factors, by lifestyle habits and previous breast pathologies. However the majority of the breast cancer cases can't be related to any known risk factor, regardless of female sex and ageing. Hereditary forms represent a minority of cases (about 5%-7%): a quarter of these cases are determined by the mutation of two genes, the BRCA1 and the BRCA2. In Italy, there are 48,000 new estimated cases diagnosed per year. This number has been increased every year within the last few decades. This can be ascribed to both a generational phenomenon and to the timeliness of the diagnoses in relation to screening campaigns and/or health information. The percentage of new cases is higher in early-stage than in the advanced stage due to the prevention's campaign: 90% vs. 10%. The new mammography's techniques allow to identify even small tumours and in pre-invasive phase: carcinomas in situ in about 25% of cases; <1 cm in diameter in about 40-45% of cases; with histological negative lymph node in around 75% of cases. The mortality rate for breast cancer has shown a decrease, as a consequence of the diagnosis of early breast cancer and therapeutic progresses. Due to the high incidence and the relative good prognosis, even in Italy breast cancer is the neoplasm with a higher prevalence: more than 690,000 alive women with a previous breast cancer diagnosis has been estimated in 2015. The integration of the various therapeutic modalities should be considered as strategic lines of treatment: surgery, radiotherapy, pharmacological treatment and consequently the final collaboration of various specialists within multidisciplinary teams. The knowledge of the clinical and biological prognostic factors (pT, pN, G, ER, PgR, Ki67 or MIB-1, HER2) is also fundamental in order to identify the opportunities and the most appropriate options in the systemic therapy both in the early and metastatic stages. It is therefore important a prospective evaluation of:

	• The criteria with which the clinician daily assesses the risk of the patient with early-stage breast cancer; • The criteria with which the clinician decides to carry out an adjuvant or neoadjuvant therapy to patients with a stage I-II-III breast cancer; • Types of systemic therapy carried out in adjuvant, neoadjuvant and first line settings for metastatic disease; • Implementation in the Italian clinical practice of the AIOM v.2017 guidelines;
Study objectives	The primary objective of this study is to evaluate the distribution of patients with a stage I-II-III breast cancer candidate to a systemic adjuvant and neoadjuvant therapy and to determine both the parameters that could influence the physician choice between a systemic adjuvant therapy or a systemic neoadjuvant therapy and the type of the chosen treatment in this setting of patients. Simultaneously, to evaluate the types of treatment in the stage IV patients at the time of diagnosis and in the stage IV patients at 1^ disease recurrence (locoregional and/or metastatic). Secondary objectives are: • To estimate the disease free survival (DFS), progression free survival (PFS) and the overall survival (OS); • To evaluate implementation in the clinical practice of AIOM V. 2017 Breast guidelines.
Study design	This is an observational, prospective, multicentre, secondary data use study.
Target population for data extraction	• Histological diagnosis of in situ breast cancer (DCIS, LCIS) or diagnosis of invasive carcinoma • Stage I-III patients or stage IV (according to TNM v. VII) at the first diagnosis or stage IV patients at the first disease recurrence (loco-regional or metastatic) • Availability of the following clinical and/or pathological parameters: cT cN M; pT pN M • Availability of the following biological parameters: G, ER, PgR, Ki67 or MIB-1, HER2 on primary tumour and/or metastatic lesion • Female, aged ≥ 18 years old at time of diagnosis • Provision of a written informed consent signed prior to enrollment

	according to GPP. **STUDY SIZE** Data from approximately 4,500 patients from ≥30 Italian oncologic centers
Length of study	The overall duration of the project is expected to be 5 years, divided as follows: 12 months for population selection, followed by 4 years of follow-up for each patient.
Selection of centres and data	**SELECTION OF CENTERS** The oncologic centers, as may be representative of Italian reality, will be selected in order to reflect in the same percentages the Italian oncologic centers listed in the AIOM white book v.2016, both for geographic distribution (North, Center and South of Italy) and for type of institution (IRCCS, Private Institutes, Academic Institutes, Public Hospital). The centers will be identified even according to the number of new cases per year. **SELECTION OF DATA** Medical charts data related to 4,500 consecutive eligible female patients with breast cancer stage I-IV, afferent to the participating Italian Oncologic centers during the population selection period, will be considered for the analysis.
Evaluation criteria	The following evaluation criteria will be considered: demographic and clinical characteristics of the patients, tumor characteristics, information regarding previous treatments (adjuvant, neoadjuvant and metastatic settings).
Data source	The source of data will be patients' medical charts.
Variables	• Centre characteristics: experience of operator, multidisciplinary discussions, number of patients treated/year, academic/research centers; The following already available data will be recorded from medical charts: • Demographic and clinical characteristics: age range, BMI, ECOG Performance Status, menopausal status and concomitant pathology; • Tumour characteristics: Rx-mammography and cito-histological collection before surgery, type of surgery performed and sentinel node biopsy analysis; • Tumour evaluation according to the "TNM AJCC version VII

	classification and staging" and performed methods ; • Biological characterization of primary tumour (estrogen receptors, progesterone receptors, HER2 status, proliferative index); • Mutation status of BRCA1 and BRCA2 genes; • Evaluation of genetic profile and performed method (es. ONCOTYPE dx, MAMMAPRINT, ENDOPREDICT); • Adjuvant/neoadjuvant treatment (chemotherapy regimens, radiotherapy, hormone therapy, immunotherapy, target therapy, other) and pathological response; • Patient participation in a previous study; • Patient inclusion to a concomitant clinical trial; • Discontinuation assessment; Patients outcomes will be assessed 1-2-3 and 4 years after enrollment closing. Data used in this phase will be referred to: • Possible disease recurrence (yes-no-site-date); • Pathological response and outcomes related factors (Disease Free Survival - DFS; Progression free survival - PFS; Overall Survival - OS); • Any disease progression after the first line treatment in the case of metastatic patients at the time of study entry; • Any patient lost to follow-up; • Any death(yes-no-date).
Study endpoints	Primary endpoints are: • Percentage of patients with a stage I-II-III breast cancer candidate to initiate a systemic adjuvant and neoadjuvant therapy; • Proportion of systemic adjuvant therapy and systemic neoadjuvant therapy started in this setting of patients. In this context, patients characteristics (age range, BMI, performance status, menopausal status) and center characteristics (experience of operator, dedicated units, number of patients treated/year, academic/research centers, etc.) that influenced the physician choice will be evaluated; • Frequencies with which different therapeutic schemes were chosen;

	• Frequencies of the different types of treatment administered in the stage IV patients at the time of diagnosis and in the stage IV patients at 1^ disease recurrence (locoregional and/or metastatic); Secondary endpoints are: • DFS, defined as the time from study entry to the first among the following events: local or regional relapse, distant metastasis, contralateral breast cancer, other invasive cancer different than breast, death; • OS, defined as the time from study entry to the time of death from any cause; • PFS, defined as the time from study entry to radiological or clinical tumour progression, second primary malignancy or death from any cause. • For each patients populations subgroup (stage I-II-III, stage IV or metastatic) and each center the proportion of patients treated according to the AIOM v. 2017 breast guidelines will be therefore considered. More in details, to evaluate the implementation of the AIOM v. 2017 Breast guidelines, the following indicators will be considerate: • percentage of patients discussed in the multidisciplinary group; • percentage of patients undergoing Rx-mammography and cito-histological collection before surgery; • the interval between surgery and the beginning of the adjuvant systemic therapy ≤ 8 weeks; • percentage of patients with invasive stage I-II cancer and negative axillaries lymph nodes (not neoadjuvant candidate) subjected to a sentinel node biopsy analysis; • percentage of patients with positive hormone-receptors treated with adjuvant hormone-therapy; • percentage of patients with invasive stage I-II cancer subjected to adjuvant therapy after conservative surgery; • percentage of patients that have done only Rx-mammography within 9-12 months after the surgery; • percentage of patients with invasive stage IV HER2+ cancer treated

	with a first line anti-HER2 agent; • percentage of patients with invasive stage IV cancer with bone metastases who have received bisphosphonates, anti-RANK, etc.
Study size	No formal statistical hypothesis for comparison is planned. It is estimated that 150 to 300 patients per centre, per year will be available. According to the guidelines compliance objective, approximately, an agreement not lower than 80% should be expected. Assuming a variability between 50% and 100% of the prevalence in each patients populations subgroup (stage I-II-III, stage IV or metastatic), it can be calculated that the precision of the statistical estimates (defined by the length of confidence interval of 95%) will vary between 3% and 5%. According to these considerations at least 4,500 patients' data should be obtained.
Statistical analyses	Demographic and baseline data (including disease characteristics, diagnostic measures and therapies) will be summarized descriptively. The probability of the agreement with the guidelines will be considered in function of the patients and the centers characteristics (experience of the operator, dedicated unites, expected annual volume of patients, typology [academics and of research vs. Generals] etc.). A binominal distribution test will be applied in order to evaluate the analysis agreement with the guidelines. A logistic regression analysis with correlated data will be performed in order to take into account the patients clustering in the centers, for each questions relating to the guidelines application. The patients outcomes analysis (DFS, PFS and OS), will be described using a Kaplan-Meier curve of survival with the semi parametric regression of Cox model.